ATTACHMENT 1

4-11-05 Statement from Victoria Hampshire.

For [redacted].

Dear [redacted] These disc should work in E (if labeled so) or D(if labeled so) computer drives. To view hyperlinks put your cursor on the link and hit control and left click the mouse, or enable the word document for hyperlinks by going to Tools, Options, then hit the edit tab and check the box entitled "enable click and type".

My name is Victoria Hampshire, VMD. I am a veterinarian (Penn 88). I am also a Commander in the United States Public Health Service. Until January 7, 2005 I worked as the sole Adverse Drug event Coordinator at the Center for Veterinary Medicine, the smallest center of the US Food and Drug Administration. An organizational chart is here.

I have had a spotless government career; mostly at NIH until 1999 where I developed a humane animal care program I have received nine public health service awards for conduct that portrays consumer and taxpayer trust. I worked independently for one year between 2000 and 2001 and then joined the FDA as the Adverse Drug Event Coordinator, Center for Veterinary Medicine. My most recent evaluation (December 2004) is attached here. I was responsible for interacting with hundreds of bereaved pet owners and for coordination of the review of thousands of adverse drug event reports through 6 separate safety reviewers at CVM between February 2003 and January 7, 2005.

ProHeart 6 was a novel canine heartworm preventative delivered by 6-month injection at the veterinary office. It was launched in June 2001. Between launch and recall, 5000 or so adverse events were reported by Fort Dodge Animal Health (FDAH) to the FDA. This drug was heavily marketed by FDAH as a "hook" to get owners back in the door twice a year. Despite two label changes and two "Dear Dr. Letters" regarding safety issues, it remained popular to veterinarians and the firm continued to promote its safety. It was recalled at the request of Dr. Crawford and the CVM senior management team in September 2004 because of ongoing safety issues.

A narrative of the findings at a recent VMAC meeting as well as the consumer opinion on this drug can be located by going to http://www.dogsadversereactions.com. Click on the moxidectin 6 month injection link for news stories, the FDA and FDAH position statements, presentations. The status at this stage is that the drug is voluntarily withdrawn. Fort Dodge Animal Health is working with the FDA to provide additional safety information.

Between the recall of ProHeart 6, I was the subject of a retaliatory conflict of interest investigation requested by Lester Crawford through FDA internal affairs following complaints by Wyeth (the parent company) CEO Robert Enser. Wyeth alleged that my motive in assessing ProHeart 6 as unsafe was to make profits from the sales of competition products through my prescribing account with an on-line veterinary prescribing site I used for my disclosed and approved outside activities.

I was reassigned with no reason on January 7th, 2005 (subsequently discovering the reason was the conflict of interest allegation). This allegation was, in my humble estimation a direct effort to minimize the impact of my presentation at the VMAC meeting January 31, 2005. I have also come to find out that Wyeth is persisting in pressing Dr. Crawford for the outcome of the investigation so that they might use it in future legal battles to try to salvage ProHeart 6.

Background

Like most veterinarians working for CVM, I file outside activities for limited ventures in moonlighting in the Metropolitan Emergency Animal Clinic (MEAC) and consulting for the Humane Society of the United States (HSUS). The forms are attached here, here and here I don't try to make money but to keep my hand in the clinical and humane aspects of my profession. I also have an outside activity that I file for a company I formed in 2000 (prior to employment with the FDA) called Advanced Veterinary Applications which accommodates any other veterinary request such as house calls, relief work and prescribing for the limited number of clients, friends, family or work colleagues that ask me for advise. So, in total, I normally file 3 outside activities each year. Sometimes I even file additional ones for activities buried within these outside activities because I think they could cause concern. I have always divulged everything that I can think of as an outside interest. The most recent example was a talk in Philadelphia on lack of effect heartworm products; a sticky issue for the center. I never conduct business at work, I don't use government phones or computers for such activities. This was eventually discovered by the agents who have been tracking me.

I was significantly involved in the review ProHeart 6 by Fort Dodge Animal Health (FDAH); Animal Division of Wyeth Pharmaceuticals. I was also significantly involved

in the review of safety problems of the competitors' drugs and fairly evaluated their problems. Over the last 2 years in this job I have put in an average of 60 hours per week looking at other drugs for safety problems as well; including 2 of 3 competitors of this drug. ProHeart 6 was associated with over 5000 dog adverse events and 500 deaths between 2001 and 2004. In or around February 2004 a large consumer watch group had formed and initiated over 2 -dozen local and some national news stories. The group and the stories can be found at the 6 month moxidectin link found on the website http://www.dogsadversereactions.com. I had significant and ordinary business contact with hundreds of consumers who presented their cases to me over a 2-year period. Many had emptied their savings accounts trying to save their dogs. In November of 2003 I urged the product manager and team leader [redacted] respectively) to take further action regarding this drug. [redacted] refused and [redacted] stated that the drug would go away on its own after enough animals died. They were eventually given an award for pharmacovigilance just this past month. I was not given any awards. [redacted]. The Division Director Dr. Post, although in agreement with me, continued to tell me that he had no control over [redacted] and [redacted] and that eventually they would come around.

The consumer group continued to press CVM until July of 2004 Dr. Steve Vaughn, head Office of New Drug Evaluation asked the question "when are we going to do anything?". There were over 26 national news stories about this drugs' problems. By mid July it was agreed that senior management (SMT) would listen to a presentation that I would make regarding the unsafe nature of the drug. It was unanimously agreed that the drug was a problem and should be recalled. The firm should be asked to conduct additional safety studies. Dr. Sundlof, the CVM center director took the case to Dr. Lester Crawford with a plan to ask Fort Dodge to voluntarily recall the drug in September. Dr. Crawford urged him to step up the process because the fall heartworm test and prophylactic season was approaching; more dogs would be exposed. A meeting was scheduled between Dr. Sundlof, Dr. Post (my division director) and Tom Corcoran (FDAH president) on August 11, 2004. I was on vacation at the time with my family. A copy of my slides from the mid July presentation were given to Mr. Corcoran. The slides were in draft form.

On September 1 of 2004, in a meeting of top FDAH and FDA officials, I presented the opinion that the drug was unsafe. My slide show is here. My father who lives in a nearby town had died two nights before but I went ahead with the presentation because I did not feel anybody else knew the information and my mother wanted me to leave her alone for a time in her garden.

My opinion was delivered in 15 minutes of what was supposed to have been an hour long presentation after FDAH used 45 minutes of my time. It was based on the scientific evaluation and synthesis of 7 different safety reviewers' evaluations of these events. My supervisors (one Division Director, Two Office Directors and Senior Center Management Staff (Center Director, Deputy Center Director, Associate Directors) concurred. The Acting Commissioner and his legal counsel also concurred. The meeting was somewhat contentious. I interrupted the firm three times to correct their statements that were distortions of my previous slides. After I was finally allowed to present, I did a reasonably good job of condensing an hour of information into 15 minutes and SMT still believed the information warranted a recall of the product. Between September 1 and September 3, I took some time to be with my mother but came into work periodically to help prepare answers that were a result of last minute pleas from FDAH to the Commissioner. The first was to try to state that another heartworm competitor (Revolution by Pfizer) had just as many adverse events. We had already addressed the adverse events with this drug in 2002 and they had been declining since repackaging the dose form and warning veterinarians not to give the drug under certain conditions. We had also required Pfizer to conduct post approval studies because of rising complaints regarding ineffectiveness. Additionally, two other competitors (Sentinel and Interceptor by Novartis) were the subject of an inspection for refusing to turn over lack of effect complaints to CVM. I lead that inspection in January 2004. The final competitor (Heartguard by Merial; animal division of Merk) has had rising numbers of ineffectiveness reports in which the follow up and reporting was lacking in substance. I have been responsible for communicating with this firm for improved follow up. We explained all of this to Dr. Crawford and he concurred that we had been fair.

FDAH also took their case to the FDA Chief Counsel Dan Troy and try to claim it was not substantive. The response from Dan Troy was that CVM did not act rashly and he believed he would uphold CVM's recommendation. The firm voluntarily recalled the drug on September 3, 2004 on the condition that CVM would convene an outside panel of experts as a veterinary medical advisory committee because they had concerns that the adverse experience information was misinterpreted. The press release from FDAH and CVM are here and here.

Between September 3 and approximately November 1, I was told to work on a narrative for the VMAC members. It was a lot of material on over 5000 reports. The VMAC meeting was tentatively scheduled for mid January 2005 so that if the decision was in favor of the drug, FDAH could make the spring heartworm season. I did not think that with finding the experts, clearing them through ethics, etc, that was enough time. I decided to make an interactive CD like this one so that they could view as much information as possible in what would be a short timeframe. I linked every statement to a data table or a full text document. There were over 300 data tables and 55 references fully linked to a 97- page narrative containing highlighted case reports. It was extremely transparent and easy to read. There was also an internal group of CVM experts to help prepare for the VMAC meeting. The VMAC meeting was finally scheduled for January

31, 2005. I worked diligently to prepare for this event. Some of my colleagues did not agree with a few of the more vague but increasing signs such as tumors and cardiovascular events and asked me to re-evaluate those events. I did; taking into account the majority opinion on some isolated and very difficult cases. I still believed the events were possible given a review of the scientific literature.

In November I was told not to come to the weekly meetings, that the remainder of the inside panel would review my work and verify it. I agreed that was a good idea; it should be an agency document and I felt that I had prepared a robust document that could be edited. I began to notice a cold shoulder treatment about that time and it intensified through Christmas. Regardless, my Division Director Dr. Post continued to ask me for information, data sets, etc because nobody was really taking the project to heart. Two of the key members were out for over three weeks; one for a vacation and the other for surgery. I recommended the government have more time. My managers felt that we should try to stay with the January 31 meeting so that if the drug was found safe, FDAH could benefit from sales during the early spring heartworm test/prophylaxis season. Some of the other internal members decided to take out any information regarding ineffectiveness complaints, blindness and neoplasia. I was also asked to help find outside experts for the VMAC and provided names of consultants. What was eventually delivered to the consultant and to the VMAC panel members was a dramatically shortened document. No hyperlinks were available to data sets or full text articles and they had less than a full week to review all of it.

On December 23 and 29th, we had an outside consultant Dr. Judith Jones from the Deggee Group in Arlington Virginia review the gist of the narrative. Despite its shortened version, she thought it was very compelling and made several good suggestions.

On January 7th I was called to see the Deputy Director Dr. Linda Tollefson and the Director Office Surveillance Compliance Dr. Daniel McChesney. Dr. Tollefson stated that the reason I was there was that Wyeth had "pulled all plugs" at the level of the commissioner. I was not permitted to know any further detail but said hopefully I would be vindicated after the public meeting and that this reassignment was not punitive but protective. I assumed the case was some allegation of bias. Dr. Tollefson stated that I was to be reassigned to the FDA biologics facility in Bethesda. I protested and asked to be reassigned to another office here at CVM. She called the Executive Officer David Wardrop to see if we could work out a reassignment here at CVM in the same building. While she was talking to Mr. Wardrop Dr. McChesney told me I should view my circumstance as a police officer who had been placed on administrative leave after shooting somebody in the line of duty. I asked him what he meant by that and he said he could not tell me. I told them that if the concern was possible allegations of bias I had already volunteered to Dr. McChesney to stay home during the VMAC meeting, already arranged with my colleague Dr. Margarita Brown to give the presentation to the VMAC, and had not been going to the weekly internal meetings so as to prevent any weighted input from myself. I did not understand the rationale for a reassignment if I had already stepped back.

They agreed to reassign me to the Office Level (one step up) under Dr. McChesney and that I could write my own statement of duties focusing on other things I did This is an e-mail from Dr. Tollefson (Deputy Center Director and also Deputy Surgeon General) the day following this meeting. Oddly, when I was reassigned, I noted that David Wardrop, the chief executive officer, directed Dr. McChesney that the reassignment be quick. When I got the reassignment memo on the 12th, it was backdated to the 7th and directed the reassignment effective the 10th. I later learned from an informant that Wyeth may have threatened Dr. Crawford with either a news story, or something in the public package if they did not have proof of my reassignment by the time the public package was delivered. The public package from FDAH was due in to CVM on the 10th and was delivered by hand from a FDAH representative that day. I suspect, but cannot confirm that Wyeth attempted this by extortion; that they would either print a media scandal in what they believed to be a conflict of interest story, or alter the public presentation with the allegation of bias.

I then called David Graham at CDER and asked for his attorney's name. That's how I got Tom Devine's name. I also called Congressman Chris Van Hollen to tell him of the reassignment.

I was afraid to talk to Senator Grassley because this drug firm is an Iowa company. Chris Van Hollen asked his legislative affairs contact Phil Alperson to stay in touch with me. Eventually he prepared a letter to the FDA Acting Commissioner which was sent on January 28. A copy of that letter is here. I also filed a complaint with the OSC but withdrew it on January 11 after reading in the Washington Post and in Mr. Devine's book that this may be a trap. I received confirmation from the OSC that the complaint had been withdrawn.

On Saturday January 30, I received a call from Dr. McChesney at home. He asked me to help him with a media response if consumers asked where I was at the VMAC meeting. I helped him with a response that said I was on vacation and had been reassigned to bigger and better things. I also received calls from consumer groups who tracked me to home to ask if I was all right. I told them I'd been reassigned and they are suspicious but I asked them not to mention it at the VMAC meeting because I thought it might damage the government and it was important for the government that the presentation be objective.

On Monday January 31, the VMAC meeting proceeded. The website with the presentations, the government's case and Fort Dodge's case is here. The Government prevailed by a narrow vote of 8 who said the drug was unsafe to 7 that said it was safe. Of the 7 that said it was unsafe 5 apparently qualified their answer with great hesitancy. Several voters stated that the government delivery was dispassionate. A transcript of the meeting and the voters' comments should be available shortly.

On about February 8th I received an e-mail from the FDA Ethics Office asking why I had not filed an outside activity for Advanced Veterinary Applications as I usually did. I

returned a replay stating that I listed it on my financial disclosure because it was a holding but I was not active in it. I had planned to close this company anyway after March 2005 when the corporate returns were due. I was not aware that I needed to renew an outside activity for an inactive activity but would if they wanted one. They replied that I should fill out one anyway. I filed one out that briefly described what I would be doing if it was active and subsequently thought about whether since I had to file on it, it might make sense to keep it open. I scheduled a meeting with my accountant to pose these questions. I also became suspicious and paranoid but I could not figure out what might be going on because no money is made in this inactive activity and I disclose it each year. I routed it through Dr. McChesney who then took it to the agency contact here Linda Callahan. E-mail traffic regarding my attempts to probe the establishment is here. I felt the level of inspection and persons copied were unusual. Normally, my superiors hardly look at these filings. I've never seen an Executive Officer copied. It has even been the case that I initiated the filings in the past and was told nobody ever reads them! I had always filed, far back into my employment at NIH before coming to FDA.

On February 11th I went to lunch with my colleague [redacted]. She told me that I should consider other employment; my career here was on the line. When pressed to tell me why she said that Fort Dodge Representatives had (sometime in November 2004) obtained information that I had the outside activity Advanced Veterinary Applications. We think they did this by obtaining my curriculum vitae through a reporter who was doing a dummy story on women veterinarians in government and had asked for an interview with me only three weeks after the recall. We have pretty good evidence that [redacted] misrepresented himself in order to obtain this information. Through a web search, Wyeth also determined that I had a prescribing account with a commonly used service called Vetcentric and made the allegation that because I had this prescribing account I was biased and stood to gain from the sale of prescription competitors (monthly oral dog heartworm products). They had threatened a media scandal if I was not removed from the case of ProHeart 6 by January 7 (a Friday).

[redacted] did not tell me any more about who might be investigating me or anything. She made me promise not to tell she'd revealed this information to be because it was leaked to her by [redacted] and they could both loose their jobs. I was panicked. By this time it was nearing the end of Friday. Dr. McChesney was not around. I found my outside activity waiting in a pile of things Dr. Sundlof had to sign and detailed the vendors I used for my outside activity (a level of detail that was new and unusual). I did this because I was not certain that it would be obvious to a non-veterinarian that vets require prescribing privileges with veterinary pharmacies and because I believed that they had intent to harm me by trumping up the interest in this disclosed and inactive activity. I was under the impression that Dr. McChesney was no longer at work and that David Wardrop had not yet seen it. I did not want to reveal the reason for why I detailed this because I did not want [redacted] to be fired.

I asked David Wardrop to call me with any questions. He pretended he had not reviewed my outside activity as rewritten. A copy of that e-mail correspondence is here.

The Vetcentric prescribing account is a veterinary service I barely use. You can read about it here. Veterinarians who have small numbers of clients or practice on a limited basis like it because it saves them having to have overhead and they can choose to mark up the prescription with a margin. I usually don't. At the most I charge $5.00 to write a prescription to cover my time. I have a total of around 20 or so clients; most are family, teachers, friends or former clients. Most of the time when they need something I make them meet me at the Emergency Clinic where I work every other Saturday night. Sometimes I don't even open the envelope from Vetcentric and have accidentally thrown away or failed to cash checks. I had not been active in any of my outside activities since October 2004 and had a few phone calls I dismissed at the time as persistent people trying to get me to write a prescription for heartworm products. These occurred sometime in the fall 2004. It was later revealed to be by inspector McCormack on February 24, 2005 that these were FDAH imposters and themselves trying to see if I would dispense heartworm prescription products without a valid veterinary client relationship.

Over the weekend between February 11 and February 15, I contacted Vetcentric. I asked the business manager Micheal Fox if he could send me my account information, whether there had been any illegal activity on it, etc. He mailed me the account activity. It is here. Pages 1-2 are the detailed client reports for activity between opening the prescribing account in 2001 and the last sale in 2004. I received it on Monday the 14th of February 2005. I noticed immediately a one Tom O'Hare (page 2) had purchased roughly $3000.00 of over the counter supplies on October 15, 2004. I had not opened any mail and/or thrown away the Vetcentric mailings because I expected not to have any checks in them and don't want to see the promotional material. I asked Mr. Fox to close the account and if he could tell me where Mr. Tom O'Hare ordered from. He gave me the address and phone number registered for the sale and stated the man lived in Copiague, New York. I pulled up a background check for $69.00 on the web. It is here.

I determined that Mr. O'Hare lived in a row house somewhere near New York City and imagined that he was probably a hired thug by Wyeth who tried to penetrate my account to buy heartworm products. I dismissed this as paranoia but later learned it was true. Since I would not ok a prescription for him he did the next best thing and bought over the counter products. Mr. Fox said that Vetcentric had mailed me a check for something like $600.00 as a margin on the purchase but I'd never cashed it. I presumed I threw it out thinking it was junk mail and asked Mr. Fox not to send another one.

On February 24, 2005 I received an e-mail from Mr. Mark McCormack telling me he needed to speak with me at 9:30AM on 2/25/05. That e-mail is here. I called Mr. McCormack to see if I could come at 1:30PM on 2/24/05 and he said yes. I drove to 1 Church Street Rockville. Mr. McCormack introduced himself and his colleague Mr. Micheal Redmond and told me this was not a criminal investigation and that "the DA has

declined to prosecute you". I was shown into a small room with a round table and we sat down. I was asked if he was treating me all right and whether or not I needed to go to the bathroom or needed anything to drink. I said I was fine. Mr. McCormack stated that the reason I was there was that the District Attorney had declined to prosecute me for criminal charges of conflict of interest and they wanted to get a statement from me regarding the events surrounding my outside activities before they finished their report. They showed me their badges. Mr. McCormack told me that he was an ex-Secret Service investigator who had taken his present job with FDA internal affairs. Mr. Redmond told me he was an ex military intelligence officer doing the same. They told me a history starting with the fact that Wyeth had hired a thug to penetrate my account and order over the counter supplies in order to prove to Dr. Crawford and FDA legal counsel that I had the activity. Since the activity was disclosed as a veterinary relief and moonlighting/consulting, it was not immediately obvious to the inspectors that it was a prescribing account. Wyeth had initially made the allegation that it was a partnership with Vetcentric and that I had motive to gain sales in monthly heartworm products by shutting down their injectable product. Mr. Redmond and McCormack had tapped my phone, computer and obtained corporate records between November 2004 and February 2005. They had determined that most of my clients were old friends, neighbors and a few work colleagues or family. They determined I made no money in my inactive disclosed business. They had tested me by trying to order prescription products without a valid veterinary client relationship and I passed. I was not guilty of misuse of government equipment or of conducting business on government time.

They then asked me why I changed my outside activity between February 8th and February 11th and whether I intended to deceive my leadership? I stated that I was panicked and changed it because I was under the understanding that I would loose my job if I did not disclose every detail of my clinical activities in this disclosed inactive activity. That I thought somebody inside CVM might be trying to trump it up as something substantive when it was not and that I had promised not to reveal the leak from Linda Grassie and I was afraid that if I did, they would try to fire or discipline her. I also told them I had become suspicious and paranoid that somebody inside FDA might be trying to frame me and that Dr. McChesney was someone I did not trust because he had already told me I didn't need a lawyer and was not in the habit of directly answering my e-mail. I was under the impression from David Wardrop he had not reviewed the outside activity but had come to learn he had. Linda Callahan was only a conduit for outside activities to the FDA ethics office and atop that they had lost my last outside activity because it was stuck on Dr. Sundlof's desk whereupon the secretary told me "they never read them anyway". Mr. Redmond then smacked his cheeks in disbelief. Mr McCormack rolled his eyes. I repeated that my intent in the paranoid frame of mind I was in was to clarify, not conceal. Mr. Redmond said he saw my changing my outside activities without telling Dr. McChesney about it was an integrity problem. If it were he in my boss's shoes, he would have my uniform. I repeated my intent was to clarify, not conceal and that I had repeatedly sent e-mails to my superiors asking them if they required clarification, whether I needed waivers, etc. They had shut me out. I believed at the time they were trying to entrap me for something I did not do. I reminded him that it was late on Friday the 11th when I made the change and by Monday I knew I had been framed by FDAH and

that I didn't know if I could ever get past seeing a FDAH or work colleagues as a threat to me or my family. They asked me again why I did not renew the outside activity for AVA by December 31 when it was due and I repeated that I had planned to close it after the corporate returns were due in March 2005, that as far as I knew, it was inactive (because I did not know about Wyeth's activities at the time) and therefore did not require an HHS 520. I underscored that I did list the company as a holding on my financial disclosure which I filed in November 2004. I t old them that I had discussed all of this with Chris Van Hollen. They asked if I had called off the congressman and I said yes, once I knew what the reason for the reassignment was I wrote Chris VanHollen and told him that it had occurred over a perceived conflict of interest. They asked me whether once I found out on February 11th why I was reassigned on January 7th did I let the congressman know that I had been told by an informant why and I said yes. Mr. McCormack and Mr. Redmond thanked me for telling them the truth. I told him I blamed my self for not thinking in the fame of mind a drug company might think and I was sorry it had brought so much unnecessary attention upon the agency.

Mr. McCormack asked me to write a statement of the events we discussed and to sign it. When I was done he asked me if I was all right and whether he had treated me ok. I told him I was a bit upset that nobody asked me in the first place what this outside activity was about and how the prescribing function worked. I could have given him the vetcentric account activity and corporate records in 30 minutes. I told him it was demoralizing, that I'd never been in trouble in my life and that I did not feel I should have to go through something like this for doing the right thing for consumers and the agency. The attached documents represent the inspector's credentials, the statement I signed and the Kalkine's Rights that I signed. They are here.

Mr. McCormack and Mr. Redmond thanked me for telling the truth and showed me to the door. They asked me again if they had treated me alright and I said yes.

On February 28th I called Mr. McCormack because I could not find my copy of the Kalkine's Rights. I got his voice mail. Before long I found them between the car seat. I called him back and he answered. He asked me how I was and I said I had not slept much and that I was still scared. He told me to try not to worry, his report was nearly finished and if he had any further questions he would call me back.

On February 28th I also wrote Dr. Linda Tollefson. I told her everything that happened on 2/24/05, repeated that I was not a liar or a criminal and asked for her assistance in gaining new employment. I also told her that if necessary I would help prepare any media answers to state the truth about this disclosed holding, the total amount of work done with it over the last 3 years, etc. She has never responded. I have not been given any form of apology or reinstatement in my old job. No explanation for my sudden reassignment has been given to my colleagues or the consumers. I have located a detail in another area of FDA to try to improve my self esteem and do meaningful work as well as to avoid further adverse actions from my organization. I am very scared.

At this point I believe my PHS commission may be at steak. My colleagues are afraid to touch FDAH or take any future severe regulatory action against a regulated entity for fear there will be personal attacks.

I have taken a 120 detail at CDRH to work on cardiovascular device approvals. It also has some hurdles to cross as my husband is a scientist in cardiovascular research at NIH and signs CRADAS (cooperative research agreements between NIH and industry). We have a meeting scheduled next week to work with NIH and FDA ethics on the best way to protect myself in this detail. My past veterinary support activities of animal studies at NIH will come in useful for this work, I believe the people in this particular branch are first rate and kind and that I will enjoy it. If I have not knowingly committed any crimes, I wish to stay with meaningful work; preferably away from what I believe to be an unsafe work environment in FDA. I am under the understanding from David Wardrop that Wyeth CEOs and GC continue to press Dr. Crawford for the outcome of his investigation into my activities and that they may try to harm me in the future.

I do not believe that my center staff became ugly to me until whatever happened with Dr. Crawford, his GC and the Wyeth GC met. I wish to know what Wyeth threatened him with and why he chose a full criminal investigation over picking up the phone and calling me. They had no reason to distrust me and had considered me an outstanding and valuable employee until then. I wish for them to ensure that my achievement award (which was put in the system last fall) is given to me and that some thanks for the work on ProHeart 6 safety is given minimally to my colleagues (all 6 of them) in the safety office. [redacted]

Lastly, I wish to know if the action that Wyeth took to hire Mr. Tom O'Hare of Copiague, NY to knowingly and fraudulently purchase over the counter supplies from my disclosed and otherwise nearly quiescent account represents fraud and racketeering against a government safety officer and whether I have any recourse for the damage it has created to my person.

I realize that you may not be able to answer many of these questions but I want you to know how awful and sinister and unfair this situation is. I did the right thing for the American people and I did an outstanding job for the agency.

Victoria Hampshire, VMD
4-11-05

ATTACHMENT 2

Food and Drug Administration
Office of Internal Affairs (HFH-560)
One Church Street, Suite 700
Rockville, Maryland 20850

February 23 , 2005

Mr. Steven M. Dunne
Assistant United States Attorney
District of Maryland
400 U.S. Courthouse
6500 Cherrywood Lane
Greenbelt, Maryland 20770

Dear AUSA Dunne:

In November of 2004, the CEO of Wyeth Pharmaceuticals presented information to Dr. Lester Crawford, FDA Commissioner, which appeared to indicate FDA employee Victoria Hampshire, DVM, Senior Regulatory Staff, Center for Veterinary Medicine (CVM), (the subject in this case) was operating an Internet pharmacy for animal drugs and other products; a conflict of interest.

Independent investigation by Criminal Investigators from FDA's Office of Internal Affairs (OIA) corroborated the information provided by Wyeth. The subject is the listed owner and sole proprietor of a web site known as Advanced Veterinary Applications, which was incorporated in November of 2000. The subject's EOD date with the FDA is 10/21/02.

As one of her duties at the FDA, Dr. Hampshire was compiling Adverse Event Reports (AERS) for Pro Heart 6, a reportedly very profitable canine medication for heartworm prevention. Pro Heart 6 is administered by injection by veterinarians. Pro Heart 6 is manufactured by Fort Dodge Animal Health, which is a wholly owned division of Wyeth Pharmaceuticals.

By September 2004, Dr. Hampshire had compiled in excess of 5,000 AERS, including reports of 500 canine deaths, involving Pro Heart 6. Officials from CVM met with representatives from Fort Dodge Animal Health, who voluntarily agreed to remove Pro Heart 6 from the market.

Officials from Fort Dodge Animal Health conducted a Google search of Victoria Hampshire, and discovered her web site. Fort Dodge Animal Health has since taken the position that the subject has a conflict of interest regarding her involvement in the Pro Heart 6 issue.

Through the web portal of Advanced Veterinary Applications (AVA), the subject also advertises heartworm medications which compete with Pro Heart 6. An agent acting on behalf of Fort Dodge Animal Health had two orders filled through AVA. Wyeth also pointed out that the subject is also quoted by animal activists on the web as allegedly making derogatory comments against Pro Heart 6 (hearsay).

Since discovering the existence of the subject's web site Fort Dodge Animal Health has taken the position that Pro Heart 6 is both a safe and effective drug and requested a Public Advisory Meeting, which took place on 1/31/05. In an 8-7 vote the Public Advisory Group ruled against Pro Heart 6. Fort Dodge Animal Health has vowed to continue its fight.

When an order is placed through the subject's web site it is actually filled by a firm named Vet Centric which fills and ships the order. Vet Centric, a third party fulfillment house, is located in Annapolis, MD. An FDA Office of Criminal Investigations Intelligence Research Specialist found no evidence of a Nexus between Dr. Hampshire (the subject) and Vet Centric.

HHS/OIG joined in this investigation and served an administrative subpoena on Vet Centric.

Generally the subject receives only $5.00 for each order filled by Vet Centric. Between her EOD of 10/21/02 and the present the subject has received approximately $ 774.55 from Vet Centric for orders filled; of which $472.57 was paid to her in November of 2004, from the second order placed by the agent for Fort Dodge Animal Health to cement their Conflict of Interest Allegation. In this regard it is the opinion of the investigating agent that although the dollar amount may seem minimal, as an employee of the FDA, the subject has a grave and continuing conflict of interest.

Per Ms. Jenny Slaughter, Director, FDA Office of Ethics, the subject would need approval for any outside activity from her EOD date with the FDA. On her OGE 450 (Confidential Financial Disclosure Report) dated 3/10/03, under Part 3: Outside Positions, the subject lists AVA Consulting, and describes the activity as Consulting (not a web site or portal to order veterinary medicines). That OGE 450 expired on 7/1/2003.

On her next OGE 450, dated 11/03/04, the subject lists Director, Advanced Veterinary Applications (AVA) for income from the Humane Society of the United States. Under "Type of Organization" the subject typed "Clinical Care and consulting," (not a web site or portal to order veterinary medicines).

On 1/6/05, the facts of this case were presented to officials at the CVM. On 1/7/05, CVM officials advised the Office of Internal Affairs that Dr. Hampshire was being immediately reassigned and recused from any involvement in the Pro Heart 6 issue.

A download from an FDA server of the subject's FDA issued PC was conducted. There was no inappropriate email or internet activity (i.e. the subject does not appear to be running her website on a U.S. Government time).

At the request of OIA, the Office of Ethics requested the subject to update her OGE 450 and HHS 520-1. In her response the subject lists AVA (Advanced Veterinary Applications) on her OGE 450 and on her HHS-5201-1 under the additional comments page she writes in part "this is a consulting company for the development of humane scoring paradigms (pain and distress)." Examples include a request from NAS to evaluate animal care at the National Zoo. No mention is made of an internet pharmacy.

At some time during the sign-off process of this paperwork at the Center for Veterinary Medicine the subject asked for her paperwork back to make a copy. It was later determined that the original HHS520-1 was removed and different HHS-520-1 had been substituted. For the first time since her employment at the FDA the subject mentions a home business pharmacy for friends and family. (Possible 18USC1001).

There is no evidence to suggest the subject committed any fraud when compiling Adverse Event Reports for Pro Heart 6.

This synopsis is being presented for consideration of potential violations of the Ethics in Government Act (18USC208, 209, or 5USC App. 501, 502, 101) and 18USC 1001.

If additional information is required, please contact me at (301) 827-0243.

Sincerely,

Mark S. McCormack
Senior Special Agent
FDA/Office of Internal Affairs

cc:
Chron
Case File
Case Agent

ATTACHMENT 3

ProHeart 6 (moxidectin)

Fort Dodge Animal Health
A Division of Wyeth

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

EXECUTIVE SUMMARY

Canine heartworm infection (*Dirofilaria immitis)* occurs in many parts of the world, including all 50 states in the US. Despite widespread availability of monthly heartworm preventatives, the infection rate in the US increased in the 1990s, and use of heartworm preventatives declined. Surveys have shown that compliance (i.e., reliable monthly treatments by owners) is problematical and a limiting factor in the control of heartworm in the dog population.

The active ingredient in ProHeart® 6 is moxidectin, a macrocyclic lactone. Moxidectin has been thoroughly evaluated to determine its toxicological and metabolic properties in multiple animal species and is approved as an anthelmintic agent for use in cattle, sheep, swine, dogs,and horses, in 70 countries. ProHeart 6 has been carefully evaluated for the treatment of heartworms and hookworms in dogs. In registration studies sponsored by Fort Dodge Animal Health (FDAH) (a Division of Wyeth), the product has been demonstrated to be safe and efficacious. Further, it appears to be well tolerated in canine breeds that do not tolerate some of the monthly products.

In June 2001, Proheart 6 (moxidectin) was approved and launched in the US by FDAH to prevent canine heartworm disease for 6 months, and to treat existing larval and adult stages of the canine hookworm. Since then, the product has also been registered in Italy, Canada, Japan, France, Greece, Portugal, Spain, and Korea. A similar product, ProHeart SR12, which contains approximately 3 times the amount of moxidectin as ProHeart 6, is registered and marketed in Australia since October 2000.

Among heartworm preventative medications for dogs, ProHeart 6 is an innovative product. Unlike conventional products that require monthly dosing for a minimum of 1 month prior to mosquito exposure through 1 month after mosquito exposure, in order to achieve protection against heartworm infection over a mosquito-infestation season, 1 injection of ProHeart 6 (moxidectin) sustained-release product provides 6 months of protection. ProHeart 6 was specifically developed to overcome field efficacy problems that result from poor compliance with monthly treatments. The introduction of ProHeart 6 provided an avenue for continuous protection against heartworm infection.

Shortly after launch of ProHeart 6, FDAH received a number of reports of allergic-type reactions after administration. The reactions ranged from mild and self-limiting to severe anaphylactoid reactions. Product analysis of minor component profiles between batches of ProHeart 6 revealed a trend to lower reactions for lots with no detectable residual solvents. At this time, FDAH was continuing to optimize the manufacturing process. As part of this process, the decision was made that all ProHeart products would be produced from moxidectin technical material with no detectable solvents. After the manufacturing change was implemented, there was a decline in the adverse-event reporting rate from all markets.

Since the launch of the product, FDA expressed concern about the number and seriousness of adverse event reports (AERs). The vast majority of the AERs were submitted by FDAH based on field reports from veterinarians and dog owners. The reports were submitted under mandatory reporting regulations without assessment of the likelihood of association of the AER with Proheart 6 administration. As a result of FDA's concern, FDAH has made revisions to the product label and issued "Dear Doctor" letters. On September 3, 2004, based on continued FDA concerns, FDAH agreed to voluntarily recall the product from the U.S. market. The recall prompted regulatory authorities in Canada, Australia, Japan and Europe to further review the safety of ProHeart 6. These authorities have allowed continued marketing of all FDAH moxidectin products for canine heartworm control.

FDAH's postmarketing surveillance and analysis of AERs from June 2001 through August 2004 show the number of these AERs were generally decreasing. The peak of AERs in the second quarter of each year corresponds to peak-use periods and also appear to be decreasing over time. Analysis of AERs for ProHeart 6 by category show that the occurrence of injection-site reports remained low and consistent with other injectable products in the FDAH database. Allergy AERs trended down over time at 1.26 per 10,000 doses. Non-allergy AERs were low and consistent over time at 1.19 per 10,000 doses (neurologic at 0.12 per 10,000 doses; hematologic at 0.09 per 10,000 doses; hepatic 0.07 per 10,000 doses; cardiac at 0.02 per 10,000 doses; neoplasia at 0.06 per 10,000 doses). When taken in context with usage, the overall rate for AERs was low and trending down over time, up to the point of the recall.

FDAH recently sponsored a study of the safety of ProHeart 6 use in general veterinary practice and a comparison to the monthly oral products. The study utilized a database covering 403 full-service veterinary hospitals in 42 states and did not rely on voluntary reporting. The review evaluated approximately 7 million canine office visits with an emphasis on comparison of heartworm product safety with and without concomitant vaccine administration. Overall, the safety profile of ProHeart was similar to that of 2 commonly used monthly oral products. Many of the adverse events could be attributed to concomitant vaccine administration. The results of the study provide no support for the withdrawal of ProHeart 6 from the market.

In conclusion, FDAH has performed additional research and further evaluation of the ProHeart 6 database to add to the extensive safety and toxicology database for moxidectin and formulated products. These evaluations provide additional support for the safety and efficacy of the product and were conducted to address questions raised by FDA.

1.0 INTRODUCTION

Moxidectin is a semi-synthetic methoxime derivative of nemadectin that is a fermentation product of *Streptomyces cyaneogriseus* subspecies *noncyanogenus*. It is a pentacyclic 16-membered lactone macrolide. Moxidectin is licensed and marketed worldwide by Fort Dodge Animal Health (FDAH) (a Division of Wyeth) as an anthelmintic agent that causes the paralysis and death of affected parasites in cattle, sheep, swine, horses, and dogs. It is currently being developed in a collaboration between Wyeth and the World Health Organization (WHO) for humans with onchocerciasis (river blindness), a disease caused by infection with the tissue filarial nematode *Onchocerca volvulus*.

ProHeart® 6 (moxidectin) was approved in the US and launched by FDAH in June 2001, to prevent canine heartworm (*Dirofilaria immitis)* disease for 6 months, and to treat existing larval and adult stages of the canine hookworms (*Ancylostoma caninum* and *Uncinaria stenocephala*). Since then, this product has also been registered in Italy, Canada, Japan, France, Greece, Portugal, Spain, and Korea. A similar product, ProHeart® SR 12, which contains approximately 3 times the amount of moxidectin as ProHeart 6 and provides 12 months of protection is registered and marketed in Australia since October 2000.

Among heartworm preventative medications for dogs, ProHeart 6 is an innovative product. Unlike conventional oral tablets or topical applications that require monthly dosing for a minimum of 1 month prior to mosquito exposure through 1 month after mosquito exposure, in order to achieve protection against heartworm infection over a mosquito-infestation season, 1 subcutaneous (SC) injection of ProHeart 6 (moxidectin) sustained-release product provides sustained 6-month protection. The single administration of ProHeart 6 for a 6-month period of protection eliminates the possibility of the pet owner missing 1 or more monthly doses, which is the primary cause of lack of efficacy associated with these heartworm medications.

ProHeart 6 has been well received by veterinary professionals and dog owners as evidenced by its increasing market share in major markets since launch. By the third quarter of 2004, ProHeart 6 was the number two product in the US with a 24% market share. In Italy, it is expected to

achieve a 35% share by the end of 2004. ProHeart SR 12 is the market leader in Australia, presently with a 47% share.

Subsequent to the product approval in June 2001, the FDA Center for Veterinary Medicine (CVM) raised concerns over the number of reports of adverse events associated with ProHeart 6.[1] Further concern was raised that "many of the reports received have involved serious, life-threatening adverse events such as anaphylaxis, convulsions, hematopoetic disorders, hepatopathies" and also "neurologic problems and unusual cardiac signs." It was also stated that "Pet owners should be advised on appropriate alternative heartworm preventatives for their dogs." FDA requested "that the firm continue to conduct research to determine the cause of related adverse reactions...before the product is marketed again."

On September 3, 2004, FDAH announced that it was voluntarily ceasing production for the US market and recalling ProHeart 6 from the US market until resolution of FDA safety concerns, based on reports of adverse events. Despite the voluntary recall, FDAH maintains that ProHeart 6 is safe and efficacious with acceptable field performance. Regulatory authorities in Canada, Australia, Japan, and Europe have allowed continued marketing of the FDAH moxidectin products for heartworm. FDAH supports the FDA formation of an independent Advisory Panel to review safety data on ProHeart 6. In order to provide the Advisory Panel with extensive analyses of available scientific data on ProHeart 6, FDAH sought assistance from independent experts. As requested by the FDA, additional research has been conducted to better define the adverse reactions. FDAH anticipates that comprehensive review of available ProHeart 6 data by the Advisory Panel will satisfactorily resolve FDA safety concerns.

Careful evaluation of the nature and timing of the AERs identified that allergy-based signs could be attributed to treatment and occurred shortly after treatment. The true incidence of allergic events to ProHeart6 is confounded because many dogs receive concurrent vaccinations. These are recognized to trigger allergic manifestations. A range of commonly occurring disease conditions that affect dogs is also seen in the AERs. These appear to represent baseline occurrence of these conditions in the canine population.

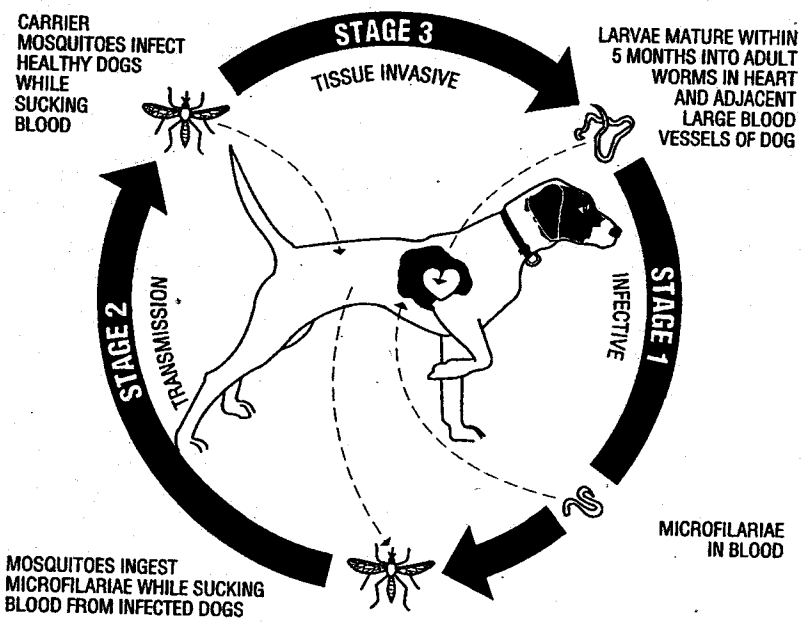
The purpose of this document is to present an overview of moxidectin and ProHeart 6 information from non-clinical studies, clinical trials, adverse event reporting, and analysis of safety and efficacy data for review by the Advisory Panel. This information includes new data on pharmacokinetics, new pharmacological investigations, new evaluation of adverse event findings, and epidemiological information from 7.0 million canine visits to veterinary clinics. FDAH is confident that the new research and re-evaluation of previous data support the safety and efficacy of ProHeart 6 and looks forward to returning this product to the market.

2.0 REVIEW OF HEARTWORM IN DOGS

2.1 Life Cycle of Dog Heartworm (*Dirofilaria immitis*)

The life cycle of the dog heartworm can be described in 3 stages as shown.

Figure 2.1-1. Life Cycle of Dog Heartworm



Stage 1: Adult female worms release tiny immature heartworms called microfilariae into the bloodstream of the infected dog. Adult worms are reported to live for 2 to 7 years.

Stage 2: The infection is spread from dog to dog by mosquitoes. When a mosquito bites an infected dog and feeds on blood, it takes in some of these microfilariae. Within 2 to 3 weeks, these microfilariae will develop into a stage which can infect other dogs when they are bitten by the same mosquito as it feeds.[2,3]

Stage 3: Following infection, the immature stages grow and develop over 2 to 3 months in the subcutaneous (SC) tissues, muscle, and fatty tissues of the dog. They then migrate, and from 70 to 120 days post infection, stages of heartworm may be found in the heart or pulmonary artery. These develop into adult heartworms which are long slender roundworms, normally living in the right side of the heart and nearby blood vessels. The worms may be up to 35 cm in length when mature.[2,3]

Mature female *Dirofilaria immitis* begin releasing microfilariae into the blood stream some 6 to 7 months after infection, thus completing the lifecycle.

Heartworm preventative products exert their effect at Stage 3, the tissue migrating stage.

Heartworm tests rely on detection of the parasite either at Stage 2, by detection of circulating microfilariae, or at Stage 3, by detection of female heartworm antigen. Heartworm antigen tests are not positive until the infection is at least 5 months old, they are inconsistently positive at 5 to 7 months, and are not considered to be reliably diagnostic until the infection (with female worms present) is at least 8 months old. These tests are highly sensitive and specific. If clinical signs raise any doubt about the accuracy of the particular test result, the test should be repeated, preferably with a different test kit or laboratory.[4]

2.2 Heartworm Disease in Dogs

Many dogs may be infected for several months with *Dirofilaria immitis* without showing clinical signs. This is particularly true for inactive dogs. However, immature worms in the pulmonary artery can initiate disease as early as 3 months after infection.[5] Adult worms in the heart cause inflammation of the heart lining and valves, and can eventually lead to heart failure. The effect on blood flow can lead to problems in other organs, particularly lungs and kidneys.

It can be difficult to know that a dog is affected in all stages of the disease because symptoms may be slight. The dog may only be listless and tire easily. Performance in working dogs may be affected. As the disease progresses, there may be cough, loss of condition, and build-up of fluid in the abdomen. Severely affected dogs may die.

Treatment of the disease can be risky, and early detection before chronic damage occurs to heart and lungs is important. This is because thromboembolic complications may occur, particularly in heavily infected dogs with pulmonary arterial vascular obstruction, and especially if congestive heart failure is present. The approved adulticide treatment is melarsomine, trade name Immiticide, an arsenical compound. While melarsomine is less toxic and more effective than its predecessor, thiacetarsamide, it is administered as a deep intramuscular injection into the lumbar muscles to reduce swelling and soreness at the injection site. Pulmonary thrombo-embolism and/or shock may occur following adulticide treatment even in symptomless dogs. Exercise restriction during the recovery period (weeks) is essential to minimize cardiopulmonary complications. Off label use of ivermectin for this purpose has been reported, but is not recommended because of progression of heartworm disease in the treated dogs.[6]

2.3 Canine Heartworm Epidemiology in the US

Heartworm infection in dogs has been diagnosed in many parts of the world, including all 50 states of the United States. While heartworm is considered endemic in the 48 contiguous states and Hawaii, transmission has not been documented in Alaska, even though there has been importation of infected dogs. It is likely that the climate is not conducive to the maturation of infective larvae. Adequate temperature and humidity are required both to support a suitable mosquito population and also to provide sufficient heat for maturation to the infective larval stage (L_3). Laboratory studies indicate that at 80°F, 10 to 14 days are required for maturation to infective stage, this period is longer at lower temperatures or where significant diurnal temperature fluctuation occurs.[2,3]

Therefore, the length of the heartworm transmission season varies with geographical location and climatic factors. The peak months for heartworm transmission in the northern hemisphere are July and August. Estimates of the duration of the transmission season vary from less than 4 months in Southern Canada to essentially all year in sub-tropical areas such as Florida and the Gulf Coast. It is believed that transmission occurs for 6 months or less above the 37th parallel.

The prevalence of heartworm in dogs varies from state to state, with higher infection rates in southern states, and particularly higher along the Mississippi and Ohio rivers. The number of adult heartworms present in infected dogs has been reported to be lower in the North (Michigan) than in the South.[7] A survey undertaken by the American Heartworm Society in 2001, published

in 2002, reported the highest infection rates in Texas, followed by Florida, Louisiana, North Carolina, Georgia, Mississippi, Tennessee, South Carolina, Alabama, and Indiana. Of significant veterinary concern, the survey reported that despite the widespread availability of monthly heartworm preventatives, the rates of infection with heartworm had not decreased over the previous 10 years.[2,8,9] For further information see Section 4.5.

For the past 2 decades, heartworm prevention relied on monthly administration of macrocyclic lactones, sometimes in combination with other active ingredients to treat other parasites. Commonly used products include ivermectin, milbemycin oxime, and selamectin. Combination products include ivermectin plus pyrantel (for roundworm control) and generics, and milbemycin oxime plus lufenuron (for flea control). For dogs that suffered toxic effects from these compounds, the only alternative available was daily treatment with diethyl carbamazine.

The introduction of ProHeart 6 in the US in the second half of 2001 provided 6 months of continuous protection against heartworm infection without having to rely on monthly treatment by the dogs' owners, a major source of lack of efficacy.

3.0 MOXIDECTIN OVERVIEW

3.1 Pharmacology – Mechanism of Action

Moxidectin has been shown to have activity at the γ-aminobutyric acid (GABA)-A receptor-chloride channel complex resulting in an influx of chloride ions and hyperpolarization of cell membranes. Hyperpolarization causes the nerve fibers to be less excitatory and results in paralysis and death of the parasitic organism. Another proposed mechanism of action for moxidectin is through activity at glutamate-gated chloride ion channels. The specificity of moxidectin for the parasite versus the mammalian host results from 1) a low affinity for mammalian GABA-gated chloride channels, and 2) GABA-containing neurons and receptors are found in mammals in the central nervous system, whereas in arthropods and nematodes these are found in the neuromuscular junctions of the peripheral nervous system and thus are more accessible to a blood-borne therapeutic.

In dogs, the approved oral monthly dosage of moxidectin for prevention of heartworm is 3 µg/kg; the approved SC dosage of moxidectin as ProHeart 6 is 0.17 mg/kg administered every 6 months. In this and the sections that follow, dosages of ProHeart 6 or moxidectin expressed as mg/kg refer to mg of moxidectin per kg of animal body weight.

3.2 Pharmacokinetics and Drug Metabolism

Studies were conducted in various animal species to characterize the absorption, distribution, metabolism, and excretion of moxidectin after oral administration. Moxidectin was moderately absorbed with a bioavailability of 19% in rats, and had a long serum half-life of 23 to 45 hours in rats and 8.1 days in dogs after oral gavage administration. A single SC injection of the approved dosage of 0.17 mg/kg as ProHeart 6 to beagle dogs resulted in peak concentration in serum (C_{max}) of 5.1 ng/mL, a time to peak concentration (t_{max}) of 7 to10 days, an area under the concentration-versus-time curve ($AUC_{0-\infty}$) of 217 ng•days/mL, and an apparent elimination half-life ($t_{1/2}$) of approximately 35 days. After SC injection of ProHeart 6 once every six months for a total of 6 injections, there was no evidence of alterations in pharmacokinetic parameters or indication of accumulation. A recent study of the single administration of moxidectin in the diet to female dogs at 45 ppm (corresponding to approximately 1 mg/kg used in the 1-year toxicology study) resulted in a C_{max}, $AUC_{0-\infty}$, and $t_{1/2}$ values of 290 ng/mL, 678 ng•day/mL and 8.3 days, respectively. These recent studies in the dog, and an ongoing 28-day pharmacokinetic study in rats were designed to further evaluate the systemic exposure to moxidectin under the conditions of the previously conducted toxicology studies.

After oral administration, the major site of moxidectin distribution was in fat in rats, cattle, sheep, and horses. It was eliminated largely unmetabolized in the feces. The $t_{1/2}$ in fat in the rat was 11.5 days, much longer than in serum. Limited metabolism was noted in all species and minor metabolites were identified as predominantly mono- and di-hydroxylated moxidectin.

Moxidectin did not result in significant in vitro inhibition of cytochrome P450 isozymes, indicating that drug-drug interactions mediated through cytochrome P450 are unlikely to occur.

P-glycoproteins (P-gps) are transmembrane proteins that transport a wide variety of endogenous and exogenous molecules across cell membranes. Moxidectin, similar to other macrocyclic lactones, is a substrate for P-gps. This relationship is of clinical importance in the development of nematode resistance to ivermectin and plays a significant role in breed sensitivity. A mutation in the P-gp gene of ivermectin-sensitive Collie dogs has been shown to be responsible for ivermectin-induced CNS toxicity. Moxidectin, however, was well-tolerated by these ivermectin-sensitive dogs (see Section 4.1.3.2). Thus, moxidectin transport is less dependent on P-gp and subsequent toxicity is less likely manifest due to factors which alter P-gp activity.[10]

3.3 Toxicology

The toxicologic profile of moxidectin administered by the oral route has been well established. This profile is relevant to other routes of administration because of limited metabolism of moxidectin in the body and the long terminal half-life regardless of the route of administration. A more detailed discussion of the pharmacokinetics and toxicity assessment of moxidectin is presented in Appendix 6.1.

3.3.1 In Vitro Side-Effect Profiling

Moxidectin and moxidectin microspheres (as present in ProHeart 6) were recently tested in vitro for binding activity at 64 different biological receptors. This assay is commonly used in drug discovery and development to identify any ancillary pharmacologic activities of a molecule which may result in undesirable biological effects. A final concentration of 10 ng/mL moxidectin was tested, which is approximately two-fold the average C_{max} value in serum of dogs after an SC injection of ProHeart 6 at the clinical dosage of 0.17 mg/kg. The receptors tested included those for neurotransmitters and neurotransmitter-related receptors, ion channels, steroids, second messengers, prostaglandins, growth factors/hormones, brain/gut peptides and enzymes. Moxidectin in either form did not significantly inhibit the binding of appropriate

radioligands to these receptors, indicating a lack of significant, competitive binding activity for moxidectin at the concentration evaluated.. These results are consistent with the absence of undesirable pharmacologic and toxic effects of moxidectin in animal studies at plasma levels greater than those required for efficacy.

3.3.2 Single- and Repeat-Dose Toxicology Studies

Single-dose toxicology studies of moxidectin were conducted to assess effects after a single administration of large doses in the event of accidental overdose and to assist in selection of dose levels for subsequent repeat-dose toxicology studies. In single-dose toxicity studies of mice and rats given moxidectin orally, the median lethal dosage (LD_{50}) values were 118 mg/kg and 42 to 78 mg/kg in male and female mice, respectively, and 122 and 97 mg/kg in male and female rats, respectively. After a single SC dose, LD_{50} values were 285 and 247 mg/kg in male and female mice, respectively, and > 640 mg/kg in rats. Common clinical signs in these studies were decreased activity, tremors, and prostration. These studies demonstrate a large margin of safety for ProHeart 6 since the lethal SC dose in rats is more than 3700-fold the approved ProHeart 6 dose of 0.17 mg/kg.

Repeat-dose oral (diet) toxicity was evaluated to assess long-term consequences of repeated, daily oral exposure to moxidectin. The objective of these studies was to expose animals to high levels of moxidectin to identify potential toxic effects, and to include lower doses to assess a possible dose-response relationship and a dose without significant adverse effects (NOAEL).

The following studies were conducted: 4-week studies in mice, rats, and dogs; 13-week studies in rats and dogs; and a 1-year study in dogs. Evaluations consisted of mortality, clinical observations, body weight, food consumption, hematology, clinical chemistry (except mice), organ weights, and macroscopic and microscopic examinations of organs and tissues. Ophthalmic examinations and urinalysis were also included in the dog studies.

In repeat-dose diet toxicity studies in rats and dogs of durations up to 2 years in mice and rats, and 1-year in dogs, no target organs of toxicity were identified. There were no significant adverse histologic or biochemical effects to any organ system. There were no proliferative lesions identified in any tissue which may signal the development of neoplasia, and no increase in tumors in 2-year studies in mice or rats. The toxicity of moxidectin manifested at high doses in clinical signs such as lethargy, ataxia, tremors and mortality (rodents only) with concomitant decreases in food consumption and body weight. Such clinical signs of hypoexcitation are consistent with an exaggerated pharmacologic effect of moxidectin mediated via the GABA-receptor. Interim analysis at day 21 in an ongoing 28-day diet pharmacokinetic study of moxidectin in dogs at a concentration of 45 ppm in feed (approximately 1 mg/kg, the NOAEL in the 1-year dog toxicity study) revealed a serum concentration of 278.5 ng/mL 24 hours after the preceding dose in feed (ie, trough level). This value is approximately 234-fold the $AUC_{0-\infty}$ (217 ng•days/mL) observed for moxidectin after a single SC dose in dogs of ProHeart 6.

3.3.3 Carcinogenicity Studies

3.3.3.1 Mice

A 2-year carcinogenicity study was conducted in male and female mice at diet doses of 15, 30, and 60 ppm (lowered to 50 ppm due to high mortality at week 9). Mortality was increased in females at doses of 60/50 ppm during the last 13 weeks of the study. There were no compound-related findings in hematology values, organ weights, or at macroscopic or microscopic examination. There was no evidence of moxidectin-related target-organ toxicity or tumorigenicity.

3.3.3.2 Rats

A 2-year carcinogenicity study was conducted in male and female rats at diet doses of 15, 60 and 120 ppm (lowered to 100 ppm due to high mortality in females at week 8). There were no compound-related findings for hematology values, organ weights or at macroscopic or microscopic examination; there was no evidence of moxidectin-related target-organ toxicity or tumorigenicity.

3.3.4 Reproductive and Developmental Toxicity Studies

Reproductive toxicity was evaluated in a rat multigeneration diet study and in developmental studies in rats and rabbits dosed daily by oral gavage. Based on the results from these studies, moxidectin was not found to be a selective reproductive toxin in rats, nor a teratogen in rats or rabbits.

3.3.5 Genotoxicity Studies

Moxidectin was tested for genotoxicity in 4 in vitro and 2 in vivo standard test systems. These assays assessed the ability of moxidectin to induce gene mutations, chromosome damage, or increased DNA repair which may be related to the carcinogenic potential of the test article. Moxidectin was uniformly negative in these assays, indicating that moxidectin is not a genotoxic compound.

3.4 Experience with Oral Moxidectin in Human Volunteers

A study in healthy, male volunteers was conducted to assess the pharmacokinetics and safety of moxidectin given orally as part of the development of this compound for onchocerciasis therapy in humans. Safety assessments indicated that moxidectin was safe and well tolerated, with a slightly higher incidence of transient, mild, and moderate CNS adverse events (dizziness and somnolence) as compared to placebo. Moxidectin was safe and well tolerated in humans after single oral doses of 3 mg to 36 mg, the highest dose evaluated.

3.5 Conclusions

Moxidectin is a potent antiparasitic therapeutic that acts to paralyze susceptible organisms through activity at GABA- and glutamate-gated chloride ion channels. Moxidectin has a long half-life, distributes predominantly to fat, shows little metabolism, and is excreted primarily in the feces. In single-dose toxicity studies, the lethal SC dose in rats was more than 3700-fold the efficacious dose of moxidectin given as ProHeart 6 to dogs. In repeat-dose diet toxicity studies of durations up to 2 years in mice and rats, and 1 year in dogs, no target organs of toxicity were identified. There were no significant adverse histologic or biochemical effects on any organ system. There were no proliferative lesions identified in any tissue which may signal the

development of neoplasia, and no increase in tumors in mice or rats. The toxicity of moxidectin manifested itself at high doses in clinical signs such as lethargy, ataxia, tremors and mortality (rodents only) with concomitant decreases in food consumption and body weight. Such clinical signs of hypoexcitation are consistent with an exaggerated pharmacologic effect of moxidectin mediated via the GABA-A-receptor. Moxidectin was not genotoxic or carcinogenic and was without reproductive or developmental toxicity. The highest dosage evaluated in the 1-year dog study resulted in an estimated monthly exposure 234-fold the exposure observed after a single SC dose in dogs of ProHeart 6. Based on the toxicology studies of moxidectin where the dose, dosing duration, and resulting systemic exposure to moxidectin were significantly exaggerated, clinical SC administration of 0.17 mg/kg as ProHeart 6 to dogs is expected to be without significant adverse effects.

4.0 PROHEART 6 OVERVIEW

4.1 Clinical Trials with ProHeart 6 in Dogs

ProHeart 6 (moxidectin) is indicated for use in dogs ≥6 months of age for the prevention of heartworm disease caused by *Dirofilaria immitis* and for existing larval and adult hookworm infections (*Ancylostoma caninum* and *Uncinaria stenocephala*). The safety and efficacy of ProHeart 6 was demonstrated during a development program that was established in close collaboration with the FDA that included agreement on study requirements, protocol review, in-life inspections of selected development studies and a thorough review of data obtained during the program. Moxidectin is well established as an anti-parasitic product for cattle, sheep, horses, and dogs and is generally recognized as safe for these uses in all animals. The efficacy profile of ProHeart 6 was demonstrated in a series of dose-determination and dose-confirmation studies conducted in accordance with Good Clinical Practice guidelines. The safety of the product was evaluated through a series of safety studies in the target population as well as unique canine populations that would receive the product. These included reproducing males and females, dogs that had existing heartworm infections, and Collie dogs that had a demonstrated sensitivity to ivermectin. Safety and efficacy studies were conducted not only in laboratory Beagles but also in a variety of breeds and cross-breeds. In the sections that follow, dosages of ProHeart 6 expressed as mg/kg refer to mg of moxidectin per kg of animal bodyweight.

4.1.1 Heartworm

4.1.1.1 Dose Determination

Two (2) studies were conducted to determine the dosage of a single injection of ProHeart 6 required to effectively prevent *Dirofilaria immitis* infections for 6 months. Both studies had a similar experimental design. Study animals determined to be negative for *D. immitis* by antigen and a modified Knott's test were included in the studies. One study (0899-C-US-1-96, Georgia) utilized Beagle dogs (12 males and 20 females) and a second study (0899-C-US-2-96, Pennsylvania) utilized mongrel dogs (16 males and 16 females).[11,12] ProHeart 6 was administered as a single SC injection to dogs at a moxidectin dosage of 0.06, 0.17, or 0.50 mg/kg. Control animals received saline. At approximately 180 days (6 months) after treatment, all dogs were inoculated by intravenous (IV) injection with 50 *D. immitis* L_3 infective larvae. Infections were allowed to develop for 150 days, at which time each animal was euthanized, necropsied, and the heart and lungs removed for the recovery and quantification of heartworms. Immediately after treatment with ProHeart 6 and at various times throughout the studies, dogs were observed for adverse reaction to treatment. Additionally, injection sites were evaluated after treatment and throughout the study as well as histologically at necropsy.

In the Georgia study, an average of 25 worms were recovered in the saline treated controls. No worms were recovered from any of the dogs dosed with ProHeart 6, indicating that all dosages tested were 100% effective in preventing heartworm disease for 6 months.

In the Pennsylvania study, an average of 36 worms were recovered from the saline treated controls. No worms were recovered from any dog that received ProHeart 6 at 0.17 and 0.50 mg/kg. However, 14 adult *D. immitis* worms were found in 1 dog in the low-dose group (0.06 mg/kg). The results of this study indicated that a ProHeart 6 dosage of 0.17 mg/kg was appropriate to prevent canine heartworm disease for a period of 6 months.

During the dose determination studies, moxidectin concentrations were quantified in the serum of treated dogs. Following injection with ProHeart 6, peak moxidectin levels (approx. 5 ppb) were observed at 7 to 14 days post-treatment. At the end of the 6-month treatment period, residual moxidectin concentrations were negligible and generally below the limit of quantification of the assay methods. The drug did not accumulate with repeated doses. Serum

moxidectin levels evaluated after 4 treatments (6 months apart) confirmed that there was no accumulation of moxidectin in the serum of animals after successive doses (0899-C-US-9-98, Texas).[13]

4.1.1.2 Dose Confirmation

4.1.1.2.1 Adult Dogs

The efficacy of ProHeart 6 for the prevention of heartworm disease in dogs was confirmed in a series of studies conducted using the proposed commercial ProHeart 6 dosage of 0.17 mg/kg. Efficacy was evaluated at 6 months post-infection, 12 months post-infection and in dogs with existing heartworm infections to determine retroactive efficacy. The 6- and 12-month infection studies used similar experimental designs as the dose-determination studies. Animals were treated and challenged with L_3 infective larvae at either 6 or 12 months after treatment and necropsied for quantification of adult heartworms after the infections had matured. For activity against existing infections (retroactive efficacy), animals were challenged with L_3 infective larvae at various times prior to treatment with ProHeart 6 and necropsied after an appropriate period for the development of microfilariae to become adult heartworms.

ProHeart 6, administered to dogs at an SC dosage of 0.17 mg/kg, was 100% effective for prevention of heartworm disease for 6 or 12 months (0899-C-US-10-98, Texas).[14] When administered to dogs at an SC dosage of 0.17 or 0.27 mg/kg (0899-C-US-20-99, Pennsylvania), ProHeart 6 was 100% effective against development of canine heartworm disease for 12 months after treatment.[15]

The retroactive efficacy of ProHeart 6 with existing heartworm infections was evaluated at 4 and 6 months after challenge with L_3 infective larvae (0899-C-US-11-98, Georgia, Table 4.1.1.2.1-1).[16] At 0.17 mg/kg, ProHeart 6 was highly effective against 4-month-old *D. immitis* infections (85.9%). Efficacy was even higher (97.2%) against 4-month-old infections, when a second injection was given 6 months after the first injection; *D. immitis* was found in only 1 of 5 animals in this group. A single injection had low efficacy against 6-month-old infections (24.7%). Efficacy was not improved with 3 additional treatments 6 months apart. In a second retroactive study (0899-C-US-28-01, Georgia, Table 4.1.1.2.1-2), ProHeart 6 at 0.17 or 0.50 mg/kg was highly effective against 3-month-old infections (98.8 and 96.0% efficacy, respectively).[17]

Table 4.1.1.2.1-1. Retroactive Activity of ProHeart 6 at 0.17 mg/kg versus 4- and 6-Month Heartworm Infections

Treatment (Time Post-Infection in Months)		Geometric Mean Worm Counts (Percent Efficacy)		
Saline	Moxidectin	Male	Female	Total
4 and 6		14.07	17.31	31.66
	4	1.24* (91.2)	3.42* (80.3)	4.46* (85.9)
	6	12.09 (14.1)	11.61 (32.9)	23.85 (24.7)
4, 6, 10, 12, and 18		8.97	7.86	15.24
	4 and	0.32* (96.4)	0.25* (96.9)	0.43* (97.2)

*Statistically significantly different ($p < 0.05$) from control group based on analysis of geometric means.

Table 4.1.1.2.1-2. Retroactive Activity of ProHeart 6 versus 3-month Heartworm Infections

Treatment (mg/kg)	Geometric Mean Worm Counts (Percent Efficacy)		
	Male	Female	Total
Saline	16.0	22.0	38.3
0.17	0.3 (98.4)	0.3 (98.8)	0.4 (98.8)
0.50	0.6 (96.3)	1.1 (95.1)	1.5 (96.0)

Evaluation of efficacy was for male dogs only, where adequate infection was observed in control animals.

4.1.1.2.2 Puppies

When administered to 12-week-old small, medium and large breed puppies at 0.17 mg/kg (0899-C-US-30-02, Pennsylvania), ProHeart 6 reduced heartworm infection >99.8% compared with control puppies.[18] Treatment completely prevented heartworm infection in small and

medium breed puppies. One of six large breed puppies was infected with a single worm following challenge with 50 L_3 *D. immitis* infective larvae.

4.1.2 Hookworms

Efficacy was determined to be 100% for both larval and adult stages of *A. caninum* in three dose confirmation studies (0899-C-US-12-98, North Carolina; 0899-C-US-15-99, Georgia; 0899-C-US-16-99, Michigan).[19,20,21] Efficacy against both larval and adult *U. stenocephala* infections was 100% in study 0899-C-US-16-99.

Three (3) additional experimental infection studies were conducted to demonstrate the effectiveness of ProHeart 6 versus larval and adult stages of the hookworm *U. stenocephala*. Studies 0899-C-US-17-99 (Michigan), 0899-C-US-18-99 (New Jersey), and 0899-C-US-19-99 (Georgia) provided additional data that confirmed the efficacy of the product as >99.0%.[22,23,24]

Two studies were conducted to evaluate the persistent activity of ProHeart 12 against subsequent hookworm infections in dogs following treatment. In this program, animals were challenged with larvae of *U. stenocephala* and *A. caninum*. ProHeart 12 prevented infections of these 2 species of hookworm for a period of 4 months in a study in Georgia. In a study conducted in Michigan, ProHeart 12 prevented infection by *U. stenocephala* for a period of 8 months and *A. caninum* for 5 months.

4.1.3 Safety

4.1.3.1 Healthy Dogs

The clinical and possible pathological effects were evaluated when ProHeart 6 was administered to healthy dogs at either 1, 3 or 5 times the recommended dosage of 0.17 mg/kg in Study 0899-C-US-4-98 (Wisconsin).[25] Physical examinations were conducted prior to treatment and throughout the study. Blood and urine samples were collected for hematology, clinical chemistry, coagulation, and urinalysis. Dogs were also evaluated for clinical signs, food consumption, and body weight. At the end of the study, dogs were necropsied and evaluated for overt changes. Tissues from the control (saline treated) and 5-times dosage groups were examined microscopically. Dogs treated with ProHeart 6 did not demonstrate any signs or findings associated with the possible systemic toxicity of the drug. A single SC injection of

Proheart 6 equivalent to either 1, 3, or 5 times the commercial dosage caused swelling/slight edema at the site of injections starting within 8 hours of injection and lasting for up to 3 weeks. One dog, that received the 5-times dosage of ProHeart 6, displayed excessive salivation after treatment on Day 78. The only overt lesion observed was a 2.0 cm red focus at the SC injection site in 1 male at the 5-times dosage.

The safety of multiple injections of ProHeart 6 was studied in dogs given injections at 6 monthly intervals (0899-C-US-9-98, Texas) through 2 years.[13] No adverse reactions to treatment were observed following 5 injections. The injection sites were palpated externally, then the skin and underlying muscle tissue excised and examined. There were no gross findings at the injection sites. Microscopically, the injected areas generally had granulomatous panniculitis with microvacuolation (spheres) that was interpreted to be a reaction to the injected microspheres. Three (3) of the experimental dogs were maintained and received a total of 14 ProHeart 6 injections. At necropsy, there were no adverse reactions attributed to test article during this time, including no gross findings in the injection sites at necropsy.

The safety of ProHeart 6 was demonstrated in reproducing females (0899-C-US-3-98, Michigan) and males (0899-C-CN-1-98, Canada) at 3 times the recommended commercial dosage (0.5 mg/kg).[26,27] No adverse effects were observed in reproductive parameters of treated breeding females or the seminal quality of treated males.

When administered to healthy 10-week-old puppies at 3 or 5 times the recommended dosage rate of 0.17 mg/kg (0899-C-US-37-02, Michigan), ProHeart 6 caused no physical or neurological changes, and no changes in clinical chemistry or urinalysis parameters.[28]

4.1.3.2 Ivermectin-Sensitive Collie Dogs

Some genetic lines of Collie dogs are sensitive to the administration of ivermectin. A safety study (0899-C-US-13-98, Illinois) was conducted to determine the safety of a single dose of ProHeart 6 at 1, 3 and 5 times the proposed commercial SC dosage of 0.17 mg/kg.[29] Collie dogs shown to react to a 120 µg/kg bodyweight dosage of ivermectin (depression, ataxia, mydriasis, and excessive salivation) were enrolled in the study. Following treatment, dogs were observed intensively for the first 24 hours and twice daily through 21 days. There were no health conditions suggestive of toxicity in any of the dogs treated with ProHeart 6.

4.1.3.3 Heartworm-Positive Dogs

The safety of ProHeart 6 in heartworm-positive dogs was evaluated in 2 studies. The first study (0899-C-US-14-98, Alabama) tested a 3 times the proposed SC dosage in dogs with patent heartworm infections as measured by circulating microfilarial counts and heartworm antigen.[30] Clinical observations, physical exams, and microfilarial counts were used to evaluate the effects of treatment. The results demonstrated that a dosage of 0.51 mg/kg did not cause adverse reactions in dogs with patent heartworm infections. There were no post-treatment adverse health effects. Reduction in microfilariae compared with controls began as early as Day 7 post-treatment and peaked at 99.6% on Day 21 post-treatment. There was no significant ($p < 0.05$) adulticidal effect observed with ProHeart 6.

As part of the ProHeart 12 development program, the safety of this product for dogs was evaluated in dogs that had been surgically implanted with 20 adult heartworms via the jugular vein (0899-C-US-39-02, Georgia).[31] On Day 61 following implantation, dogs were treated with ProHeart 12 at 1.5 mg/kg (approximately 9 times the ProHeart 6 and 3 times the ProHeart 12 proposed commercial dosages). Animals were observed twice daily for signs of toxicity with physical and clinical examination. There were no treatment-related effects in any of the dogs. Microfilariae counts were reduced to almost 0 at 3 weeks after treatment, with no effect on the adult population demonstrating no adulticidal activity in heartworm-positive dogs.

4.1.4 Field Studies

The safety and efficacy of ProHeart 6 at 0.17 mg/kg was evaluated under field conditions in dogs dosed twice at 6-month intervals (0899-C-US-5-98, California; 0899-C-US-6-98, Texas; 0899-C-US-7-98, Wisconsin; 0899-C-US-8-98, Connecticut).[32,33,34,35] A total of 374 client-owned dogs representing 84 breeds (280 ProHeart 6 treated, 94 ProHeart oral tablet controls) completed the study. Dogs were ≥6 months of age and were of a variety of breeds, weights, physical condition, and were of both sexes (either intact or altered). Prior to enrollment, animals were tested for both heartworm antigen and microfilariae to ensure that dogs were negative for existing heartworm. None of the 374 dogs that completed this study tested positive for heartworms at either 3, 6, or 12 months after the initiation of ProHeart 6 treatment. The following potential adverse drug reactions were observed (number of cases): vomiting (3), diarrhea (2), weight loss (2), listlessness (1), seizures (1), injection site pruritus (3), and elevated

body temperature (1). Injection site evaluation revealed no abnormalities. This level of potential reactions for the 374 dogs that completed the study was extremely low and demonstrated the safety of the product under field conditions. Twelve (12) ProHeart 6 animals were euthanized or died during the 18-month study. It was determined following thorough review of each case that these deaths could not be attributed to treatment with ProHeart 6.

4.1.5 Exaggerated Moxidectin Overdose in Dogs

FDAH markets an oral formulation of moxidectin for use in horses to control internal parasites. This product is supplied as a syringe with a plunger calibrated by weight so that the correct dose can be given to horses varying in weight up to 1150 pounds.

While uncommon, dogs have been exposed to this product. Sometimes this exposure is intentional; owners believe it is cost effective and safe to administer the product to dogs. Occasionally dogs find discarded syringes and chew on them or they consume gel mixed with treats intended to entice a reluctant horse.

From 1997 to 2004, FDAH received approximately 250 reports. These cases were characterized by a wide range of neurological manifestations. Most (90%) of these dogs recovered to normal; the remaining 10% died. Thus, very high doses of moxidectin may lead to neurological manifestations of toxicity that are often reversible with no evidence of any long-term or non-neurological toxic effects

4.1.6 International Studies

ProHeart products have been registered in a number of international markets including Australia, Canada, the European Union (France, Greece, Italy, Portugal, Spain), Korea, and Japan. Length of activity claims and active ingredient concentration vary depending on the market. US data formed the basis of each registration with supporting local data, where required. These studies included dose-confirmation and field-efficacy testing.

Three (3) studies (0899-C-IT-01-99, 0899-C-IT-02-99, 0899-C-IT-03-99) were conducted in Italy to evaluate ProHeart 6 (trademark Guardian SR in Europe) at a dosage of 0.17 mg/kg for the prevention of heartworm disease caused by *Dirofilaria immitis* and *Dirofilaria repens*.[36,37,38] Two hundred and fifty-one (251) client-owned dogs of various breeds (41) completed this series

of field-efficacy and safety studies. ProHeart 6 given at 6 month intervals was 100% effective in protecting animals from heartworm infection in this heartworm endemic area (verified by untreated animals enrolled in the same area). No adverse reactions to treatment were reported.

In Australia, 3 studies (0899-C-AU-01-97 dose confirmation, 0899-C-AU-02-00 puppy safety, and 0899-C-AU-02-98 clinical field study) were conducted in support of a 12-month protection product administered at a dosage of 0.50 mg/kg.[39,40,41] ProHeart SR 12 was 100% effective in preventing heartworm disease in the laboratory dose-confirmation study. When administered at 3 times the recommended dose (9 times the ProHeart 6 dosage) in puppies 10 to 12 weeks of age, no clinically apparent adverse effects or adverse injection site reactions were observed. Breeds of dogs included Maltese cross, Lhasa Apso cross, Fox Terrier, Staffordshire Bull Terrier, Poodle, Border Collie, Labrador Retriever, German Shepherd and Rottweiler and represented small, medium, and large breeds. Two hundred and ten (210) animals representing 75 breeds completed the field clinical study. The study demonstrated the effectiveness of ProHeart SR 12 at 0.50 mg/kg (3 times the ProHeart 6 dosage) in protecting dogs from heartworm infection for 12 months. No adverse reactions or drug interactions were observed in treated dogs.

4.1.7 ProHeart 12

ProHeart 12, a moxidectin based product similar to ProHeart 6 is currently in development in the US. This product, administered at an SC dosage of 0.50 mg/kg will protect dogs from heartworm disease for a period of 12 months and is identical to the commercial product in Australia. A safety and field clinical program has been conducted. These studies demonstrate the same safety profile as ProHeart 6 in reproducing males and females, heartworm-positive dogs, ivermectin-sensitive Collies, and a variety of canine breeds during the field evaluation program.

4.1.8 Conclusion

The efficacy and safety of Proheart 6 has been thoroughly evaluated during the initial development program and in subsequent studies designed to expand label claims for the product. These programs were designed in close cooperation with the FDA and are comprehensive in scope. ProHeart 6 has been shown to be efficacious in the protection of dogs from heartworm disease. It is safe when administered to healthy dogs and to unique canine populations, such as heartworm-infected or ivermectin-sensitive dogs.

4.2 Postmarketing Surveillance of Adverse Events

FDAH designed a postmarketing surveillance system to detect a signal of potential drug effects and subsequently to estimate the incidence and causality of a potential drug effect. The data used for postmarketing surveillance generally consisted of adverse event reports (AERs).

To determine if AERs have clinical relevance, incidence is estimated and comparisons are made with a group representative of the general population that has not been treated with the drug. FDAH calculates reporting rates using the number of reports divided by an estimate of the doses sold to veterinarians for the same period. In contrast, regulatory authorities generally do not utilize estimates of the frequency of drug administration. Additionally veterinary epidemiologists lack an understanding of the rate of occurrence of even commonly observed medical problems. Thus, it is difficult in assessing AERs to determine whether a drug is directly related to the observed events. Even after determining that an adverse event may be likely related to drug administration, the clinical importance of the reaction is unknown without an understanding of its incidence. Frequent serious reactions may warrant withdrawal of a drug from the market, while rare reactions may require appropriate warnings to prescribers and clients.

Further confounding the interpretation of AERs is the potential for bias. There is a considerable opportunity for extraneous eventsto stimulate over-reporting of adverse observations in animals as possible drug associated adverse events. For ProHeart 6 in particular, there are additional biases that may have impacted reporting of adverse observations. Because ProHeart 6 is a new innovative product, veterinarians lack a frame of experience from which to judge whether or not adverse observations are likely to be associated with the drug. The long duration of action makes it appear plausible that adverse observations might be associated with drug administration that occurred several months earlier. Further, since ProHeart 6 is administered parenterally by veterinarians and the monthly oral medicines are administered by pet owners (often as a treat), there is a potential for greater apparent concern with ProHeart 6. Also, veterinarians received Dear Doctor letters discussing ProHeart 6 safety issues that may have stimulated AERs. Lastly, there were several widely-disseminated news reports and website postings critical of ProHeart 6 that may have stimulated AERs.

Thus, while postmarketing surveillance of AERs is a valuable tool in monitoring drug safety, the use of this system for regulatory decisions is complicated by the absence of a control group, the lack of an estimate of use, the lack of knowledge of the background rate of systemic diseases in the canine population, and the impact of reporting bias to stimulate over-reporting.[42,43,44]

4.2.1 Overview

In the subsequent sections, FDAH further evaluates AERs (1) relative to product usage, (2) relative to likelihood that they were associated temporally with ProHeart 6 administration, and (3) relative to independent expert assessment of the possible causality of the event as result of drug administration. On September 3, 2004, FDAH announced the voluntary recall of ProHeart 6 from the US market until resolution of FDA safety concerns. The primary concerns cited by FDA were the large number of AERs that were attributed to ProHeart 6 and that the numbers of these AERs were increasing in the months leading up to the recall. Additionally, the FDA expressed concerns regarding symptoms associated with several different body systems. These included neurologic, hematologic, hepatic, and cardiac systems, as well as a concern regarding neoplasia in association with ProHeart 6 administration.

FDA's website cites the submission of "more than 5500 AERs in compliance with federal regulations (21 CFR 514.80) that require sponsors to submit serious and unexpected AERs within 15 working days of first receiving the information." FDAH respectfully disagrees that all of these reports are medically serious or unexpected, or attributable to ProHeart 6. AERs defined as serious and unexpected are submitted to FDA within 15 working days. Those reports defined as not serious or not unexpected are normally submitted yearly in the annual Drug Experience Report. However, because of FDA's continuing concerns, FDAH began submitting all reports in a 15-day window in the third quarter of 2003, including those that were not serious and unexpected. Additionally, all events reported to FDAH were relayed to FDA in an unfiltered manner, regardless of causality assessment. Many AERs contain an assessment by the reporting veterinarians that their suspicion of product involvement in the event is low. This is particularly true for reports that were not deemed allergic events. FDAH has also assessed many of these events as having a low causal relationship. Thus, FDAH considers most of the AERs to be unrelated to ProHeart treatment.

Approximately 18 million doses of ProHeart 6 have been sold with more than 12 million doses administered. The calculated reporting rate is 2.5 reports per 10,000 doses, based on doses sold to veterinary clinics through August of 2004. This is the equivalent of one report (without regard to causality) per 4000 doses sold. It is recognized in a voluntary reporting system that not all potential adverse events associated with product use are reported. However, the trends over time need to be considered and indicate that the rate of AERs for ProHeart 6 was low and declined over time.

Another critical element is the background rate of disease in the canine population at large. The concerns regarding specific body systems are addressed in detail in section 4.2.2.2. Several independent experts were consulted and their conclusions, which are included for consideration, strongly support the safety of ProHeart 6 and indicate that most of the AERs were not causally-related to ProHeart 6 treatment.

One should consider the system used by FDA to assign causality to each AER. The six point causality assessment system considers previous experience with the drug, whether alternative etiologic candidates exist, timing of the event, overdose, and dechallenge and rechallenge. The system was primarily established for immediate release products. ProHeart 6 is a 6-month sustained-release product. Sustained-release products have not previously been evaluated using this system. Dechallenge (drug removal from the patient's body) is not possible for at least 6 months and FDA has acknowledged that the "challenge" and "dechallenge" components of their scoring system are not applicable in this instance. The modified scoring procedures to account for this fact may have created unintended bias among their reviewers.

4.2.2 Review of Adverse Event Reports

Upon receipt of an AER, the reporting party is asked a series of questions by FDAH professionals, including patient description and identification, previous history, date of product administration, its dose, body location of administration, time to observation of the adverse event, concurrent treatments employed, diagnostic testing, and event outcome. Regardless of causality assessment by FDAH, every AER involving an FDA regulated product received by FDAH is submitted to the FDA.

To assist in the analysis of AERs, FDAH developed an AER categorization system. Each AER is assigned into one or more of the following categories:

1. Injection site reports
2. Allergic reports (signs consistent with an allergic response in the species involved, occurring less than 48 hours after product administration)
3. Non-allergy systemic reports

To calculate reporting rates for evaluation of the incidence of events, the number of reports received is divided by the number of doses sold to veterinary clinics in the same period. The total number of vials of product sold is converted to an estimate of doses using an average number of doses per vial. Based on interviews with a large number of veterinarians, FDAH determined that the average number of doses per vial was 21. This dosage is equivalent to an 18 kg dog which is consistent with the average weight of the population at large.

There is a significant seasonality to the pattern of use of all heartworm preventative products. Figure 4.2.2-1 illustrates this seasonal pattern for doses of heartworm preventatives dispensed by veterinarians in the course of a typical year. This pattern is important to understand, when analyzing report numbers and reporting rates, as discussed below.

Figure 4.2.2-1. Seasonality of Dispensing Heartworm Medication 2002 (All Products)

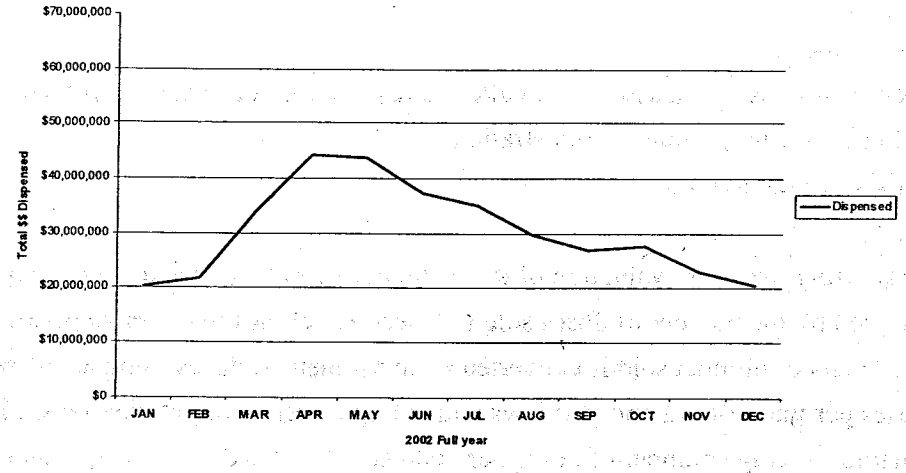


Figure 4.2.2-1 demonstrates the strong seasonal use patterns of heartworm preventative products in the US. The risk (and heightened awareness) of heartworm infection increases as mosquito populations either reappear after a typical northern winter, or crescendo after the more mild winters in southern areas of the US. Therefore, there is a large peak in use of all heartworm preventatives in April and May of the year.

Figure 4.2.2-2 demonstrates the sales patterns of ProHeart 6. Sales are increasing over the period. Sales peaks also occur in each year in essentially the same periods of time as the use patterns of heartworm products demonstrated in Figure 4.2.2.2-1.

Figure 4.2.2-2. Doses Sold by Quarter

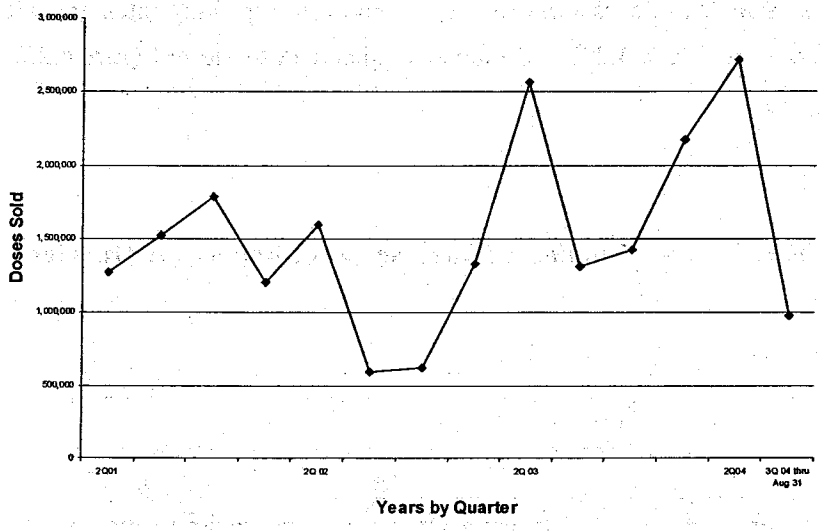


Figure 4.2.2-3 demonstrates the number of AERs received by FDAH associated with ProHeart 6. The number of AERs from launch through August of 2004 is generally decreasing. The peaks in the number of AERs in the second quarter of each marketing year correspond to the peaks in seasonal use and sales previously described. These peaks in AER numbers decrease in each marketing year despite large increases in sales of ProHeart6 shown in Figure 4.2.2-2. This seasonality in use, in conjunction with the increasing sales trends marketing dynamics of ProHeart 6, results in patterns of AER numbers that are difficult to interpret without proper perspective on the number of doses administered. Therefore reporting rates are calculated using report numbers found in Figure 4.2.2.-3 divided by sales data found in Figure 4.2.2.-3 to create Figure 4.2.2-4.

Figure 4.2.2-3. Number of Adverse Event Reports by Quarter

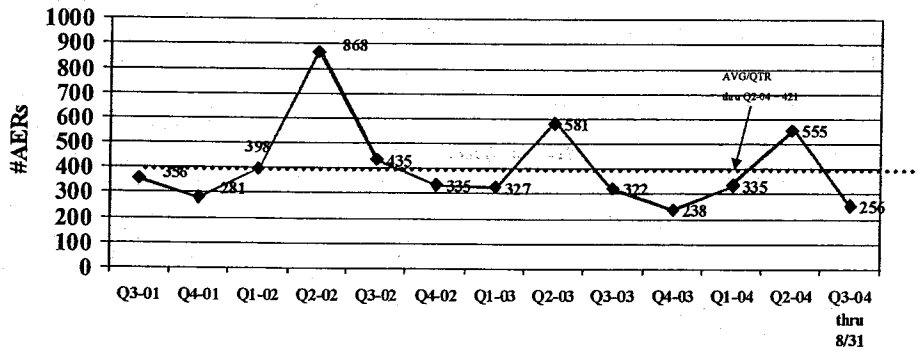
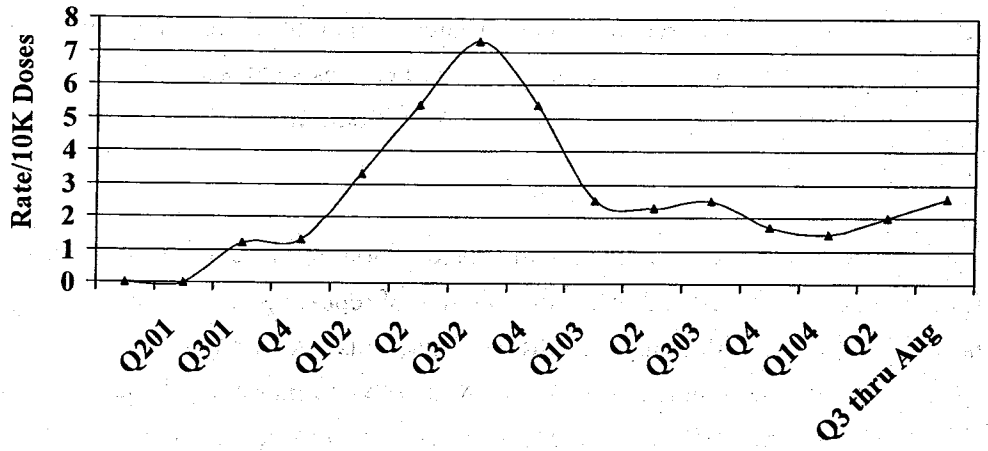


Figure 4.2.2-4. Reporting Rate by Quarter



The reporting rate shown in Figure 4.2.2-4 puts these trends into perspective. Marketing year two produced higher reporting rates, after which a more steady reporting rate was observed. Higher AERs were recorded in the 2nd quarter of 2002 (refer to Figure 4.2.2-3), but tapered off considerably following the August 2002 implementation of the manufacturing change of zero tolerance for residual solvents in the moxidectin used to manufacture ProHeart 6 (see Section 4.3). In the 2nd quarter of 2002, reporting rates peak not only due to an increased number of reports but also due to the return of large amounts of product in 2002, as a result of outdated product sold in 2001.

Evaluation by marketing year, which eliminates reporting rate fluctuations due to seasonality of use, reveals that the average reporting rate for AERs is less than 4 reports per 10,000 doses sold per year. By this same method of analysis, reports that include the death of the patient (regardless of causality) are fewer than 0.5 reports per 10,000 doses sold per year. Additionally, there is no peak in the number of death reports during the peaks in AERs seen in the 2nd quarter of each year. Further, the adverse event case fatality rate associated with ProHeart 6 reports is lower than many FDAH pharmaceuticals and similar to case fatality rates for the FDAH canine vaccine product lines including Duramune Max 5/4L. Thus the incidence of death does not appear to be causally related to ProHeart 6 usage.

Most AERs occurrred within 10 days of product administration. Overall, 72% of the AERs occurred within 48 hours of administration, (17%) were reported from 2 days to 10 days post-administration, and 10% occurred at 11 days or later. This information suggests that a significant percentage of reports occur in a short time frame, consistent with a possible allergic etiology from administration of ProHeart 6 alone or in combination with vaccines or other medication.

When the numbers of AERs were evaluated with consideration of the seasonality of use and the increases in the numbers of doses sold over time, the rate of reporting associated with ProHeart 6 was low and was decreasing with time. In addition, the seriousness of reports as estimated by case fatality rates was not increasing and was consistent with commonly used pharmaceutical and biological products. Thus, FDAH concludes that AERs were rare and the product should remain available as an alternative for prevention of canine heartworm disease.

4.2.2.1 Analysis by Report Category

4.2.2.1.1 Injection Site Reports

The reporting rate for injection site reports through 31 August 2004 was 0.2 reports per 10,000 doses sold. The majority of the events were self-limiting and consisted of swelling, pain and/or pruritus at the site of administration.

The occurrence of injection site reports after the use of ProHeart 6 has remained consistently low and the types of events reported were similar to other injectable products in the FDAH database. For comparison, 2 of the most widely used vaccines in the FDAH line have reporting rates of 0.1 reports per 10, 000 doses sold (Duramune Max 5/4L, a distemper/parvo/leptospirosis combination vaccine) and 0.5 reports per 10,000 doses sold (Rabvac 3, a rabies vaccine).

4.2.2.1.2 Allergy Event Reports

The allergy report category has trended down over time. The reporting rate through 31 August 2004 was 1.26 reports per 10,000 doses sold. The occurrence of allergy events was most prevalent in the most popular breeds, supporting the conclusion that there are no specific breed sensitivities. Thirty seven percent (37%) of the reports include concurrent vaccine

administration, which likely contributed to the reporting rate. For the vaccines previously cited, Duramune Max 5/4L has an allergy reporting rate of 0.4 reports per 10,000 doses sold and Rabvac 3 has an allergy reporting rate of 0.5 reports per 10,000 doses sold.

The occurrence of allergy events are described in the product label. The observations include facial swelling, angioedema, and urticaria, alone or in combination with gastrointestinal (GI) signs such as vomiting or diarrhea, anaphylaxis, or a low percentage of less common signs such as lethargy.

4.2.2.1.3 Non-Allergy Event Reports

Non-allergy events are those not considered to be an allergic response and not categorized as injection site. This non-allergy category includes systemic responses (regardless of the plausibility of product association) and may overlap with other categories. For example, an individual event report describing injection site swelling would be classified as an injection site report; however if fever and myalgia also occur, it would also be categorized as a non-allergy event. Similarly, there is an overlap in the symptoms designated as allergy and non-allergy. Acute GI symptoms occurring within 48 hours of product administration may be categorized as an allergic event, whereas the same symptoms occurring at 96 hours after product administration would typically be categorized as a non-allergy systemic event. Forty five percent (45%) of reports categorized as non-allergy occurred within 48 hours of product administration. In many cases, some of the clinical signs reported are consistent with allergy, while other signs vary enough to result in the event being placed in the non-allergy category. Therefore, FDAH concludes that a significant number of events placed in the non-allergy category are actually allergy mediated.

As observed in the allergy group, no specific breeds appear to be over-represented in the analysis when the population at large is considered. The overall reporting rate for the non-allergy category through 31 August 2004 was 1.19 reports per 10,000 doses. Concurrent vaccine use was reported in 42% of the non allergy reports. Duramune Max 5 /4L has 0.3 reports per 10,000 doses recorded in the non-allergy group and Rabvac 3 has 0.35 reports per 10,000 doses.

The signs reported in the non-allergy group cover a wide range, with a large number of the signs being reported in relatively few cases. The more commonly reported events include vomiting

and/or diarrhea, lethargy, seizures and ataxia. With the exception of ataxia, all of the above clinical signs are included in the product label.

4.2.2.2 Causality Analysis of Medical Events by Selected Body Systems

Events involving specific body systems were further analyzed to establish causality. These included events associated with neurologic reports, hematologic reports, hepatic reports, cardiac reports, and reports with a diagnosis of neoplasia.

Each ProHeart 6 case was individually reviewed to assess the likelihood that the observation was the result of administration of ProHeart 6. Medical association assessments were based on the approved International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) pharmacovigilance draft guidelines. These draft guidelines were developed with regulators from Europe, Japan, and the US to provide guidance on global pharmacovigilance harmonization. All events were assigned to the medical association "possible" category as a starting point. When the causality was considered "unlikely," sufficient information existed to establish that a reported event was not likely associated with product use because there were other more plausible explanations for the reported event. For the analysis by body system that are presented in the sections that follow only the medical association "possible" group was reviewed.

This medical association "possible" group was further reviewed to distinguish between events that could potentially be associated with a specific body system compared with those events for which it is probable that the specific body system was involved. Therefore, for each body system to be analyzed, 2 case definitions were developed: "potential" and "probable." The "potential" case definition is intended to include all clinical signs potentially reflective of an adverse effect on that body system. The "probable" case definition is more refined to include only those clinical signs that have a reasonable probability of being related to that body system, and the "probable" excludes all events classified as allergic. If any individual report included more than 1 of the body systems evaluated, it was included in multiple evaluations. For example, if the report involved a dog with anemia and elevated hepatic enzymes, it was reviewed under both the hematologic and hepatic body systems.

4.2.2.2.1 Neurologic

The analysis of neurologic events is hown in Table 4.2.2.2.1-1. The rate of reporting is low at 0.12 reports per 10,000 doses. The difference between the number of potential and probable neurologic events is relatively large because events classified as allergic and events with non-specific neurologic signs are included in the number of potential events but not the number of probable events. Non-specific neurologic signs are clinical signs (eg, muscle tremors) that are seen without other clinical signs and, therefore, are not likely to include a primary neurologic disorder.

For neurologic events, seizure and ataxia are the primary clinical signs while other individual clinical signs each account for less than 10% of the total in the neurologic group. As is true with each of the systems, causality assessments are confounded by concurrent vaccine use in 47% of the AERs. Additionally, 54% of the reported events occurred within 48 hours or less, suggesting that many may be allergic events.

Table 4.2.2.2.1-1. Neurologic Adverse Events – Number of Reports

Year	Potential	Probable	Rate (Probable) per 10K Doses Sold
2001	98	23	0.05
2002	342	85	0.21
2003	235	69	0.10
2004-Aug	211	68	0.12
Total	886	245	0.12

The "probable" neurologic reports were reviewed by Dr. Alexander deLahunta D.V.M., PhD., diplomate of the American College of Veterinary Internal Medicine, specialty neurology and honorary member of the American College of Veterinary Pathologists (Appendix 6.2). FDAH randomly selected about 75% of the neurologic AERs for his review. Dr. deLahunta noted that seizures were the most common clinical sign reported in the cases, which is consistent with the general observations in the practice of clinical neurology. He also commented that the most common cause of seizures in dogs is idiopathic epilepsy. Dr. deLahunta concludes his assessment with the following statement: "The extensive toxicologic studies performed by

FDAH clearly support the safety of ProHeart 6 at the dose injected in these dogs. There is no rational scientific reason to believe that this product played any role in the post-injection clinical signs reported in these case summaries."

4.2.2.2.2 Hematologic Events

The analysis of hematologic events is shown in Table 4.2.2.2.2-1. The rate of reporting is low at 0.09 reports per 10,000 doses. As is true with each of the systems, causality assessments are confounded by concurrent vaccination in 49% of the AERs.

Table 4.2.2.2.2-1. Hematologic Adverse Events – Number of Reports

Year	Potential	Probable	Rate (Probable) per 10K Doses Sold
2001	75	13	0.03
2002	212	63	0.16
2003	172	48	0.07
2004-Aug	139	60	0.10
Total	598	184	0.09

FDAH consulted with Dr. Alan Rebar, a diplomate of the American College of Veterinary Pathologists with a specialty in clinical pathology, to review all potential hematologic events (Appendix 6.3). Dr. Rebar was provided with clinical case summaries and all available clinical laboratory data for all the clinical cases identified by FDAH criteria as probable hematologic or hepatic adverse events to ProHeart 6. (The review of the hepatic events follows in Section 4.2.2.2.3.)

In contrast to FDAH's assessment (Table 4.2.2.2.2-1), Dr. Rebar determined that 151 of the AERs he reviewed should be categorized as probable hematologic AERs. Particular emphasis was placed on potential toxic-induced hematologic events: immune mediated hemolysis (IMHA), immune mediated thrombocytopenia (ITP), Heinz body hemolysis, and bone marrow hypoplasia /aplasia (IMMD). Of these, only IMHA, ITP and/or IMMD were identified among the 151 hematologic reports.

Dr. Rebar also evaluated the 151 probable hematologic events to determine which may have been immune mediated. Using a conservative case definition he determined that 79 could be immune mediated. In many of the 79 cases, however, not enough data were provided to establish a definitive diagnosis of IMHA, ITP or IMMD. For example, in many cases, blood films were not evaluated for the presence of spherocytes, direct antiglobulin tests (DAT, Coombs' tests) were not run, and blood films were not scanned to confirm an instrument reported thrombocytopenia.

Of the 79 cases determined to be potentially immune mediated, 76 cases were determined to be IMHA/ITP. Of these, 53 cases occurred after the first injection of ProHeart 6, and 26 occurred after 2 or more injections. Of the 53 cases occurring following a single ProHeart 6 injection, only 23 (those occurring 8 to 30 days post-injection) were considered possibly related to ProHeart 6. Fourteen (14) occurred too soon following ProHeart 6 injection (0 to 7 days) to have allowed sufficient antibody to form against ProHeart 6 to precipitate an immune-mediated hematologic event. Thirteen (13) occurred after 30 days or more, too long an interval to suggest a likely role for ProHeart 6 injection.

Of the remaining 23 cases, it is not possible to rule out a role for ProHeart 6, although IMHA and ITP are relatively common disorders in all breeds of dogs.

Of the 26 cases occurring following multiple injections of ProHeart 6, twenty two (22) (those occurring between 0 and 30 days post ProHeart 6 injection) were considered possibly related to ProHeart 6. The 10 cases occurring within 7 days post-injection are relatively unlikely to be related to ProHeart 6 injection but are included because of potential anamnestic immune response to multiple injections.

Three (3) cases of apparent IMMD were identified. The cause of the IMMD in each case could not be determined from the diagnostic data available. Two (2) cases occurred after the first dose of ProHeart 6; the first occurred at 7 days post administration and the second occurred at more than 30 days post administration. The third case occurred more than 30 days after the dog had received its fourth dose of ProHeart 6. The timing of all 3 events indicates that they were unlikely to be related to ProHeart 6 administration.

In summary, 45 cases of hematologic AERs may have been induced by ProHeart 6. However, since more than 18 million doses of ProHeart 6 have been sold it is possible that these findings represent the normal baseline incidence in canines.

4.2.2.2.3 Hepatic Body System

The analysis of hepatic events is shown in Table 4.2.2.2.3-1. The rate of reporting is low at 0.07 reports per 10,000 does sold. As is true with each body system, causality assessments are confounded by concurrent vaccine use in 38% of the AERs.

Table 4.2.2.2.3-1. Hepatic Adverse Events – Numbers of Reports

Year	Potential	Probable	Rate (Probable) per 10K Doses Sold
2001	36	12	0.03
2002	125	48	0.12
2003	109	49	0.07
2004-Aug	118	47	0.08
Total	388	156	0.07

One hundred (100) probable hepatic AERs were reviewed by Dr. Rebar. This number of 100 probable hepatic reports is different from the total probable hepatic reports in Table 4.2.2.2.3.-1 because Dr. Rebar removed 56 reports that he determined were not probable hepatic events. Forty-three (43) cases of possible primary liver disease were identified among the 100 AERs evaluated. Fifty-seven (57) cases were probably not primary hepatic events, and the mild non-specific elevations in hepatic enzyme(s) were thought to be due to anorexia and/or stress.

Of the remaining 43 cases, 42 occurred between 0 and 3 days post- injection; again, however, a causal relationship with ProHeart 6 cannot be ruled out. However, since more than 18 million doses of ProHeart 6 have been sold it is possible that these findings represent the normal baseline in the canine population.

Pathology reports from all the probable hepatic AERs that contain any pathology reports (15 cases) were reviewed by Dr. Keith Harris D.V.M., Assistant Vice President Pathology and Bioresources, Wyeth Research and diplomate of the American College Veterinary Pathologists. There was no pattern of liver pathology indicative of a common toxicological agent in all or a subset of the 15 cases (other than corticosteroids in two cases). Only one case out of the 15 exhibited histomorphologic changes consistent with a direct acting hepatotoxin that could be temporally related to ProHeart 6 administration. Pathology reports from 15 cases with liver disease were reviewed. There was no obvious pattern of liver pathology that would indicate toxicity common to all or a subset of the 15 cases (other than corticosteroids in two cases). Only one case out of the 15 exhibited histomorphologic changes consistent with a direct acting hepatotoxin that could be temporally related to ProHeart 6 administration. The acute hepatocellular necrosis described in this particular case is a non-specific finding and could have been caused by a number of different toxicants.

4.2.2.2.4 Cardiac Events

The analysis of cardiac events is seen in Table 4.2.2.2.4-1. The reporting rate is low at 0.02 reports per 10,000 doses.

Table 4.2.2.2.4-1. Cardiac Adverse Events – Numbers of Reports

Year	Potential	Probable	Rate (Probable) per 10K Doses Sold
2001	100	7	0.02
2002	254	15	0.04
2003	186	10	0.02
2004-Aug	153	15	0.02
Total	693	47	0.02

Concurrent vaccination confounds the assessment of the cardiac events. Forty-nine percent (49%) of the cases classified as cardiac events included concurrent vaccination. Sixty percent (60%) of the reports occurred within 48 hours of ProHeart 6 administration. The timing of these

reports is not indicative of a direct cardiac effect. Many events appear to overlap as non-typical allergic events, as observed for the other body systems, so that an indirect effect associated with an allergic event cannot be ruled out.

Dr. Keith Harris DVM, Assistant Vice President Pathology and Bioresources Wyeth Research, and diplomate of the American College of Veterinary Pathologists, reviewed the histopathological slides from 2 cases of cardiac necrosis thought to be associated with ProHeart 6 administration. Histopathologic evaluation of tissue specimens from the 2 dogs identified in an FDA presentation revealed cardiac pathology secondary to uremia in a Boxer dog and chronic heart disease that clearly predated ProHeart 6 administration in a Labrador Reteiever. The two IDEXX pathologists who had originally indicated that these cases might be associated with ProHeart 6 subsequently concurred with this interpretation.

Based on these data, including timing of the events and histopathological assessments, FDAH concludes that there is no causal relationship between ProHeart 6 and these cardiac events.

4.2.2.2.5 Neoplasia Events

The analysis of neoplasia cases is shown in Table 4.2.2.2.5-1. The rate of reporting is low at 0.06 reports per 10,000 doses.

Table 4.2.2.2.5-1. Neoplasia Adverse Events – Numbers of Reports

Year	Potential	Rate per 10K Doses Sold
2001	7	0.01
2002	38	0.09
2003	41	0.06
2004-Aug	36	0.06
Total	130	0.06

Dr Philip Bergman, D.V.M, MS, PhD, diplomate American College of Veterinary Internal Medicine, Oncology (Appendix 6.4) reviewed all 130 cases involving a diagnosis of neoplasia, regardless of medical association. A summary of Dr. Bergman's comments follows.

The vast majority of ProHeart 6-related cancers occurred within 21 days or less of ProHeart 6 administration. Veterinary oncologists agree that at least 6 to 8 weeks are required to develop a tumor after exposure to a carcinogen. Therefore, cases that were diagnosed with cancer within a 3 to 4 week period after ProHeart 6 administration likely had a tumor present before ProHeart 6 administration. There was not a relationship between additional doses of ProHeart 6 administered and increasing reports of neoplasia. This lack of a dose-response relationship with repeated ProHeart 6 administration further supports the conclusion that ProHeart 6 is not responsible for canine tumor induction. This is further supported by the moxidectin nonclinical toxicology studies showing no evidence of carcinogenicity (see Section 3.3.3 and Appendix 6.1).

Dr. Bergman's review of the 130 cases revealed that 100 cases were clearly not associated with ProHeart 6 administration. Twenty eight (28) cases did not allow the immediate exclusion of an association to ProHeart 6 administration. However the association was deemed unlikely due to 1 or more of the following factors: 1) a time period from product administration to observation of the neoplasia was too short to be considered a causal relationship; 2) most of the reports revealed no association between the site of administration and the location of the neoplasia; 3) there was a broad cross section of neoplasia types, rather than a predilection for a specific tumor type, as would be expected in a product-specific effect; and 4), the types were representative of those seen in the general dog population. There were 2 cases in which a relationship to ProHeart 6 administration could not be ruled out.

4.2.3 Conclusions

Based on the in-depth analysis described in this summary section, it is the conclusion of FDAH that ProHeart 6 is a safe and effective product for the prevention of canine heartworm disease. The overall reporting rate for AERs was low and generally trended down over time to the time of the recall. At that time, the frequency and severity of AERs was not increasing. Analysis of specific body and organ systems support the conclusion that the AER clinical finding were generally not causally related to ProHeart 6 administration and appeared to occur at a rate consistent with naturally occurring disease in the canine population.

4.3 Manufacturing Change

ProHeart 6 was launched in the US in June 2001. Shortly after launch, FDAH received a number of reports of allergic-type reactions after administration. The reactions reported ranged from mild and self-limiting (eg, urticaria, itching at injection site, an episode of vomiting or diarrhea) to severe anaphylactoid reactions.

A working group of FDAH and Wyeth immunology experts was convened to investigate the possible causes, and outside experts were retained to assist. There were 2 aspects of the investigations: (1) field reports and their follow-up, and (2) product analysis for any abnormalities, contaminants, and/or reactive components.

A "cluster effect" was observed where some practices reported several adverse events, while others in close proximity with usage patterns of ProHeart 6 did not report reactions. This was observed in both the US and Australia. Visits were made to practices to evaluate product storage, handling, and administration, and veterinarians and dog owners were interviewed to try to identify any predisposing factors. No age or breed predispositions were found, nor any interactions with concurrent treatment with other veterinary therapeutics or biologicals.

Extensive investigations into reactor dogs (dogs which showed allergic reactions) found no evidence that the allergies were IgE (immunoglobulin E) or IgG (immunoglobulin G) mediated (L. Gershwin, Department of Pathology, Microbiology and Immunology, School of Veterinary Medicine, University of California, Davis, and R. Schultz, Professor and Chair, School of Veterinary Medicine, Department of Pathological Sciences, University of Wisconsin, Madison [see Appendix 6.5]). The reactions appeared to be idiosyncratic and mediated either by histamine or complement.[45,46,47] Attempts to induce reactions in dogs using passive cutaneous allergy testing after sensitization with serum from reactor dogs were unsuccessful.[48,49]

Extensive testing of all raw materials and formulated products used in manufacture of ProHeart 6 showed that all were within quality specifications. Tests for 16 trace metals did not reveal any contamination. Quality Assurance audits were conducted at the manufacturing sites of glyceryl tristearate (Germany) and hydroxypropyl methylcellulose (US) to evaluate the potential for cross contamination during or after manufacturing. No potential problems were found. Cleanout

validation was repeated at the formulation plant to confirm that no carryover from other manufacturing processes could occur.[50,51,52]

Both in the US and Australia, differences were found in reaction rates between batches, so investigations focused on trying to identify any batch differences. Thin layer chromatography (TLC) analyses detected no unknown components either in moxidectin technical material or in finished product. However, evaluation of minor component profiles between batches revealed a trend to lower reactions for lots with no detectable residual solvents. Coincident with this investigation, FDAH was optimizing the manufacturing process and initiated a manufacturing change to produce moxidectin with no detectable solvents.

Although additional studies were done to better understand the cause of the allergic-type reactions, no conclusive findings were generated. Nevertheless, there has been a decline in the adverse event reporting rate from all markets since the manufacturing change was implemented.

4.4 Safety Profile in Dogs

In August of 2004, FDAH requested a review of the safety of ProHeart 6 use in general veterinary practice and a comparison of its safety profile with that of commonly used oral monthly heartworm drugs by Dr. Larry Glickman VMD, DrPh, FACE, Professor of Epidemiology and Public Health and Head, Section of Clinical Epidemiology, School of Veterinary Medicine, Purdue University (Appendix 6.6). This section summarizes the experience with ProHeart 6 by Banfield the Pet Hospital™ veterinarians nationwide who had administered 735,654 doses of ProHeart 6 to dogs from January 1, 2002 through August 31, 2004.

4.4.1 Methods

The source of data for this analysis was the medical records of Banfield the Pet Hospital™. Banfield was founded in 1955 in Oregon to deliver primary health care to companion animals, and by 2005 will operate a national network of 440 full-service veterinary hospitals in 42 states. Banfield practices employ more than 900 full and part-time veterinarians, have over 1.4 million active patients, and conduct approximately 50,000 patient visits per week. The Banfield database is paperless and contains over 8 million patient records in electronic format. A quality assurance team consisting of veterinarians and veterinary technicians regularly monitors the safety profile of all medications, vaccines, and procedures used by Banfield veterinarians and tracks the incidence of diseases that are preventable by these vaccines or drugs.

All encounters (office visits) were characterized as being associated with ProHeart 6, 2 oral monthly heartworm preventative drugs (Heartworm Preventative 1 or Heartworm Preventative 2), vaccine, or none of these exposures. Adverse events (AEs) of interest included liver disease, neurological disease, ocular disease, immune-mediated disease, allergic reaction, death, cancer (mast cell, lymphosarcoma, and histiocytoma), cardiovascular disease, anaphylaxis, or inflammatory bowel disease. The specific diseases or laboratory findings comprising each of these AEs based on Banfield computer codes are shown in Table 4.4.1-1. Each encounter was then evaluated for potential AEs over the following 30 days. Of these encounters, 275,189 that occurred from August 1 to August 31, 2004, were excluded from analysis because they lacked a full 30-day followup interval. This followup period was

terminated early if a dog had another exposure to ProHeart 6, either of the 2 monthly heartworm preventatives, a vaccine, or died. Except in the case of death, a new followup period was initiated after this new exposure. The incidence of AERs, expressed as either the number of AEs per 10,000 encounters or the number of AE per 10,000 days at risk following an exposure, were calculated for the following exposure groups: no exposure, vaccine alone, ProHeart 6 with or without vaccine, and Heartworm Preventative 1 or Heartworm Preventative 2 with or without vaccine. Formal testing to identify statistically significant differences in the AE rates between exposure groups was generally not done for the univariate analyses due to the very large sample size within each exposure group. That is, the power to detect statistically significant differences was so high for common events that even very small differences in event rates were likely to be statistically different at $p < 0.001$. However, the same was not necessarily true for less common events. For this reason, the focus was placed on the clinical relevance of differences in the AE rates and the 95% confidence intervals of the odds ratios in multivariate analysis.

Table 4.4.1-1. Adverse Events

Disease Category	Adverse Event	Identification Criteria
Liver Disease	liver any dx	dx = hepatopathy, hepatitis, hepatic enceph, hepatic acute, hepatic dis, hepatic conserv, hepatic extensv
	liver alp	lab = alp >= 393
	liver alt	lab = alt >= 236
	liver gam	lab = gamma gt >= 24
	liver bil	lab = tot bilirubin > 1.0
	liver lab	any liver adverse lab code
	liver any dx + any lab	any liver adverse dx + any liver adverse lab code
	liver any	any liver adverse dx or any liver adverse lab code
Neurological Disease	neuro	dx = enceph mening, epilepsy, behavioral uk, shock-cardio, seizures-acq lab = paresis, paralysis, ataxia
Ocular Disease	ocular	dx = optic neuritis, retinal-degen-s, anisocoria lab = vis acuity, vis deficit-lft, visual deficit-rgt
Immune Mediated Disease	Thrombocytopenia	dx = thrombocytopenia, thrombo im
	immun_med1	dx = (immune med dis or AHA) and lab = abnormal reticulocyte count
	immun_med2	dx = (immune med dis or AHA) and not lab = abnormal reticulocyte count
	immune any	any immune mediated disease adverse event
Allergic Reaction	allergic reaction	dx = allergic reaction, drug reaction, drug induc dis, allergic rct acut, vaccine reaction, urticaria, drug eruption
Death	death	dx = dead on arrival, sudden death death date within 30 days based on reported death in demographics records
Anaphylaxis	anaphylaxis	dx = anaphylaxis
Cardiac	cardiac murmur	dx = murmur
	cardiac arrhythmia	dx = cardiac arrest, atrial fibrillation, atrial premature contractions, atrial tachycardia, bundle branch block, heart block 1st deg, heart block 2nd deg, heart block 3rd deg, cardiac arrhythmia, ventricular premature contractions, ventricular tachycardia
	cardiomyopathy	dx = cardiomyopathy, canine dilated, cardiomyopathy; canine hypertrophic, cardiomyopathy; boxer, cardiomyopathy; canine familial, cardiomyopathy; dilated, cardiomyopathy; hypertrophic
	cardiac any	any cardiac adverse dx
Cancer	mast cell tumor	dx = mast cell tumor
	lymphosarcoma	dx = lymphosarcoma
	histiocytoma	dx = histiocytoma
	cancer any	any cancer adverse dx
Inflammatory Bowel Disease	ibd	dx = inflammatory bowel disease

For the purposes of this study, it was assumed that oral monthly heartworm preventatives had been administered by owners on the same day of the encounter in which they had been dispensed. In contrast, ProHeart 6 and vaccines were assumed to have been administered during the same office encounter indicated in the medical record. Also, a search for potential AEs was limited to the 30 days immediately following an encounter of interest. The potential consequences of these assumptions would be to underestimate the incidence of AEs associated with oral monthly heartworm drugs, compared with those associated with ProHeart 6 or vaccines, because it was not certain if, or when, the monthly heartworm preventative dispensed for a dog was actually given to the dog by its owner. That is, some of the oral heartworm preventatives dispensed by Banfield veterinarians were probably never given to the dogs, yet AEs were calculated as if these drugs had been administered.

4.4.2 Results

From January 1, 2002 to August 31, 2004, there were 6,800,061 dog visits or encounters at 403 Banfield hospitals. The following number of encounters was associated with the administration of: ProHeart 6 (735,654), Heartworm Preventative 1 (411,082), Heartworm Preventative 2 (18,405), or vaccine (2,230,202), (Table 4.4.2-1). In addition, there were 5,634,016 encounters during which no heartworm preventative was administered or dispensed. Heartworm preventatives were often administered or dispensed at the same time as a vaccine. The proportion of encounters associated with vaccination was 62.9% for Proheart 6, 59.9% for Heartworm Preventative 1, and 65.1% for Heartworm Preventative 2. In contrast, vaccines were only administered during 26.4% of the encounters for which no heartworm preventative was given. That is, these dogs may have presented with signs of disease for which diagnostic tests were performed and other drugs administered. The number of doses of ProHeart 6 administered monthly by Banfield veterinarians increased over time since January 2002 and a higher number of doses was administered each year during the peak time of mosquito activity, namely from March through September (Figure 4.4.2-1).

Table 4.4.2-1. Rate per 10,000 of Any Adverse Event by Treatment Category Total Number of Encounters = 6,800,061

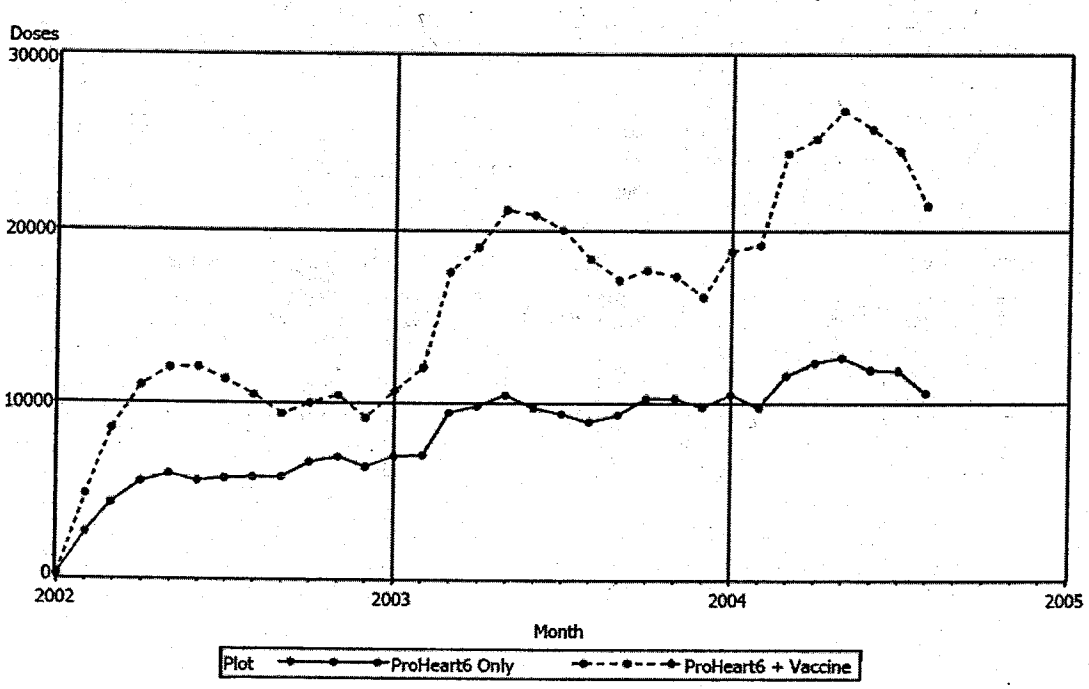
Vaccine	ProHeart6			HW Prev 1			HW Prev 2			No HW Treatment		
	N	N_A	Rate	N	N_A	Rate	N	N_A	Rate	N	N_A	Rate
Yes	483,064	6,292	130.3	246,131	2,804	113.9	11,975	120	100.2	1,489,032	17,406	116.9
No	252,590	2,253	89.2	164,951	1,469	89.1	6,430	45	70.0	4,144,984	120,529	290.8
Total	735,654	8,545	116.1	411,082	4,273	103.9	18,405	165	89.4	5,634,016	137,935	244.8

N = Total Number of Encounters

N_A= Total Number of Adverse Events

Rate = Number Adverse Events Per 10,000 Encounters

Figure 4.4.2-1. Doses Dispensed by Month; ProHeart 6 Only or With Vaccine



4.4.2.1 Univariate Analyses

ProHeart 6 was associated with a higher rate of liver-related AE compared with either of the 2 monthly heartworm preventatives, regardless of whether a vaccine was administered or not, while Heartworm Preventative 1 was associated with the highest death rate (Table 4.4.2.1-1). In general, vaccine administration was associated with an increased rate of liver disease for dogs receiving ProHeart 6, but not for dogs on monthly heartworm preventative. The rates of all other diseases or conditions except for cancer were similar among all of the heartworm preventatives, whether given orally or parenterally.

Table 4.4.2.1-1. Adverse Event Rate per 10,000 by Treatment Group

Treatment Category					Potentially Associated Adverse Event Type									
					Liver Disease		Neurological Disease		Ocular Disease		Immune Mediated Disease		Allergic Reaction	
ProHeart6	HW Prev 1	HW Prev 2	Any Vaccine	N	N	Rate	N	Rate	N	Rate	N	Rate	N	Rate
				4,144,984	25,531	61.6	3,157	7.6	134	0.3	2,948	7.1	6,832	16.5
			Y	1,489,032	5,207	35.0	522	3.5	27	0.2	265	1.8	6,598	44.3
		Y		6,430	14	21.8	4	6.2	0	0.0	1	1.6	12	18.7
		Y	Y	11,975	24	20.0	2	1.7	0	0.0	2	1.7	62	51.8
	Y			164,951	523	31.7	68	4.1	1	0.1	40	2.4	236	14.3
	Y		Y	246,131	671	27.3	94	3.8	2	0.1	22	0.9	1,336	54.3
Y				252,590	880	34.8	123	4.9	4	0.2	59	2.3	465	18.4
Y			Y	483,064	2,011	41.6	178	3.7	7	0.1	98	2.0	2,581	53.4
Any				6,800,061	34,866	51.3	4,149	6.1	175	0.3	3,435	5.1	18,123	26.7

Treatment Category					Potentially Associated Adverse Event Type									
					Death		Cancer		Cardio Disease		Anaphylaxis		IBS	
ProHeart6	HW Prev 1	HW Prev 2	Any Vaccine	N	N	Rate	N	Rate	N	Rate	N	Rate	N	Rate
				4,144,984	74,470	179.7	3,724	9.0	8,089	19.5	139	0.3	767	1.9
			Y	1,489,032	2,690	18.1	562	3.8	1,804	12.1	108	0.7	62	0.4
		Y		6,430	11	17.1	0	0.0	4	6.2	0	0.0	1	1.6
		Y	Y	11,975	17	14.2	2	1.7	10	8.4	2	1.7	0	0.0
	Y			164,951	363	22.0	67	4.1	219	13.3	4	0.2	17	1.0
	Y		Y	246,131	354	14.4	75	3.0	261	10.6	18	0.7	17	0.7
Y				252,590	392	15.5	155	6.1	250	9.9	13	0.5	19	0.8
Y			Y	483,064	709	14.7	205	4.2	635	13.1	34	0.7	26	0.5
Any				6,800,061	79,006	116.2	4,790	7.0	11,274	16.6	318	0.5	909	1.3

The rate of potential liver-related AEs was examined further on the basis of a clinical diagnosis only, an increase in the serum concentration of a liver-associated enzyme or bilirubin, or any combination of a clinical diagnosis plus an abnormal laboratory finding (Table 4.4.2.1-2). ProHeart 6 when administered either with or without a vaccine, was associated with a higher rate of any liver-related clinical diagnosis, enzyme ALT, bilirubin, or a combination of a clinical diagnosis plus any abnormal laboratory test result (Table 4.4.2.1-3). However, in an analysis based on the rate of potential AEs per 10,000 days at risk, the rate of liver disease was comparable between ProHeart 6 and the 2 monthly heartworm preventatives, while the rate was highest for dogs that received no heartworm drug. It should be noted that the mean days at risk per encounter for ProHeart 6 was 29.2 compared with 27.2 for Heartworm Preventative 1. This could lead to a slight underestimation of the AE rate associated with Heartworm Preventative 1 compared with ProHeart 6. The liver-related AEs appeared to occur with similar frequency during days 0 to 2, 3 to14, and 15 to 30, following the exposures of interest.

Table 4.4.2.1-2. Liver Adverse Events Definitions Based on Lab Measure or Lab Abnormal Flag

Measure	Criterion	Times Normal	Lab Measure N	Lab Abnormal Flag N
ALP	>= 393	3X	22,913	37,869
ALT	>= 236	2X	12,201	32,406
Tot Bilirubin	>= 1.0	3X	24,823	27,049
Gamma GT	>= 24	2X	485	14,092
Total			**60,422**	**111,416**

Table 4.4.2.1-3. Potential Liver-related Adverse Events per 10,000 by Treatment Group

Treatment Category					Potentially Associated Adverse Event Type															
PHi6	HW Prev 1	HW Prev 2	Any Vaccine	N	Any DX		ALT		ALP		GAM		BIL		Any LAB		DX + LAB		DX or LAB	
					N	Rate	N	Rate	N	Rate	N	Rate	N	Rate	N	Rate	N	Rate	N	Rate
				4,144,984	3,776	9.1	6,616	16.0	12,422	30.0	391	0.9	8,754	21.1	23,536	56.8	1,452	3.5	25,531	61.6
			Y	1,489,032	460	3.1	1,008	6.8	1,703	11.4	20	0.1	2,688	18.1	4,997	33.6	218	1.5	5,207	35.0
		Y		6,430	0	0.0	4	6.2	3	4.7	0	0.0	9	14.0	14	21.8	0	0.0	14	21.8
		Y	Y	11,975	0	0.0	8	6.7	8	6.7	0	0.0	13	10.9	24	20.0	0	0.0	24	20.0
	Y			164,951	52	3.2	118	7.2	201	12.2	8	0.5	237	14.4	498	30.2	20	1.2	523	31.7
	Y		Y	246,131	45	1.8	94	3.8	173	7.0	3	0.1	416	16.9	645	26.2	15	0.6	671	27.3
Y				252,590	100	4.0	215	8.5	326	12.9	7	0.3	400	15.8	836	33.1	43	1.7	880	34.8
Y			Y	483,064	206	4.3	389	8.1	696	14.4	8	0.2	984	20.4	1912	39.6	95	2.0	2,011	41.6
Any				6,800,061	4,641	6.8	8,450	12.4	15,536	22.8	437	0.6	13,502	19.9	32,467	47.7	1,845	2.7	34,866	51.3

Vaccine administration was associated with a markedly increased rate of allergic reactions for dogs on ProHeart 6 as well as for dogs on monthly heartworm preventative (Table 4.4.2.1-1). The rate of allergic reactions per 10,000 days at risk was similarly increased for vaccinated dogs compared with dogs receiving any one of the heartworm preventative drugs or those receiving no heartworm drug. Unlike liver-related AEs, allergic reactions occurred more commonly during days 0 to 2 following an encounter of interest.

There was no apparent association of immune-mediated or cardiovascular events with any of the heartworm preventatives or with vaccines, and the rate of these AEs was relatively low (Table 4.4.2.1-1).

The rate of mast-cell tumor, lymphosarcoma, or histiocytoma was generally < 3 AEs per 10,000 encounters (Table 4.4.2.1-4). ProHeart 6, whether administered alone or with a vaccine, was associated with a slight (~ 2 per 10,000 encounters), but higher rate of mast-cell tumors compared with administration of vaccines alone or any of the monthly heartworm preventatives. The rate of mast cell tumors per 10,000 days at risk was similarly elevated in dogs receiving ProHeart 6 compared with those receiving a vaccine or any one of the monthly heartworm preventative drugs. However, compared with dogs that had received 5 doses of ProHeart 6, there was no statistically significant difference in the age-adjusted risk of developing mast cell tumor for dogs that had received 1, 2, 3, or 4 doses of ProHeart 6 from Banfield veterinarians. That is, all of the odds ratios included 1.0. There was also no apparent dose-response relationship

between ProHeart 6 dose number and mast cell tumor risk. However, it is not known if any dogs had previously received ProHeart 6 from a non-Banfield veterinarian.

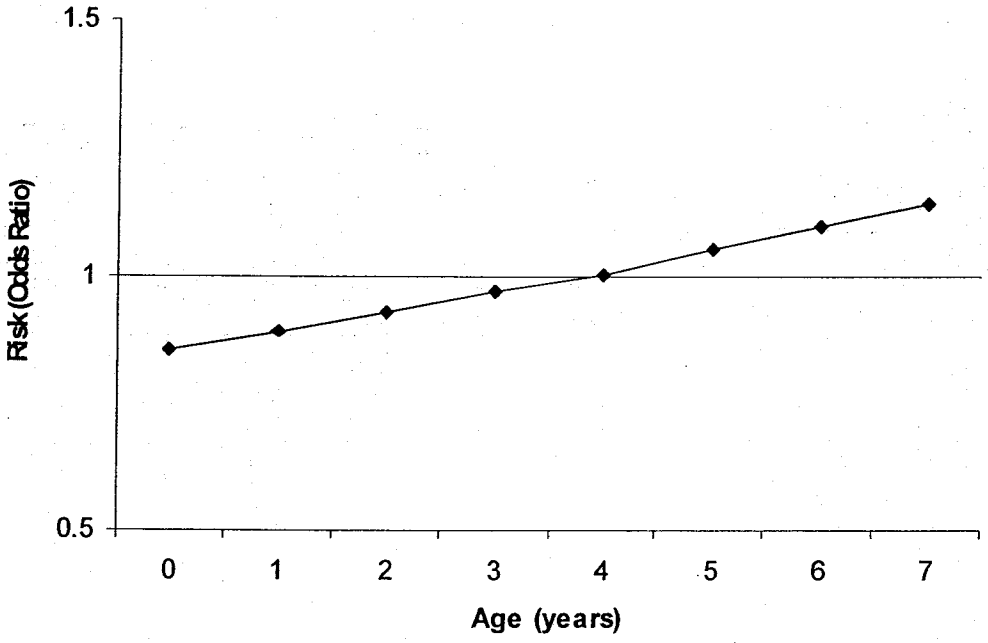
Table 4.4.2.1-4. Potential Cancer-related Adverse Events per 10,000 by Treatment Group

Treatment Category					Mast Cell Tumor		Lymphosarcoma		Histiocytoma	
PH6	HW Prev 1	HW Prev 2	Any Vaccine	N	N	Rate	N	Rate	N	Rate
				4,144,984	1,285	3.1	1,021	2.5	1,434	3.5
			Y	1,489,032	172	1.2	36	0.2	359	2.4
		Y		6,430	0	0.0	0	0.0	0	0.0
		Y	Y	11,975	0	0.0	0	0.0	2	1.7
	Y			164,951	10	0.6	12	0.7	45	2.7
	Y		Y	246,131	13	0.5	0	0.0	62	2.5
Y				252,590	54	2.1	13	0.5	89	3.5
Y			Y	483,064	90	1.9	14	0.3	101	2.1
Any				6,800,061	1,624	2.4	1,096	1.6	2,092	3.1

4.4.2.2 Multivariate Analyses

To control for potential confounding effects and to identify interactions between the variables, multivariate logistic regression models were constructed that included the following variables: heartworm preventative, vaccine, age, weight, non-steroidal anti-inflammatory (NSAID), steroid, and ProHeart 6 dose number. In the liver disease model, steroid use was associated with a 25% increased risk while ProHeart 6 was associated with a 15% reduction in risk. Each additional dose of ProHeart 6 was associated with an 8% reduction in liver disease risk. There was evidence of a strong interaction (effect modification) between age and ProHeart 6. Upon further examination of the relationship between ProHeart 6 dose number and age, the risk of liver disease increased with age, regardless of the exposure group. Using the best-fit equation generated from the logistic regression model, the relationship between the risk of liver disease associated with ProHeart 6 use was graphed as a function of age (Figure 4.4.2.2-1). ProHeart 6 administration was associated with a decreased risk of liver disease in dogs < 4 years of age, whereas there was an increased risk in dogs > 4 years of age.

Figure 4.4.2.2-1. Risk of Liver Disease by Age for ProHeart 6



Risk (1yr old) = 0.854*1.043 = 0.89; Risk(7yr old) = 0.853*1.043**7 = 1.14
Risk (age yrs) = OR(Proheart6) * OR(Proheart6*age interaction)**age

In the allergic reaction multivariate logistic regression model, ProHeart 6, Heartworm Preventative 1, vaccines, NSAIDS, and glucocorticoids, were all associated with an increased risk of allergic reactions; vaccine had the greatest affect. However, each additional dose of ProHeart 6 did not further increase the risk of allergic events.

Multivariate models for the risk of cancer indicated that ProHeart 6 was associated with a modest increase in the risk of mast cell tumor. It is not clear why NSAIDs were associated with a 423% increase in the risk of mast-cell tumor. Glucocorticoids were associated with a 182% increased risk of lymphosarcoma, probably because glucocorticoids are used as a treatment for this cancer. None of the heartworm preventatives were associated with the risk of histiocytoma.
In the multivariate model for the risk of death, only Heartworm Preventative 1 was associated with an increased risk (23%), whereas ProHeart 6 was associated with a 71% reduction in risk of

death. There was no positive relationship between the number of ProHeart 6 doses administered and risk of death (odds ratio = 0.910).

4.4.2.3 Temporal Trends in Event Rates

The rate of cancer, deaths, liver disease, and allergic reactions, were evaluated by quarter of the year for ProHeart 6 and Heartworm Preventative 1, both with and without vaccines, to determine if AEs associated with ProHeart 6 increased during the 3rd quarter of 2004, as suggested by the FDA. No evidence was found to suggest that AE rates associated with either ProHeart 6 or Heartworm Preventative 1, when used without a vaccine, increased in the 3rd quarter of 2004. In contrast, there was an increase in the 3rd quarter of 2004 in the rate of allergic events associated with either ProHeart 6 or Heartworm Preventative 1 when administered with a vaccine. Therefore, the increased rate of allergic events may be explained by 1 or more vaccines new to the market in mid-2004 that were used by Banfield veterinarians and that caused an increased rate of allergic reactions when administered with either ProHeart 6 or Heartworm Preventative 1 compared with administration of either of these heartworm preventatives without a vaccine.

4.4.3 Discussion

The results of these analyses involving almost 7 million dog encounters at Banfield clinics in the US did not reveal any clinically significant increase attributed to ProHeart 6 use in the risk of liver-related AEs, neurological disease, ocular disease, immune-mediated disease, cardiovascular disease, anaphylaxis, inflammatory bowel disease, or death, when compared with 2 commonly used monthly oral heartworm preventatives. While ProHeart 6 was associated with an increased rate of some liver-related AEs in the univariate analyses, this increased rate was not found in either the days at risk or in the multivariate analysis. In contrast, ProHeart 6, monthly heartworm preventatives, and vaccines were all associated with a clinically significant increased risk of allergic reactions in both univariate and multivariate analyses, especially during the first few days post-exposure.

The only potential AE studied that was independently associated with an increased risk following ProHeart 6 use in dogs was mast cell tumor. However, the absolute magnitude of the risk of mast-cell tumor associated with ProHeart 6 alone (2.1 events per 10,000 doses administered) or ProHeart 6 plus vaccine (1.9 events per 10,000 doses administered) was small. In addition, there was no statistically significant dose response relationship between the risk of

mast cell tumor and the cumulative number of doses of ProHeart 6 that a dog had received. Compared with the rate of mast cell tumor in dogs that had received a vaccine alone (1.2 events per 10,000 doses administered), the rate of mast cell tumor in dogs that had received ProHeart 6 plus a vaccine (1.9 events per 10,000 doses administered) does not appear to be clinically significant. There is no known mechanism that would explain how ProHeart 6 or any other heartworm preventative induces or promotes mast cell tumor in dogs, especially within 30 days of its administration.

Evidence was presented to show that the number of AEs associated with ProHeart 6 use increased in the 3rd quarter of 2004 compared with previous quarters. However, this increase primarily involved allergic reactions, was also observed in dogs that had received monthly oral heartworm preventatives, and was restricted to dogs that simultaneously received a vaccine. These findings suggest that any observed increase in adverse events associated with heartworm preventatives in the 3rd quarter of 2004, were likely due to one or more vaccines that were given with heartworm preventative drugs. Since nearly two-thirds of the heartworm preventative drugs studied were administered simultaneously or in close proximity with a vaccine, and since vaccines are generally associated with a higher rate of allergic reactions than are heartworm preventative drugs, AE reports involving administration of ProHeart 6 or other heartworm preventative drugs must be interpreted cautiously and take into account a dog's vaccine history.

4.4.4 Conclusions

In summary, the safety profile of ProHeart 6 appears similar to that of 2 commonly used monthly oral heartworm preventatives. The results of this study provide no support for the withdrawal of ProHeart 6 from the veterinary market. Lack of compliance is recognized as a common reason for lack of efficacy for both human and veterinary drugs. Since the likelihood of exposure of dogs to *Dirofiliaria immitis* infected mosquitoes is common during many months of the year, drugs are needed that prevent heartworm infection for an extended period of time, thus obviating the need for owners to remember to retreat their dog. The results of this study indicate the risks associated with ProHeart 6 use are few and similar to that for monthly oral heartworm preventatives that only offer protection from heartworm infection for a period of 30 days.

4.5 Field Efficacy

4.5.1 Overview

While the clinical efficacy of ProHeart 6 has been established in controlled laboratory and field studies, evaluation of efficacy under conditions of commercial use after launch can be complicated by many confounding factors. These include heartworm testing protocols, the age at which dogs commence a ProHeart 6 program, and timing of change from other prophylaxis to ProHeart 6.

Products for heartworm prophylaxis have been available in veterinary medicine for decades, initially as daily oral treatments; later, a range of monthly oral and topical treatments were introduced with ivermectin, selamectin, or milbemycin oxime as the active ingredient.[2,3,5] Some breeds of dogs exhibit toxic signs at doses of ivermectin and/or milbemycin oxime that are well tolerated in most other breeds, and a genetic basis for this sensitivity has been identified.[10,53,54,55,56,57,58,59] Moxidectin can be used safely in these breeds based on FDAH clinical studies.

4.5.2 Compliance

A high level of efficacy is found with these therapeutic options in controlled studies. However, under field conditions, an increasing incidence of heartworm infections in dogs in the US in the 1990s was reported with approximately 240,000 dogs testing heartworm positive in 2001. Surveys of dog owners have shown that compliance (ie, reliable administration of monthly treatments by owners) is problematical. Despite reminder systems such as calendar stickers, a survey in the US in 2000 found that >80% of participants had failed on multiple occasions to give their dogs the monthly preventative on the indicated day, and about one-third of participants completely missed the monthly dosage. Approximately one-fifth of the participants had missed giving their dogs the monthly oral heartworm preventative and then stopped altogether.[60] Another survey conducted in 2001 found that only 55% of dog-owning households in the US were using heartworm prevention, which was down from a high of 66% in 1998, despite heartworm having been diagnosed in all states.[61] Similarly, Yabsley et al. reported an increased prevalence of heartworm in shelter dogs in South Carolina in 1999-2000 (12.7%) versus 1991-1992 (8.7%).[62] Compliance with dosing schedules is a limiting factor in the control of heartworm infections in the dog population.

Several years ago, Cummings et al. demonstrated that clinic compliance failure is generally higher than predicted by individual hospitals before their records are examined.[63] A veterinary practice survey conducted by Fort Dodge veterinary technicians at Michigan State in 2004 showed a similar picture.[64] Compliance was better with ProHeart 6 than with the other heartworm preventatives studied. Average compliance was 58% for ProHeart 6 (11 clinics), 45% for Heartgard Plus (the most widely used preventative)(16 clinics), 50% for Sentinel (6 clinics), and 37% for Interceptor (3 clinics).

Moxidectin is a poor substrate for P glycoprotein compared with other macrocyclic lactones.[59,65,66] It can be used safely in ivermectin sensitive Collies. It is effective in the face of ivermectin resistance in nematodes. Additionally, recent work has demonstrated that with use of moxidectin, unlike some other compounds, animals are not more susceptible to infection with filariid parasites after product withdrawal.[67] This provides an additional safety factor, if owners are late in returning for treatment. Moxidectin has retroactive activity against *D. immitis* larval stages for 3 months, again providing a safety factor, if owners are late in returning for treatment.

4.5.3 Field Efficacy from 2001 to 2004

Field experience with ProHeart 6 in the US is limited to the time period from June 2001 to August 2004. There is a time-lag between infection and the first possible heartworm diagnosis of minimally 5 to 6 months. Therefore, the field evaluation of ProHeart 6 efficacy essentially spans the years 2002 to mid 2004. Proving "lack of efficacy" of any heartworm preventative product in client-owned dogs is inherently difficult, unless the dog is started on a prevention program at 6- to 8-weeks of age, remains on the product year-round for life and clinic records indicate the owner acquired the recommended number of doses. With orally or topically administered products, one is seldom confident the owner properly administered all of the doses. Owner compliance is greatly improved with ProHeart 6, but switching products tends to complicate the picture. To prove with reasonable confidence that a new product is completely effective, the dog must be tested prior to switching products and within 4 months later. If the dog is heartworm positive during this 4-month period, the original product failed. If the dog is positive during the next few months, it is virtually impossible to determine whether the dog was infected before or after switching products. Voluntary reports of product inefficacy to FDA are summarized in Table 4.5.3-1.

Table 4.5.3-1. Voluntary Reports of Product Inefficacy Against Larval Heartworm

Active	2001	2002	2003	2003 Market Share
IVM	16	108	13	6%
IVM+PYR	21	195	137	37%
MILB	0	0	748	21%
MILB+LUF	0	0	347	8%
SEL	16	1162	888	4%
ProHeart 6	0*	70	196	24%

* indicates year of launch

IVM = ivermectin; PYR = pyrantel; MILB = milbemycin oxime; LUF = lufenuron; SEL = selamectin

The 2003 market share information is indicative of the numbers of dogs treated and provides context when interpreting the significance of the number of reports. When ProHeart 6 is compared with the market leaders the adjusted efficacy rates for 2003 (when market share information is available) are equivalent or lower than ivermectin plus pyrantel, or milbemycin.

The overall reporting rate for ProHeart 6 is low at 1 report per 41,000 doses through marketing year 2003. Further, only 10% have a history that justifies classification as a potential efficacy concern. The majority are thought to be associated with a misunderstanding of the heartworm life cycle in relation to testing procedures and limitations. When potential dosing errors, administration errors, and mixing and storage errors are considered, the low reporting rate of failures in efficacy appears to be within acceptable parameters.

FDAH guarantees the efficacy of ProHeart 6 as a preventative for heartworm disease. This program encourages veterinarians to contact the company about potential concerns related to efficacy. When received, these reports are submitted to the FDA unfiltered. Based on unfiltered reports and doses sold, regardless of whether FDA or FDAH reports are considered, ProHeart 6 delivers a high level of efficacy under field use conditions.

4.5.4 Tuskeegee University Experience with ProHeart 6

Tuskegee University is located in Macon County, in eastern Alabama. It is a teaching hospital and unlike some universities which are predominantly referral centers, Tuskegee operates largely as a community practice. Most pets in the area receive their primary care at this hospital, so it is reflective of the population of dogs receiving preventative care, rather than specialist or tertiary care levels.

4.5.4.1 Retrospective Study: Tuskegee University School of Veterinary Medicine

The effectiveness of heartworm preventatives in this endemic area was studied during the period of 2000-2004 (unpublished data).[68] In 2001, 97.7% of the dogs on a heartworm preventative received an oral product, while 1.0% received ProHeart 6. By 2004, 82.9% received an oral product and 17.1% received ProHeart 6. During this time, the percentage of heartworm-positive dogs dropped from 14.0% (of 898) to 5.8% (of 833), and the percentage of dogs treated with Immiticide dropped from 5.2 to 3.0. More importantly, at no time was any dog receiving ProHeart 6 diagnosed as heartworm-positive, while dogs on the oral products accounted for 15.8%, 29.4%, and 50.0% of the dogs that received a first, second, or third Immiticide treatment, respectively. This study also reviewed owner compliance in a limited number of dogs that received Immiticide treatment. Of the 100 dogs studied, 61.5% of the dogs receiving ProHeart 6 were up-to-date on purchasing their heartworm product, while only 17.2% of those on oral products were compliant. Furthermore, it is known that 100% of the dogs on ProHeart 6 received their full treatment, whereas the number of oral doses administered is not known.

While this study represents a limited number of dogs, it supports the position that ProHeart 6 is highly effective in preventing heartworm infection, and along with increased owner compliance, has led to a decrease in the number of dogs requiring Immiticide treatment.

These results indicate that ProHeart 6 introduction into the canine heartworm preventative market is helping to achieve the desired goals. By overcoming the problems with owner compliance with monthly dosing, ProHeart 6 not only protects the individual dog to which it is administered, but also provides the veterinary professional with an important medicine to reduce the prevalence of heartworm in the canine population.

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6.0 APPENDICES

APPENDIX 6.1

MOXIDECTIN OVERVIEW

Pharmacology – Mechanism of Action

The mechanism of action of moxidectin is multifaceted and continues to be evaluated in laboratory studies. Moxidectin has been shown to have activity at the γ-aminobutyric acid (GABA)-A receptor-chloride channel complex resulting in an influx of chloride ions and hyperpolarization of cell membranes[1]. This hyperpolarization causes the nerve fibers to be less excitatory and results in paralysis and death of the parasitic organism. The specificity of moxidectin for the parasite versus the mammalian host results from 1) this compound having low affinity for mammalian GABA-gated chloride channels[2], and 2) the observation that GABA-containing neurons and receptors are found in mammals in the central nervous system, whereas in arthropods and nematodes these are found in the neuromuscular junctions of the peripheral nervous system and thus are more accessible to a blood-borne therapeutic. Another proposed mechanism of action for moxidectin is through activity at glutamate-gated chloride ion channels also resulting in paralysis and death of the organisms[3,4].

In dogs, the approved, oral monthly dosage of moxidectin for prevention of heartworm is 3 μg/kg; the approved subcutaneous (sc) dosage of moxidectin as ProHeart 6 is 0.17 mg/kg administered every 6 months.

Pharmacokinetics and Drug Metabolism

A series of studies was conducted in various animal species to characterize the absorption, distribution, metabolism, and excretion of moxidectin after oral administration. In rats, moxidectin was absorbed at a moderate rate, with a mean time to peak concentration (t_{max}) of 4.8 hours[5]. The bioavailability of moxidectin was moderate at 19% and the apparent terminal half-life ($t_{1/2}$) was long (22.9 to 44.6 hours). After intravenous (IV) administration in rats, the clearance of moxidectin was low and the steady-state volume of distribution (Vd_{ss}) was high, indicating that the compound is widely distributed to tissues. In beagle dogs after an oral dose of 90 μg/kg moxidectin in tablet form, the peak concentration (C_{max}) was 29.8 ng/mL with a t_{max} of

8 hours and a serum half-life of 8.1 days[6]. A single sc injection of the approved dosage of 0.17 mg/kg moxidectin as ProHeart 6 to beagle dogs resulted in a serum C_{max} of 5.1 ng/mL, a t_{max} of 7 to10 days, an $AUC_{0-\infty}$ of 217 ng•day/mL, and a half-life of approximately 35 days[6]. Moxidectin did not accumulate in the serum of dogs after injection with ProHeart 6 once every 6 months for a total of 6 injections[6]. A recent study of the administration of moxidectin once in the diet to female dogs at 45 ppm (corresponding to approximately 1 mg/kg as used in the 1-year toxicology study) resulted in a Cmax, $AUC_{0-\infty}$, and half-life values of 290 ng/mL, 678 ng•day/mL and 8.3 days, respectively. Administration in the diet at this same level for 21 days to dogs resulted in a plasma concentration of 278 ng/mL approximately 24 hours after the previous feeding (ie, trough level). The previous 2 ongoing diet pharmacokinetic studies in the dog, and an ongoing 28-day pharmacokinetic study in rats by the diet route were initiated because of FDA concerns regarding the safety of ProHeart 6, and to document the high degree of systemic exposure to moxidectin achieved in the toxicology studies conducted by the diet route.

After oral administration in rats, the major site of moxidectin distribution was fat[5]. The $t_{1/2}$ in fat was 11.5 days. Moxidectin represented the major component of total radioactivity in tissues and feces, and was primarily eliminated through feces (60% to 91% of the recovered dose over 7 days)[5]. Studies in other species such as cattle, sheep and horses have confirmed the distribution of moxidectin primarily to fat and the fecal route of excretion[7]. Six (6) metabolites were isolated from rat liver and fecal samples, none of which accounted for more than 10% of the radioactivity in tissue samples collected from animals 7 days after dosing[5]. Therefore, these metabolites are not of toxicologic concern because of the low levels observed. Similarly limited metabolism was noted in cattle, sheep and horses[7] and in rat and human liver microsomes[8] where the metabolites were characterized as hydroxylations at various positions.

In human liver microsomes, there was no significant inhibition of selected cytochrome P450 (CYP) enzyme activities (CYP2A6, CYP2C8, CYP2C19, CYP2D6, and CYP3A4) at the highest substrate concentration used (100 μM)[9]. Human CYP enzymes were used in this study since they are the best characterized. Based on plasma concentrations at efficacious doses and the high substrate concentrations, clinical metabolic drug-drug interactions for all the CYPs tested are unlikely to occur.

P-glycoproteins (P-gps) are transmembrane proteins which transport a wide variety of endogenous and exogenous molecules across cell membranes. Moxidectin, as do other macrocyclic lactones, acts as a substrate for P-gps[10]. This mechanism has been found to be of clinical importance in the development of nematode resistance to ivermectin and plays a significant role in breed sensitivity[11]. A mutation in the P-gp gene of ivermectin-sensitive Collie dogs has been shown to be responsible for ivermectin-induced CNS toxicity[12]. Moxidectin, however, was well-tolerated by these ivermectin-sensitive dogs. Moxidectin transport, therefore, is less dependent on P-gp and subsequent toxicity is less likely to be altered by factors which alter P-gp activity.

Toxicology

The toxicologic profile of moxidectin administered by the oral route has been well established. This profile is relevant to other routes of administration because of limited metabolism of moxidectin in the body and an understanding of its pharmacokinetics by different routes of administration. The toxicologic program for moxidectin was reviewed during the 45th meeting of the Joint Expert Committee on Food Additives[13] and was subsequently published[7]. In addition, this toxicology program was deemed sufficient by regulatory authorities to proceed with Phase 1 trials of oral moxidectin in normal, human volunteers in preparation for efficacy studies in people in countries where onchocerciasis is endemic. The toxicology studies were conducted in accordance with Good Laboratory Practice (GLP) regulations.

- **In Vitro Side-Effect Profiling**

Moxidectin and moxidectin microspheres (as present in ProHeart 6) were recently tested in vitro for binding activity at 64 different biological receptors[14], based on some of the safety concerns raised by the FDA. This assay is commonly used in drug discovery and development to identify any ancillary pharmacologic activities of a molecule which may result in undesirable biological effects. A final concentration of 10 ng/mL moxidectin was tested, which is approximately two-fold the average C_{max} value in serum of dogs after a subcutaneous injection of ProHeart 6 at the clinical dosage of 0.17 mg/kg. The receptors tested included those for neurotransmitters and neurotransmitter-related receptors, ion channels, steroids, second messengers, prostaglandins, growth factors/hormones, brain/gut peptides and enzymes. Moxidectin in either form did not significantly inhibit the binding of appropriate radio-ligands to these receptors, indicating a lack of binding activity for moxidectin. These results are consistent with the absence of undesirable pharmacologic and toxic effects of moxidectin in animal studies at plasma levels many fold those required for efficacy.

Single-Dose Studies

Single-dose toxicology studies of moxidectin were conducted to assess effects after a single administration of large doses in the event of accidental overdose and to assist in selection of dose levels for subsequent repeat-dose toxicology studies. In single-dose toxicity studies of mice and rats given moxidectin orally, the median lethal dosage (LD_{50}) values were 118 mg/kg in male mice[15], 42 to 78 mg/kg in female mice[16,17], and 122 and 97 mg/kg in male and female rats[18], respectively. After a single sc dose, LD_{50} values were 285 and 247 mg/kg in male and female mice[19], respectively, and > 640 mg/kg in rats[20]. Common clinical signs in these studies were decreased activity, tremors, and prostration. The decreased toxicity with sc dosing is likely the result of a lower C_{max} and daily exposure, albeit of longer duration, as compared to oral gavage dosing. These studies demonstrate a large margin of safety for ProHeart 6 in which the approved sc dose in the dog is 0.17 mg moxidectin/kg, less than 3700-fold the lethal sc dose in the rat. Field results from the accidental and sometimes intentional overexposure of dogs orally to moxidectin likewise demonstrate a large margin of safety. Oral overdoses occur when a product intended for use in horses is administered to dogs. In these cases, the dogs can receive up to a 63-fold higher dose orally (ie, 10.7 mg/kg) than the 0.17 mg moxidectin/kg when given sc as ProHeart 6, but in most cases the actual dose is not known. From 1997 to 2004, FDAH received approximately 250 such cases. In all cases the events were characterized by a wide range of neurological symptoms. In those cases where FDAH was informed, the dogs had typical hematology or serum panels. In 90% of these cases, the animals fully recovered whereas the remainder died. These cases demonstrate that neurological symptoms induced by high, oral doses of moxidectin in dogs are typically survivable without any nonneurologic toxic effects.

Repeat-Dose Studies

Repeat-dose oral (diet) toxicity was evaluated to assess more long-term consequences of repeated, daily oral exposure to moxidectin. The objective of these studies was to dose the animals high enough to identify potential toxic effects, and to include lower doses so as to assess a dose-response relationship and identify a dose without significant adverse effects (i.e., No-Observed-Adverse-Effect-Level; NOAEL).

The following studies were conducted: 4-week studies in mice, rats, and dogs; 13-week studies in rats and dogs, and a 1-year study in dogs. Moxidectin was administered in the diet providing for a continuous exposure for the duration of each study, which is a significant exaggeration of the exposure of dogs to one sc dose of 0.17 mg moxidectin/kg as ProHeart 6 every 6 months.

Evaluations consisted of mortality, clinical observations, body weight, food consumption, hematology, clinical chemistry (except mice), organ weights, and macroscopic and microscopic examinations of organs and tissues. Ophthalmic examinations and urinalysis were also included in the dog studies.

Mice

In the 4-week study in mice, doses in the diet were 33.7, 75, 100, 125, and 150 ppm[21]. Mortality occurred at ≥ 75 ppm. Microscopic examination did not reveal the cause of death in these animals. Clinical observations were tremors, hypersensitivity to touch, and urine-stained fur at ≥ 75 ppm. Body weights and body-weight gains were decreased at ≥ 100 ppm. There were no other compound-related effects. Based on mortality, the no-observed-adverse-effect-level (NOAEL) was 33.7 ppm (6.9 mg/kg/day).

Rats

In the 4-week study in rats, doses in the diet were 100, 200, 400, and 600 ppm[22]. Mortality occurred at ≥ 200 ppm and resulted from anorexia based on microscopic examination. Clinical observations included ataxia, tremors, salivation, piloerection, and diuresis at ≥ 200 ppm, as well as decreased body weight, body-weight gain, and food consumption. There were no other compound-related findings in rats that survived the study. Based on mortality, the NOAEL was 100 ppm (12.2 mg/kg/day).

In the 90-day study in rats at diet doses of 25, 50, 100 and 150 ppm, mortality occurred for 3 females at the highest dose, 150 ppm[23]. Microscopic examination did not reveal the cause of death for these animals. Clinical observations included hypersensitivity to touch at 100 ppm, and lethargy, anorexia, aggressive behavior, loss of righting reflex, ataxia, tremors, and urine-stained coat at 150 ppm. Body weight and body-weight gain were decreased in males at 100 ppm or more and in females at 150 ppm. Food consumption was decreased in males and females at 150 ppm. Adrenal gland and kidney weights were increased in females at ≥ 100 ppm, but there were no compound-related macroscopic or microscopic findings in these or any other organs or tissues. The NOAEL was 50 ppm (3.9 mg/kg/day).

Dogs

In the repeat-dose toxicity studies in beagle dogs, ophthalmic examinations and urinalysis were also included for evaluation of potential toxic effects.

In the 4-week study, there was no mortality at doses in the diet of 20, 80 and 160 ppm[24]. The dose of 160 ppm was toxic, based on debilitating clinical observations, and the dose was reduced to 50 ppm. Clinical observations included tremors, languid appearance, ataxia, emesis, and mydriasis at ≥ 80 ppm. Testes weights were decreased at ≥ 80 ppm. Microscopic findings were decreased spermatogenic activity at ≥ 80 ppm and decreased colloid in the thyroid gland in males at 80 ppm. These findings may have been related to variations in age of maturation (study dogs were 5 to 6 months old at study termination) and were not seen in the 1-year toxicity study in dogs. Based on the testicular findings, the NOAEL in this 4-week study was 20 ppm (0.8 mg/kg/day).

In the 90-day toxicity study in dogs at diet doses of 10, 30 and 60 ppm, there was no mortality and clinical observations included lacrimation at ≥ 10 ppm, languid appearance and tremors at 10 and 60 ppm, thin appearance at ≥ 30 ppm, and slight salivation and slight ataxia at 60 ppm[25]. A 60 ppm, alanine aminotransferase (ALT) was increased in 1 male and 1 female, and serum alkaline phosphatase was increased in 3 males and 3 females compared with pretreatment and/or control values (increases were small in magnitude and not toxicologically significant). However, there were no compound-related macroscopic or microscopic changes in the liver or any other tissues or organs. Based on the absence of toxicologically significant findings at any tested concentration, the NOAEL in this 90-day study was 60 ppm (1.6 mg/kg/day).
In the 1-year toxicity study in dogs at diet doses of 10, 20 and 45 ppm, there was no mortality[26]. Decreased ovarian weights were observed at 45 ppm; however, the absolute weights were within reference or historic control ranges and the decreases were not considered to be biologically important. There were no compound-related effects on clinical chemistry or hematology parameters, and no compound-related microscopic findings. Based on the absence of toxicologically significant findings at any tested concentration, the NOAEL in this study was 45 ppm (1.1 mg/kg/day).

Interim analysis at day 21 in an ongoing 28-day diet pharmacokinetic study of moxidectin in dogs at a concentration of 45 ppm in feed (approximately 1 mg/kg, the NOAEL in the 1-year dog toxicity study) revealed a serum concentration of 278.5 ng/mL 24 hours after the preceding dose in feed (ie, trough level). This concentration is not yet at steady state, but would correspond to a daily AUC of 278.5 ng•d/mL which would represent the minimal daily exposure to moxidectin

for most of the duration of the 1-year toxicology study in dogs, or an AUC of 50826 ng.day/mL over a 6-month period, the retreatment interval for ProHeart 6.. This value is approximately 234-fold the AUC $_{0-\infty}$ (217 ng•d/mL) observed for moxidectin after a single sc dose in dogs of ProHeart 6.

Carcinogenicity Studies

Mice

A 2-year carcinogenicity study was conducted in male and female mice at diet doses of 15, 30, and 60 ppm (lowered to 50 ppm due to high mortality at week 9)[27]. Mortality was increased in females at doses of 60/50 ppm during the last 13 weeks of the study. There were no compound-related findings in hematology values, organ weights, or at macroscopic or microscopic examination. There was no evidence of moxidectin-related target-organ toxicity or tumorigenicity.

Rats

A 2-year carcinogenicity study was conducted in male and female rats at diet doses of 15, 60 and 120 ppm (lowered to 100 ppm due to high mortality in females at week 8)[28]. There were no compound-related findings for hematology values, organ weights or at macroscopic or microscopic examination; there was no evidence of moxidectin-related target-organ toxicity or tumorigenicity.

Reproductive and Developmental Toxicity Studies

Reproductive toxicity was evaluated in developmental studies of rats[29] and rabbits[30] dosed orally by gavage and in pilot[31] and definitive[32] multigeneration diet studies. Maternal toxicity was evident at $\geq$10 mg/kg/day in the rat developmental study, 125 ppm (calculated dosage averaging between 10.9 and 12.0 mg/kg/day) in the rat pilot multigeneration study, and at $\geq$5 mg/kg/day in the rabbit developmental study; the toxicity consisted primarily of decreased body weight and/or food consumption. At maternally toxic dosages ($\geq$ 10 mg/kg/day) in the rat developmental study only, there were statistically significant increases in the number of fetuses with malformations and/or variations, largely reflective of increases in cleft palate and reversible delays in ossification. There was decreased fetal and/or pup survival at 10 mg/kg/day in the rabbit developmental study and at doses of $\geq$10 ppm (calculated maternal dosage of $\geq$ 0.8 mg/kg/day) in the rat pilot 1-generation and 3-generation studies. The reproductive NOAELs were

5 mg/kg/day in both the rat and rabbit developmental studies and was 5 ppm (0.4 mg/kg/day) in the rat 3-generation study. Therefore, moxidectin was not considered teratogenic in these species. This conclusion is consistent with that of the FDA Center for Veterinary Medicine, which concluded that moxidectin is neither a selective developmental toxicant nor a teratogen in rats or rabbits.

Genotoxicity Studies

Moxidectin was tested for genotoxicity in 4 in vitro and 2 in vivo universally recognized test systems. These assays assessed the ability of moxidectin to caus gene mutations, chromosome damage, and increased DNA repair which may be related to the carcinogenic potential of the test article. Moxidectin was negative in the following assays for genotoxicity: bacterial reverse mutation assay in *Salmonella typhimurium* (strains TA98, TA100, TA1535, TA1537, and TA1538) and *Escherichia coli* (WP-2 uvrA-)[33]; mammalian cell mouse lymphoma (L5178Y thymidine kinase) assay[34]; chromosome aberration assay in Chinese hamster ovary cells[35]; unscheduled DNA synthesis assay in primary rat hepatocytes[36]; in vivo micronucleus assay in mouse bone marrow cells[37]; and the in vivo chromosome aberration assay in rat bone marrow cells[38]. The in vivo studies were conducted using the oral route of administration. The results from these studies indicate that moxidectin is not a genotoxic compound.

Experience with Oral Moxidectin in Human Volunteers

A study in healthy, male volunteers was conducted to assess the pharmacokinetics and safety of moxidectin given orally as part of the development of this compound for treatment of onchocerciasis in humans[39]. A total of 37 subjects in this study were treated with single doses of 3 mg to 36 mg (approximately 50 μg/kg to 600 μg/kg). The $t_{1/2}$ ranged from 19.9 to 37.4 days, the C_{max} at 36 mg was 296 ng/mL, and the distribution of moxidectin was extensive, as indicated by a large apparent volume of distribution. The C_{max} observed for humans dosed orally with 36 mg moxidectin was 59-fold the C_{max} observed in dogs dosed sc with the clinical dosage of 0.17 mg/kg moxidectin as ProHeart 6, and exposure (based on AUC) was approximately 6-fold the exposure in dogs administered ProHeart 6.

There was no significant relationship between the overall number of adverse events and the dose of moxidectin administered. Safety assessments indicated that moxidectin was safe and well tolerated, with a slightly higher incidence of transient, mild, and moderate central nervous system adverse events (dizziness and somnolence) as compared to placebo. There were no clinically significant changes in vital signs, clinical chemistries, physical examinations or

electrocardiograms. The conclusion was that moxidectin was safe and well tolerated in humans after single, oral doses of 3 mg to 36 mg.

Conclusions

Moxidectin is a potent antiparasitic therapeutic that acts to paralyze susceptible organisms through activity at GABA- and glutamate-gated chloride ion channels. Moxidectin has a long half-life, a high volume of distribution (predominantly distributing to fat), shows little metabolism, and is excreted primarily in the feces. These characteristics of moxidectin appear constant across the mammalian species studied, including humans. In single-dose toxicity studies, the lethal sc dose in rats was more than 3700-fold the efficacious dose of moxidectin given as ProHeart 6 to dogs. In repeat-dose diet toxicity studies in mice,rats, and dogs of durations up to 2-years in mice and rats, and 1-year in dogs, no target organs of toxicity were identified. There were no significant adverse histologic or biochemical effects on any organ system including the cardiovascular, gastrointestinal, hepatobiliary, genitourinary and central nervous systems. There were no proliferative lesions identified in any tissue which may signal the development of neoplasia, and no increase in tumors in mice or rats. The toxicity of moxidectin manifested itself at high doses in clinical signs such as lethargy, ataxia, tremors and mortality (rodents only) with concomitant decreases in food consumption and body weight. Such clinical signs of hypoexcitation are expected and are consistent with an exaggerated pharmacologic effect of moxidectin mediated via the GABA-receptor. Moxidectin was not genotoxic or carcinogenic, and was without reproductive or developmental toxicity. The NOAEL in the rat 2-year study was 12.2 mg/kg/day; the NOAEL in the dog 1-year study was 1.1 mg/kg/day.

Based on ongoing pharmacokinetic studies in the dog, a single dose of moxidectin in the diet at approximately 1 mg/kg (NOAEL in the 1-year dog study), when extrapolated to infinity, results in an overall exposure over 3-fold that of a single SC dose of ProHeart 6. Repeated dosing at this level resulted in an estimated daily exposure at least 1.3-fold the total exposure observed after a single SC dose in dogs of ProHeart 6 (AUC_{1day} of 278.5 versus $AUC_{0-\infty}$ of 217 ng•days/mL, respectively). The total exposure over the duration of the 1-year study, therefore, would be approximately 365 times the daily AUC, or more than 450-fold a single SC dose of ProHeart 6. Moxidectin was also found safe in a human clinical trial after a single oral dose of

36 mg, which resulted in a C_{max} and AUC approximately 59- and 6-fold, respectively, that was observed in dogs dosed SC with the clinical dosage of 0.17 mg/kg as ProHeart 6.

Based on the toxicology studies of moxidectin where the dose, dosing duration, and resulting systemic exposure to moxidectin were significantly exaggerated without inducing significant adverse effects, the single, clinical sc administration of 0.17 mg moxidectin/kg as ProHeart 6 to dogs would be predicted to be without significant adverse effects.

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34 Pant KJ. Evaluation of AC 301423 in the L5178Y TK+/- mouse lymphoma mutagenesis assay with colony size evaluation in the presence and absence of induced rat liver S-9 with a confirmatory study. Study conducted by SITEK Research Laboratories, Rockville, MD. SITEK Study Number 0504-2400. American Cyanamid Protocol Number 9971-98-147, 1999.

35 Xu J. Test for chemical induction of chromosome aberration in cultured Chinese hamster ovary (CHO) cells with and without metabolic activation with AC 301423. Study conducted by SITEK Research Laboratories, Rockville, MD. SITEK Study Number 0504-3110. American Cyanamid Study Number 971-98-131, 1999.

36 Curren RD. Unscheduled DNA synthesis in primary rat hepatocytes with AC 301,423. Study conducted by Microbiological Associates, Inc., Rockville, MD. Project ID T9090.380025. American Cyanamid Protocol Number 971-89-176, 1990.

37 Xu J. In vivo test for chemical induction of micronucleated polychromatic erythrocytes in mouse bone marrow cells. Study conducted by SITEK Research Laboratories, Rockville, MD. SITEK Study Number 0504-1521. American Cyanamid Study Number 971-98-132, 1999.

38 Sharma RK. Evaluation of moxidectin in the in vivo chromosome aberration assay in rat bone marrow cells. American Cyanamid Study Number 89-14-002, 1990.

39 Cotreau MM, Warren S, Ryan JL, Fleckenstein L, Vanapalli S, Brown KR, Rock D, Chen C-Y, Schwertschlag US. The antiparasitic moxidectin: Safety, tolerability and pharmacokinetics in humans. *J Clinical Pharmacology* 2003;43:1108-1115.

APPENDIX 6.2

BIOGRAPHICAL SKETCH

Name:	Title:	Birthdate:
Alexander de Lahunta	James Law Professor of Anatomy	3 December 1932

Education:

Cornell University	DVM	1958	Veterinary Medicine
Cornell University	PhD	1963	Veterinary Anatomy

Professional Experience:
Veterinary Practice 1958-1960: Concord N.H. Faculty member in Department of Anatomy, New York State College of Veterinary Medicine, Cornell University 1960 to date; Chairman - Department of Clinical Sciences 1977-1986; Chairman - Department of Anatomy 1986 to 1991; Consultant in clinical neurology to Teaching Hospital 1963 to date; Diplomat - Neurology Specialty - American College of Veterinary Internal Medicine.
James Law Professor of Anatomy, 1992.

Awards:
National Teaching Award - Basic Sciences: Student AVMA 1991
Norden Teaching Award - 1973, 1984, 1992, 2001
ACVIM Dr. Robert W. Kirk Distinguished Service Award, 2000
Honorary Member - American College of Veterinary Pathologists, 2002

Research:
Correlation of clinical neurological signs with specific anatomic locations of lesions in nervous system.
Establishment of reliable data to differentiate between the various diseases that affect the nervous system in the different species of domestic animal.
Recognize and publish new diseases of the nervous system.
Recognize diseases of the nervous system of domestic animals that are models for similar diseases in man.

Textbook Publications:
Evans, H.E. & de Lahunta, A. - Miller's Guide to the Dissection of the Dog, 5th edition. 2000, W.B. Saunders Co., Phil.

de Lahunta, A. - Veterinary Neuroanatomy and Clinical Neurology, 2nd. edition. 1983, W.B. Saunders Co., Phil.

Noden, D. and A. de Lahunta - The Embryology of Domestic Animals, Developmental Mechanisms and Malformations 1985, Williams & Wilkins, Baltimore.

de Lahunta, A. and R.E. Habel - Applied Veterinary Anatomy 1985, W.B. Saunders, Phil.

Summers, B.A., J.F. Cummings and A. de Lahunta – Veterinary Neuropathology 1995, Mosby, St. Louis

260 Publications in refereed journals.

January 3, 2005

Teaching Responsibilities:

Block I: Lectures, Tutor, Gross dissection labs, Radiology labs. (Sept – Nov)

Vet Med 521: Neuroanatomy and Clinical Neurology
Entirely my responsibility, first 8 weeks of spring semester.

Block V: Applied Anatomy taught throughout most of Block V throughout the latter half of the spring semester and all of the fall semester.
Neuropathology – 12 hours, last 3 weeks of fall semester.

Vet Med 606: Advanced Neurology tanght twice, in both of the last two quarters of the spring semester.

Neuropathology Seminar: One hour per week all year. Primarily for pathology residents.

Clinical Neurology Rounds: 12 hours per week all year.

Consultant to the Teaching Hospital for neurology patients:
Examine patients daily, all year long. This is done early each morning and often attended by interested students.

I regularly receive nervous tissue from practitioners and pathologists for study or consultations and videotapes from practitioners and owners for study and diagnosis. My lab is set up for blocking these nervous tissues and photographing the lesions. Tissue sections are cut and stained by the histology lab in the pathology section.

I study these sections and report results to the contributor. This is a valuable source of material for the teaching program both at the DVM and resident level and has led to the discovery of many new disorders.

APPENDIX 6.3

REBAR, ALAN H., DVM, PhD, DACVP 1/05

EDUCATION

DVM, 1973, Purdue University
Ph.D. (Clinical Pathology), 1975, Purdue University

Internship/Residency (Pathology), 1976, Purdue University
Diplomate – American College of Veterinary Pathologists (Clinical Pathology), 1978

EMPLOYMENT

July 1996 – Present	Dean, School of Veterinary Medicine, Purdue University
July 1989 – June 1996	Associate Dean for Research, School of Veterinary Medicine, Purdue University
July 1995 – June 1996	Head, Veterinary Pathobiology, School of Veterinary Medicine, Purdue University
July 1993 – June 1995	Interim Department Head, Veterinary Pathobiology, School of Veterinary Medicine, Purdue University,
July 1987 – June 1995	Acting Director of Continuing Education, School of Veterinary Medicine, Purdue University
July 1987 – July 1989	Director of Research Programs Development, School of Veterinary Medicine, Purdue University
1986 – Present	Director, Veterinary Cytology Resource Center, Purdue University,
July 1983 – Present	Professor of Clinical Pathology, School of Veterinary Medicine, Purdue University
July 1979 – July 1987	Co-Director of Clinical Pathology Laboratory, School of Veterinary Medicine, Purdue University
July 1979 – June 1983	Associate Professor of Clinical Pathology, School of Veterinary Medicine, Purdue University
Sept. 1977 – July 1979	Clinical Pathologist, Lovelace Inhalation Toxicology Research Institute, Albuquerque, New Mexico
Jan. 1976 – Aug. 1977	Director of Clinical Pathology Laboratory, School of Veterinary Medicine, Purdue University

Jan. 1976 – Aug. 1977	Assistant Professor of Clinical Pathology, School of Veterinary Medicine, Purdue University
Sept. 1974 – Dec. 1975	NIH Postdoctoral Fellow. (Ultrastructural studies on cobalt and isoproterenol induced cardiomyopathy in swine.) School of Veterinary Medicine, Purdue University,
Sept. 1972 – Aug. 1974	Graduate Instructor, Veterinary Pathology, School of Veterinary Medicine, Purdue University
May 1973 – Sept. 1973	Staff Veterinarian, Colonial Oaks Animal Hospital, Gainesville, Florida

HONORS

Indiana Veterinarian of the Year Award. Presented by the Indiana Veterinary Medical Association, 2002.

The Waltham Award given in recognition of outstanding activities or contributions by a veterinarian that have resulted in the improvement of the well-being companion animals in the international veterinary community. Presented by the American Animal Hospital Association, 2001.

The Gaines Cycle Fido Award for outstanding contributions to small animal medicine and surgery. Presented by the American Animal Hospital Association, 1994.

Distinguished Alumnus Award, School of Veterinary Medicine, Purdue University, 1990.

REPRESENTATIVE PUBLICATIONS (more than 115 overall)

1. Herbert, R.A.,Stegelmeier, B.S., Gillett, **Rebar, A.H.**, Carlton, W.W., Singh, G., and Hahn, F.F.: *Plutonium-induced proliferative lesions and pulmonary epithelial neoplasms in the rat: immunohistochemical and ultrastructural evidence for their origin from type II pneumocytes.* Vet Pathol 31(3):366-374, 1994.
2. Stegelmeier, B.L., Gillett, N.A., Hahn, F.F., **Rebar, A.H.**, and Kelly, G.: *Expression of transforming growth factor alpha and epidermal growth factor receptor in rat lung neoplasms induced by plutonium-239.* Radiat-Res, Nov, 140(2):191-8, 1994.
3. Lipscomb, T.P., Harris, R.K., **Rebar, A.H.**, Ballachey, B.E., and Haebler, R.J.: *Pathology of Sea Otters.* In: Marine Mammals and the Exxon Valdez. Academic Press, San Diego, CA. 1994.
4. Reagan, W.J. and **Rebar, A.H.**, *Platelet Dysfunction.* In: Textbook of Veterinary Internal Medicine. W.B. Saunders Company, Philadelphia, PA. 1994.
5. Skowronek, L.A., LaFranco, L., Stone-Marschat, M.A., Burrage, T.G., **Rebar, A.H.**, and Laegreid, W.W.. *Clinical Pathology and Hemostatic Abnormalities in Experimental African Horsesickness.* Vet Pathol 32:112-121, 1995.

6. **Rebar, A.H.,** Lipscomb, T.P., Harris, R.K., and Ballachey, B.E. *Clinical and Clinical Laboratory Correlates in Sea Otters Dying Acutely in Rehabilitation Centers Following the Exxon Valdez Oil Spill.* Vet Pathol 32(4):346-350, 1995.
7. **Rebar, A.H.**, Metzger, F.: The Veterinary CE Advisor--*Clinical pathology for small-animal practitioners: Interpreting the hemogram.* Veterinary Medicine 90(6) (Suppl.):1-12, 1995.
8. Snipes, M.B., Barnett, Harkema, J.R., Hotchkiss, J.A., **Rebar, A.H.**, Reddick, L.J.: *Specific Biological Effects of an Anti-Rat PMN Antiserum Intraperitoneally Injected into F344/N Rats.* Vet Clin Pathol 24(1), 11-17. 1995.
9. **Rebar, A. H.**, Thrall, M. A.: *Blood Film Evaluation: Cytology of Circulating Blood Cells.* Vet Tech 16(9), 578-586, 607, 1995.
10. **Rebar, A.H.**, Metzger, F.: The Veterinary CE Advisor--*Clinical Pathology for Small-animal Practitioners: Profiling the Urinary System.* Vet Med 90(11) (Suppl.):1-16; 1995.
11. Christian, J.A., **Rebar, A.H.**, Boon, G.D., Low, P.S. *Methodological considerations for the use of canine in vivo aged biotinylated erythrocytes to study RBC senescence.* Experimental Hematology 24(1):82-8, 1996 Jan.
12. **Rebar, A.H.**, Metzger, , F.: The Veterinary CE Advisor--*Clinical Pathology for Small-animal Practitioners: Laboratory Evaluation of the Liver.* Vet Med 91(9) (Suppl.):1-12;1996
13. **Rebar, A.H.**, Section Editor, *Hematology and Immunology.* In: The 5 Minute Veterinary Consult, Tilley, L., and Smith, F., ed., Williams and Wilkins, Media, PA. 1997.
14. **Rebar, A.H.,** *Metabolic Anemias (Anemias with Spiculated Red Cells).* In: The 5 Minute Veterinary Consult, Tilley, L., and Smith, F., ed., Williams and Wilkins, Media, PA. 1997.
15. Christian, J.A., **Rebar, A.H.**, *Anemia, Regenerative.* In: The 5 Minute Veterinary Consult, Tilley, L., and Smith, F., ed., Williams and Wilkins, Media, PA. 1997.
16. **Rebar, A.H.**, *Anemia, Nuclear Maturation Defect (Anemia, Megaloblastic).* In: The 5 Minute Veterinary Consult, Tilly, L., and Smith, F., ed., Williams and Wilkins, Media, PA. 1997.
17. **Rebar, A.H.**, *Hemogram Interpretation for Dogs and Cats,* Ralston Purina Company, St. Louis, MO, The Gloyd Group, Inc., 1998.
18. **Rebar, A.H.**, Boon, G.D., and Christian, J.A., *Biochemical Profiling in the Dog and Cat. A Case Oriented Approach.* Ralston Purina Company, St. Louis, MO, The Gloyd Group, Inc. 1999.
19. **Rebar, A.H.**, MacWilliams, P.S., Feldman, B.F., Metzger, F.L., Pollock, R.V.H., Roche, J., *A Guide to Hematology in Dogs and Cats.* Teton NewMedia, Jackson, WY. 2002.
20. Giger, U., **Rebar, A.H.**, Feldman, B.F., *Using White Blood Cell Information More Effectively: A Logical Approach* as part of Hematology Symposium. A Supplement to Compendium on Continuing Education for the Practicing Veterinarian, Vol. 25, No. 9(A), September 2003.
21. Thrall, M.A., Baker, D.C., Campbell, T.W., DeNicola, D., Fettman, M.J., Lassen, E.D., **Rebar, A.H.**, Weiser, G., *Hematology and Clinical Chemistry*, Lippincott Williams & Wilkins, Baltimore, MD, 2004.
22. Thrall, M.A., Baker, D.C., Campbell, T.W., DeNicola, D., Fettman, M.J., Lassen, E.D., **Rebar, A.H.**, Weiser, G., *Clinical Case Presentations for Veterinary Heamtology and Clinical Chemistry*, Lippincott Williams & Wilkins, Baltimore, MD, 2005.

APPENDIX 6.4

GRANT NUMBER: _____

BIOGRAPHICAL SKETCH

Provide the following information for all ***new*** key personnel.
Copy this page for each person.

NAME	POSITION TITLE
Philip J. Bergman, DVM, MS, PhD, DACVIM	Head, Donaldson-Atwood Cancer Clinic

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	YEAR(s)	FIELD OF STUDY
University of Arizona - Tucson, AZ		Undergrad	Microbiology
Colorado State University - Fort Collins, CO	DVM, BS	1986-1990	Veterinary Medicine
Kansas State University - Manhattan, KS		1990-1991	Small Animal Intern
Colorado State University - Fort Collins, CO	MS	1991-1994	Oncology Residency
M.D. Anderson Cancer Center - Houston, TX	PhD	1994-1999	Cancer Biology

Professional Positions:

1990-1991	Rotating Small Animal Intern, Kansas State University, Manhattan, KS
1990-1994	Comparative Oncology Residency, Colorado State University, Fort Collins, CO
1994-1999	Cancer Biology Fellow, M.D. Anderson Cancer Center, Houston, TX
1994-1997	Staff Oncologist, Gulf Coast Veterinary Specialists, Houston, TX
1996-1999	American Cancer Society Physician Research Training Fellow, M.D. Anderson Cancer Center, Houston
1998-2000	Chair, ACVIM Forum, Oncology Subspecialty
1999-Present	Head, Donaldson-Atwood Cancer Clinic, The Animal Medical Center, New York, NY
2000-2002	President-Elect, Veterinary Cancer Society
2001-Present	Director, Flaherty Comparative Oncology Laboratory
2002-Present	Adjunct Associate Faculty Member, Memorial Sloan-Kettering Cancer Center & Sloan-Kettering Cancer Institute
2002-2004	President, Veterinary Cancer Society

Honors and Awards:

1989	R. Barry Prynn Memorial Scholarship. *For excellence in neurology.*
1990	AAHA Senior Student Award. *For excellence in small animal medicine and surgery.*
1993	William K. Riddell Memorial Scholarship. *For imminent success & broad impact in the biomedical research field.*
1999	R.E. "Bob" Smith Fellow, Department of Cell Biology, M.D. Anderson Cancer Center.
	AACR Symposium, Molecular Biology in Clinical Oncology. Invited Participant (Aspen, CO).
1997 & 1998	UT-Houston Graduate School of Biomedical Sciences Travel Award
1996 – 1999	American Cancer Society Physician Research Training Fellowship (PRTA #40)
	AACR Clinical Trials Symposium. Invited participant (Vail, CO)
2001	Jean Holzworth Keynote Address, Angell Memorial Animal Hospital
2001	Japanese Veterinary Cancer Society Keynote Address
2002	Adjunct Associate Faculty, Memorial Sloan-Kettering Cancer Center & Sloan-Kettering Cancer Institute
2003	World Small Animal Veterinary Association Hill's Award for Excellence in Veterinary Healthcare

Bibliography:

1. **Bergman PJ**, Withrow SJ, Straw RC, et al. Canine Infiltrative Lipoma: 16 Cases (1981-1992). *J Amer Vet Med Assoc* 1994;205:322-324.
2. **Bergman PJ**, Bruyette DS, Coyne BE, et al. Paraneoplastic Clinical Peripheral Neuropathy Associated with Canine Insulinoma. *Prog Vet Neuro* 1994;5:57-62.
3. Ogilvie GK, Moore AS, Chen C, Ciekot PA, Atwater SW, **Bergman PJ**, Walters LM. Toxicoses associated with the administration of mitoxantrone to dogs with malignant tumors: A dose escalation study. *J Amer Vet Med Assoc* 1994;205:570-573.
4. Ogilvie GK, Atwater SW, Ciekot PA, **Bergman PJ**, et al. Incidence of anaphylaxis associated with the intramuscular administration of L-asparaginase to 81 dogs with cancer: 1989-1991. *J Am Anim Hosp Assoc* 1994;30:62-65.
5. **Bergman PJ**, Ogilvie GK. Drug Resistance and Cancer Therapy. *Compend Contin Educ* 1995;17:549-558.
6. Macy DW, **Bergman PJ.** Vaccine-induced sarcomas in cats. *Feline Practice* 1995;23:24-27.
7. Gupta KP, Ward NE, Gravitt KR, **Bergman PJ**, O'Brian CA. Partial Reversal of Multidrug Resistance in Human Breast Cancer Cells by an N-myristoylated Protein Kinase C- Pseudosubstrate Peptide. *J Biol Chem* 1996;271:2102-2111.
8. **Bergman PJ**, MacEwen EG, Kurzman IL, et al. Amputation and Carboplatin for Treatment of Dogs with Osteosarcoma (48 Cases). *J Vet Intern Med* 1996;10:76-81.
9. **Bergman PJ**, Ogilvie GK, Powers BE. Monoclonal Antibody C219 Immunohistochemistry in canine Lymphoma: Predictive Ability and Sequential Analysis. *J Vet Intern Med* 1996;10:354-359.
10. **Bergman PJ**, Gravitt KR, Ward NE, Gupta KP, O'Brian CA. An N-myristoylated Protein Kinase C-Pseudosubstrate Peptide that Partially reverses Multidrug Resistance in Human Breast Cancer Cells is not a P-glycoprotein Substrate. *Cancer Chemotherapy Pharmacology* 1997;40:453-456.
11. McCaw DL, Miller MA, **Bergman PJ**, Withrow SJ, Moore AS, Knapp DW, Fowler D, Johnson JC. Vincristine therapy for mast cell tumors in dogs. *J Vet Intern Med* 1997;11:375-378.
12. **Bergman PJ**, Gravitt KR, Ward NE, Beltran P, Gupta KP, O'Brian CA. Potent induction of human colon cancer cell uptake of chemotherapeutic drugs by N-myristoylated protein kinase C-alpha (PKC-alpha) pseudosubstrate peptides through a P-glycoprotein-independent mechanism. *Inv New Drugs* 1997;15:311-318.
13. **Bergman PJ.** Etiology of feline vaccine-associated sarcomas: history and update. Vaccine-Associated Feline Sarcoma Symposium. *J Amer Vet Med Assoc* 1998;213:1424-1425.
14. **Bergman PJ.** Advances in the Treatment of Feline Vaccine-Associated Sarcomas. *Adv Small Anim Med Surg* 2000.
15. O'Brian CA, Stewart JR, Ward NE, **Bergman PJ**. Regulatory mechanisms governing protein kinase C signaling. *Electr J Pathol Histol* 2000;6:1-10.
16. Rocha TA, Mauldin GN, Patnaik,AK, **Bergman PJ**. Prognostic Factors in Dogs with Urinary Bladder Carcinoma. *J Vet Intern Med* 2000;14:486-490.
17. Kovak JR, Ludwig LL, Noone KE, **Bergman PJ**, et al. The use of thoracoscopy to diagnose pleural effusion of ambiguous etiology. *J Am Vet Med Assoc* 2002;221(7):990-994.
18. Charney SC, **Bergman PJ**, Hohenhaus AE, McKnight JA. Risk factors for sterile hemorrhagic cystitis in dogs with lymphoma receiving cyclophosphamide with or without concurrent administration of furosemide: 216 cases (1990-1996). J Am Vet Med Assoc 2003;222(10):1388-1393.
19. **Bergman PJ**, McKnight J, Novosad A, Charney S, Farrelly J, Craft D, Sadelain M, Wulderk M, Jeffers Y, Hohenhaus AE, Segal N, Gregor P, Engelhorn M, Riviere I, Houghton AN, Wolchok JD. Long term survival of dogs with advanced malignant melanoma following DNA vaccination with xenogeneic human tyrosinase: A phase I trial. Clin Cancer Res 2003;9:1284-1290.
20. **Bergman PJ**. Clinical techniques in small animal molecular oncology. Clin Tech Small Anim Pract 2003;18:88-91.
21. Simpson AM, Ludwig LL, Newman SJ, **Bergman PJ**, Hottinger HA, Patnaik AK. Canine cutaneous mast cell tumors: A prospective study of surgical margins. *J Am Vet Med Assoc* 2004;224(2):236-240.
22. Farrelly J, Denman DL, Hohenhaus AE, Patnaik AK, **Bergman PJ**. Hypofractionated radiation therapy of oral melanoma in five cats. *Vet Radiol Ultras* 2004;45(1):91-94.
23. Newman SJ, **Bergman PJ**, Williams B, Scase T, Craft D. Characterization of Spindle Cell Component of Ferret (Mustela putorius furo) Adrenal Cortical Neoplasms – Correlation to Clinical Parameters and Prognosis. *Comp & Vet Oncol* 2004;2(3):113-124.

24. Patnaik AK, Newman SJ, Scase T, Erlandson RA, Antonescu C, **Bergman PJ**. Canine hepatic neuroendocrine carcinoma: An immunohistochemical study of 10 cases. *Vet Pathol* 2005, in press.
25. Jakubiak MJ, Zenger E, Siedlecki CT, Matteucci ML, Bruskiewicz KA, Rohn DA, **Bergman PJ**. Laryngeal, laryngotracheal and tracheal masses in cats: 27 cases (1998-2003). *J Am Anim Hosp Assoc* 2005, in press.
26. Winston J, Craft DM, Scase TJ, **Bergman PJ**. Immunohistochemical detection of Her-2/neu expression in spontaneous feline mammary tumors. *Vet Comp Oncol* 2005, in press.
27. McAbee KP, Ludwig L, Newman S, **Bergman PJ**. Cutaneous Hemangiosarcoma in 18 cats. *J Am Anim Hosp Assoc* 2005, in press.
28. Allenspach K, Grone A, Doherr MG, **Bergman PJ**, Gaschen F. P-glycoprotein expression in lamina propria lymphocytes of duodenal biopsies in dogs with inflammatory bowel disease. *J Vet Intern Med* 2005, submitted.
29. Charney SC, **Bergman PJ**, McKnight JA, Farrelly J, Novosad CA, Leibman NF, Camps-Palau MA. Evaluation of intracavitary mitoxantrone and carboplatin for treatment of carcinomatosis, sarcomatosis, and mesothelioma, with or without malignant effusions: A retrospective analysis of 12 cases (1997-2002). *Vet Comp Oncol* 2004, in press.
30. Novosad CA, **Bergman PJ**, O'Brien M, Charney SC, et al (VCOG). Retrospective evaluation of adjuvant chemotherapy for the treatment of feline mammary gland adenocarcinoma. *JAVMA* 2004, submitted.

APPENDIX 6.5

Dr. Ronald D. Schultz
Professor and Chair
Department of Pathobiological Sciences
School of Veterinary Medicine
University of Wisconsin-Madison

EDUCATION: North Penn High School, Lansdale, Pennsylvania, 1962
The Pennsylvania State University
BS (1966), MS (1967), PhD (1970)
Major - Microbiology/Immunology
Minors - Biochemistry and Veterinary Pathology

MILITARY SERVICE: Captain, Medical Service Corps, U.S. Army Reserve, 1968-1975

POSITIONS HELD:

1982 - present	Professor (Tenured) and Chair, Department of Pathobiological Sciences, School of Veterinary Medicine. Professor (Joint Appointment), Department of Medical Microbiology and Immunology, School of Medicine. Professor (Affiliate Appointment), Department of Animal Health and Biomedical Sciences, College of Agriculture and Life Sciences. Professor, Environmental Toxicology Center, University of Wisconsin, Madison, Wisconsin.
1978 - 1982	Professor of Immunology (Tenured) and member of Graduate Faculty, Department of Microbiology and Animal Health Research Unit, School of Veterinary Medicine, Auburn University, Auburn, Alabama.
1977 - 1978	Associate Professor of Immunology (Tenured), James A. Baker Institute for Animal Health Research (Veterinary Virus Research Institute), Cornell University, Ithaca, New York.
1973 - 1978	Assistant Professor of Immunology and member of Graduate Faculty, James A. Baker Institute for Animal Health, Cornell University.
1972 - 1978	Associate Director, Human Health Services Clinical Laboratory, Department of Health Services, Cornell University, Ithaca, NY.
1971 - 1973	Research Associate, Department of Microbiology, New York State College of Veterinary Medicine, Cornell University, Ithaca, New York.

HONORS & MEMBERSHIPS:

First President American Association of Veterinary Immunologists
Honorary Diplomate of American College of Veterinary Microbiologists
Distinguished Veterinary Immunologist Award, American Association of Veterinary Immunologists, 1988
Walter F. Renk Distinguished Professor Award, Faculty, School of Veterinary Medicine, University of Wisconsin-Madison, 1989.
President of Conference of Research Workers in Animal Diseases, 1994.
Served on all School of Veterinary Medicine Committees and Numerous Campus Committees
Served on Review Committees for USDA, FDA, NIH and private foundations
Editorial Board Member for various journals

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RESEARCH INTERESTS
-Developmental aspects of immunology
-Immunopathology associated with viral diseases
-Immunomodulators
-Clinical immunology and virology
-Vaccinology
- Zoonotic diseases and foreign animal diseases

Trained approximately 50 graduate students and postdoctoral fellows

Published approximately 200 articles in peer reviewed journals, edited several books and hold a number of patents

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APPENDIX 6.6

LAWRENCE T. GLICKMAN

Biographical Sketch

Dr. Glickman is on the faculty of the Purdue University School of Veterinary Medicine. In addition to a degree in veterinary medicine, he has a doctoral degree in public health and a master's degree in physiology. He is board certified by the American College of Epidemiology. He served as Chairman of a committee of the National Academy of Sciences that authored a monograph titled *Animals as Sentinels of Environmental Health Hazards.* He has published over 275 journal articles, book chapters, and monographs, related to human and animal health. He studies relationships between humans, animals, and the environment. Dr. Glickman has received grants and contracts from federal agencies including the National Institutes of Health, the Centers for Disease Control and Prevention, the Food and Drug Administration, the U.S. Department of Education, and the U.S. Department of Agriculture, and from private foundations, breed clubs, and industry. He has been recognized for contributions to human and animal health with honors including the Award of Recognition in Veterinary Public Health and Preventive Medicine in 1988 from the Teachers of Veterinary Preventive Medicine and Public Health, the Pfizer Award for Research Excellence in 1997, an award from the University of Pittsburgh Graduate School of Public Health in 1999 as one of the 50 top contributors to public health over the past 50 years, an Alumni Award of Merit in 2002 from the University of Pennsylvania School of Veterinary Medicine for advancing animal health, and the 2003 AKC Award for Excellence in Canine Research. He has trained more than 20 PhD students in epidemiology and chairs the Section of Clinical Epidemiology at Purdue University. Dr. Glickman directed the largest prospective companion animal health study to date, involving nearly 2000 pet dogs that were followed for five years to identify the causes of gastric torsion. His current research utilizes computerized veterinary medical records to detect biological, chemical, and physical hazards, resulting from acts of terrorism and to measure the incidence of adverse health effects associated with veterinary vaccines and pharmaceuticals. Dr. Glickman recently published the results of two studies showing that lawn herbicides are a probable cause of bladder cancer in dogs and chemicals in food can linings may be responsible for the current epidemic of hyperthyroidism in cats. He developed a simple method called the *Vaccinometer* to help veterinarians weigh the risks versus benefits of vaccines for individual patients. He is a strong advocate for the evidence-based approach to veterinary medical practice and preventive medicine.

Current Position	Professor of Epidemiology & Public Health Head, Section of Cli nical Epidemiology
Office Address	Department of Veterinary Pathobiology School of Veterinary Medicine Purdue University West Lafayette, IN 47907 -1243

Education

B.A.	1964 - Biology, State University New York at Binghamton
M.A.	1966 - Physiology, State University New York at Binghamton
V.M.D.	1972 - University Pennsylvania, School Veterinary Medicine,
M.P.H.	1975 - Epidemiology and Infectious Diseases, University Pittsburgh, Graduate School of Public Health
Dr.PH.	1977 - Epidemiology and Public Health, University Pittsburgh, Graduate School of Public Health

Postgraduate Training

1975-1976	N.I.H. Postdoctoral Fellow in Cardiovascular Disease Epidemiology, Graduate S chool Public Health, University Pittsburgh
1976-1977	Research Assistant, Department of Epidemiology, Graduate School Public Health, University Pittsburgh

Military Service

1960-1966	United States Army National Guard, (Honorable Discharge)

Academic Appointments

1977-1980	Assistant Professor of Epidemiology and Preventive Medicine, Department of Preventive Medicine, and Head, Division of Epidemiology, Diagnostic Laboratory, New York State College of Veterinary Medicine, Cornell University
1980-1987	Associate Professor of Epidemiology and Chief, Section of Epidemiology and Public Health, Department of Clinical Studies, School of Veterinary Medicine, University of Pennsylvania (Tenure granted July 1, 1983)
1980-1985	Faculty in Graduate Group of Epidemiology, University of Pennsylvania
1981-1988	Faculty in Graduate Group of Comparative Medical Sciences, University of Pennsylvania
1982-1988	Faculty in Graduate Group of Parasitology, University of Pennsylvania
1985-1988	Adjunct Professor of Epidemiology, Section of General Medicine, Hospital of the University of Pennsylvania
1987-1988	Professor of Epidemiology and Head, Section of Epidemiology and Public Health, Department of Clinical Studies, School of Veterinary Medicine University of Pennsylvania
1988-1993	Head, Department of Veterinary Pathobiology, Purdue University, School of Veterinary Medicine
1988-1993	Head, Graduate Program in Veterinary Pathobiology with subspecialties in pathology, epidemiology and public health, microbiology, parasitology, and immunology, Purdue University Graduate School.
1988-present	Professor of Epidemiology and Public Health and Head of Section of Clinical Epidemiology, Department of Veterinary Pathobiology, Purdue University, School of Veterinary Medicine
1991-present	Adjunct Professor of Epidemiology, Indiana University School of Medicine, Indianapolis, IN
1991-present	Founding Member, Purdue University Interdisciplinary Graduate Program in Nutrition

Hospital and Administrative Appointments

1966-1967	Research Scientist, Research and Drug Development, Endo Laboratories, Garden City, New York
1972-1974	Practicing Veterinarian, Trooper Veterinary Hospital, Norristown, PA
1976-1977	Assistant Director, Laboratory Animal Care Facility, School of Medicine, University of Pittsburgh (Major responsibility for dogs, cats, and non-human primates)

Specialty Board Certification

1982	Fellow of the American College of Epidemiology

Awards, Honors, and Membership in Honorary Societies

- 1972- Borden Award for highest academic average in veterinary school
- 1972- J.B. Lippincott Prize for academic achievement in veterinary school
- 1972- Leonard Pearson Prize for Advancement of Veterinary Science and Research in Practice, Education and in Civilization
- 1972- 1930 Class Prize-for highest average in surgery
- 1983- Ralston Purina Small Animal Research Award
- 1987- Veterinary Student Government Award for Excellence in Teaching, University of Pennsylvania
- 1988- Award of Recognition in Veterinary Public Health and Preventive Medicine, Teachers of Veterinary Preventive Medicine and Public Health
- 1989- Delta Omega Society, for outstanding attainment in public health
- 1989- Sigma Xi National Scientific Research Honor Society
- 1991- Merck AGVET Award for Creativity in Veterinary Education
- 1991- National Society of Phi Zeta, Honor Society of Veterinary Medicine
- 1997- Pfizer National Award for Research Excellence
- 1999- University of Pittsburgh Public Health Award, Top 50 contributors to public health in past 50 years
- 2002- Alumni Award of Merit, University of Pennsylvania School of Veterinary Medicine
- 2003- American Kennel Club-American Veterinary Medical Association, Excellence in Canine Research

Memberships in Professional and Scientific Societies

- American Academy Veterinary Disaster Medicine
- American Academy Veterinary Nutrition
- American College Epidemiology (Fellow status)
- American Public Health Association (Chairman, Membership Committee, Veterinary Public Health Section, 1982-1986)
- American Veterinary Medical Association
- Association of Teachers Veterinary Public Health and Preventive Medicine
- Association of Veterinary Medical Educators
- National Association State Public Health Veterinarians
- Society for Epidemiologic Research
- Society of Toxicological Pathologists (Associate Member)
- Teachers of Veterinary Preventive Medicine and Public Health (Executive Board, 1987-1988)

Peer Reviewed Publications

Approximately 300 publications in medical journals, textbooks, and monographs
A detailed list is available upon request

ATTACHMENT 4

Cover Page

I N D E X

VMAC Meeting
January 31, 2005

Facilitated by Dr. Arthur Craigmill, Chair

KEYNOTE: "---" denotes inaudible in the transcript.
"*" denotes word was phonetically spelled.

P R O C E E D I N G S

(8:10 a.m.)

Welcome/Background

Dr. Stephen Sundlof

DR. SUNDLOF: Good morning, everyone, and welcome to the Veterinary Medicine Advisory Committee. Today we are going to be discussing ProHeart 6 and we have a full house here, and so it is very good to see all these people here. Before we go ahead and start, Aleta Sindelar has a few housekeeping issues to go over with you. So I am going to hand over the microphone to Aleta.

MS. SINDELAR: Okay. Thank you. First, there is a conflict of interest statement for the Advisory Committee to be read which covers the -- any perceptions or documentation of possible conflicts of interest. The following announcement addresses the issue of interest with regard to this meeting and is made part of the public record to preclude even the appearance of a conflict of interest at this meeting on January 31st, 2005. Federal conflict of interest laws preclude the participation of committee members and consultants in Advisory Committee meetings if they have a conflict of interest unless a waiver from exclusion is granted by the agency. The Associate Commissioner for External Relations FDA has appointed Dr.

Charles Bennett, Dr. John Glisson, Dr. Samuel Groseclose, Dr. Michael Luster, Dr. C. Thomas Nelson, Dr. Michael Peterson, Dr. Gatz Riddell, and Dr. Lauren Trepanier as temporary voting members for this meeting.

Based on the submitted agenda for this meeting and a review of all financial interests reported by the committee participants, it has been determined that all interests in the firms regulated by the Center for Veterinary Medicine which have been reported by the participants present no potential for a conflict of interest at this meeting with the following exceptions. Dr. John Glisson discloses consulting with the sponsor; magnitude is less than 10,001. Dr. Katrina L. Mealey discloses consulting with the competing firm; magnitude is less than $10,001. She discloses a grant with a competing firm; magnitude is less than 300,000. Dr. Mealey discloses one speaking interest with a competing firm; magnitude is less than $5,001. And a speaking interest with a competing firm under negotiation; magnitude is less than $5,001. Dr. Mark G. Papich discloses two consulting interests, both with competing firms and both interest are less than 2,000 -- excuse me, $10,001 each. Dr. Papich discloses two grants. Both are with a competing firm; both are less than 100,000 each. Dr. Richard Sams discloses one consulting interest

with a sponsor under negotiation; magnitude is less than $10,001. Dr. Sams discloses one contract with the sponsor under negotiation; magnitude is less than 100,000. He will be granted a limited waiver and will not vote. In accordance with 18 USC 208(B)(3) a waiver has been granted to Dr. John Glisson, Dr. Katrina L. Mealey, and Dr. Mark G Papich. Under the terms of the waiver, Drs. Glisson, Mealey, and Papich will be permitted to participate fully in discussions and deliberations to accept the safety of the drug product voluntarily recalled and make recommendations with regard to the agency's risk management strategy. Dr. Richard A. Sams will be permitted to fully participate in discussions to address the safety of the drug product voluntarily recalled and make recommendations, but will not vote.

In the event that the discussions involve specific interests, products, or firms not on the agenda for which FDA's participants have a financial interest, the participants are aware of the need to exclude themselves from such involvement, and their exclusion will be noted for the public record. With respect to all other meeting participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose products they wish to comment on.

Two housekeeping notes. I would like to make sure everyone knows that the parking is free, but there is a pass code that you will need to punch in. If you are in the garage, please press the pound key and 1204. That is 1204. If you are not in the garage, please do not press the pound key. Number two, we have a very busy schedule ahead of us. We would appreciate if everyone sticks to their time limit. Thank you very much. Steve, thank you.

DR. SUNDLOF: Thank you, Aleta. Okay. We will begin with a series of presentations. Let me just go first of all and introduce the people who are sitting at the front. I am Steve Sundlof. Sitting right to my left is Jenny Gresock. She is with the Office of Chief Counsel of the Food and Drug Administration. Margarita Brown is the veterinary medical officer who reviews the adverse drug event reports that we are going to be talking about extensively today, and Dr. Lynn Post who is the Director of the Center -- I'm sorry, the Office of -- the Division of Surveillance. It is tough living in a bureaucracy.

(Laughter.)

DR. SUNDLOF: And the Office of Surveillance is the office that conducts post-market approval studies like the ones we are going to be talking about today. So those are the folks in the front panel here.

(Slide.)

The purpose of today's meeting is to review the safety of ProHeart 6, which is a heartworm preventive drug approved for use in dogs. The sponsor, Fort Dodge, has voluntarily recalled ProHeart 6 from the market at the urging of the Center for Veterinary Medicine because of reports from veterinarians, pet owners and others filed through the Center's adverse drug experience reporting system. They raised questions about the product safety. So in a few minutes you will be hearing a description of the ADE system, and so let me just define ADE right now. That is adverse drug event or adverse drug experience. We are going to primarily refer to them as adverse drug events today. So ADE is adverse drug events, and we will be discussing those extensive as they pertain to ProHeart 6 today and to some other similar heartworm preventive products.

(Slide.)

I want to introduce the members of the panel here today, the Advisory Committee meeting, and so let me go through the list and tell you a little bit about these folks. Our chairman is Dr. Arthur Craigmill. He is an expert in veterinary toxicology and represents that discipline on the VMAC in addition to his role as chairman,

and we welcome you, Art, as the new chair. Also today with us is Susanne Aref, but I don't see her here, so maybe she didn't make it. Susanne Aref is our expert in biostatistics at Virginia Polytechnic Institute and State University. Dr. Corrie Brown is with us today. She is an expert in pathology with the University of Georgia. She made it up from the south, but apparently Skip Jack didn't. So Sherman Skip Jack, he is our expert in minor use in minor species. Maybe he will be able to get here later today. I don't know. Representing the consumers is Greg Jaffe, and Greg is with the Center for Science and Public Interest. Dr. John McGlone, there's John, is an animal science expert and does represent animal science as a discipline on the VMAC. Dr. Katrina Mealey is an expert in companion animal medicine and represents that discipline. She is from Washington State University. Lisa Nolan is an expert in veterinary microbiology with Iowa State University. Mark Papich is an expert in pharmacology with North Carolina State University, and Dr. Richard Sams is an expert in chemistry with the Ohio State University.

In addition to the regular members we also have some consultants with us today because of the nature of the subject. Really we are going to be going through a number of various disciplines. So we have with us today

Charles Bennett who is an expert in pharmaco-epidemiology with the Feinberg School of Medicine and with the Midwest Center for Health Service Policy Research. Dr. John Glisson is an expert in Avian Medicine with the University of Georgia, and I think like Dr. Jack was unable to get out of the Atlanta. Dr. Tom Nelson is a heartworm expert and President of the American Heartworm Association -- or, I'm sorry, American Heartworm Society and with the Animal Medical Center in Anniston, Alabama. Dr. Michael Peterson is an expert in zoonotic and infectious disease epidemiology with the Office of the Assistant Secretary of Defense. Dr. Gatz Riddell is an expert in food animals, food animal medicine, with Auburn University, and Dr. Lauren Trepanier is an expert in dramatic differences in drug metabolism with the University of Wisconsin. So that concludes the list of experts who will be helping us with this, with the decisions that we will be making today. Oops. Should have done that sooner.

(Slide.)

Just to talk a little bit about CVM's mission, and this is taken directly from our mission statement. It is part of our mission statement. Not the whole thing, but it says "We foster public and animal health by approving safe and effective products for animals and by

enforcing other applicable provisions of the Federal Food, Drug, and Cosmetic Act and other authorities." So a lot of the things that we will be talking about today tie directly back to this mission. Not only our mission to protect animal health, but also how we enforce those responsibilities through the various legal channels.

(Slide.)

Our responsibility to determine a drug safety does not end after the drug is approved. We have an extensive pre-market review process that is intended to try and pick up any abnormalities or adverse events prior to the approval, and we deal with those in the pre-approval stage. But we can't always pick up all of them, as folks are well aware, and as a result there are some -- there are adverse events that occur after the approval that were not anticipated during the pre-approval stage. So we have an extensive post-approval surveillance system to try and pick up these unintended events. In this case we received several adverse events regarding this particular product, ProHeart 6, and so we will be discussing our reasons for taking the positions that we have during the rest of the day.

(Slide.)

Okay. The information we collect through our

adverse drug event system is carefully and thoroughly analyzed. We use an established review process for ADEs that provides standards and gives an ordered and structured system that can be used to analyze information and make unbiased decisions about product safety. The system CVM uses to analyze these adverse drug events is much the same as that that is used in our human counterpart, the Center for Drug Evaluation and Research; and in just a little while we will provide you with a description of how that system works, how the causality grading system is set up, et cetera.

(Slide.)

Due to our concerns from the ADE reviews, we approached Fort Dodge Animal Health and at first asked for label changes, which Fort Dodge changed. So there were label changes. Generally we asked the company to change the label if there are adverse events that were not originally listed but that appeared on post-market evaluation. Oftentimes that yields a reduction in the number of adverse drug events and has a substantive effect in improving the safety. In this case, however, even after the label changes went into effect we did not see a subsequent reduction in the number of adverse drug events. So after studying this very thoroughly the Center took the position that in light

of the fact that the adverse events were not decreasing we asked the company to voluntarily recall the product, which they did.

(Slide.)

So the reasons for this VMAC meeting is in the spirit of openness and transparency. We want to present our case in a public forum, which is this Veterinary Medicine Advisory Committee meeting. This is an important product obviously to veterinarians and to the company. We think that it deserves a very thorough discussion, and we want to be sure that all the information gets thoroughly reviewed not only by CVM, but by independent specialists on the Veterinary Medicine Advisory Committee so we can get their opinions and benefit from their experience. This is a fairly common use of an advisory committee, and this is one of the reasons that we have these advisory committees, to bring in as much outside expert opinion into the decisions that CVM makes as possible.

(Slide.)

So in conclusion, CVM has the ultimate responsibility for determining the safety of animal drugs. The amount of information that we can get about products through adverse event reports is often broad and can be complex and affected by confounding factors. We appreciate

the advice and insight of the members of the VMAC and we hope you will help us to be sure that we are making the right decisions. With that, I will close my remarks and turn the podium over to Jenny Gresock.

Legal Framework

Jennifer Gresock, Esquire

MS. GRESOCK: Thank you, Dr. Sundlof. My goal today is to provide a brief look at the legal background against which CVM operates.

(Slide.)

The Center for Veterinary Medicine has the regulatory responsibility for insuring the safety of marketed animal drug products through an approval process. Drug approval depends on a showing of effectiveness, but also of safety, and today our focus is on safety. Section 512 of the Act details the requirements for new animal drug approval.

(Slide.)

When submitting an application for a new animal drug product the applicant must show that the product is both safe and effective for its intended use. For drugs used in food animals an evaluation of a drug's safety includes focusing for instance on human food safety. For companion animals target animal safety is the primary

concern.

(Slide.)

Under the Act, an applicant must submit as part of the new animal drug application full reports of investigations which have been made to show whether or not a drug is safe and effective for use. With regard to safety, an application may be refused if it doesn't contain these full reports and adequate tests by all methods reasonably applicable to show whether the drug can be safely used as suggested in the labeling proposed by the applicant.

(Slide.)

Note that the attention to labeling is a key part of the process of approving new animal drugs. The labeling for an approved animal drug product should indicate how to use the product in a safe and effective manner. The safe use of a drug may for instance require caution statements that alert the users of the product to particular species in which the drug should not be used, or the labeling may note particular effects that a veterinarian or pet owner should be aware of when using the product. In short, the labeling of an approved animal drug product must provide adequate directions for use or it is misbranded under the Act, and that means that FDA can take legal action against it. The labeling is extremely important.

(Slide.)

After a drug has been approved, CVM monitors the safety and effectiveness of the drug as it is used more widely. The law requires drug sponsors to establish and maintain records and to make reports to FDA of data relating to experience or other date and information received or otherwise obtained by the sponsor. Specifically the regulations require drug sponsors to report adverse drug experiences.

(Slide.)

What is an adverse drug experience? Note that it is any adverse event, whether or not considered drug related and regardless of whether or not the drug was used in a manner consistent with its labeling. This includes both ineffectiveness reports as well as events related to safety of the product. The regulations have special reporting requirements for adverse drug experiences that are both serious and unexpected.

(Slide.)

What is a serious adverse drug experience then? This slide highlights the types of experience that are categorized as serious. Note that they include those that are fatal or life threatening, but also those that require professional intervention.

(Slide.)

What then is an unexpected adverse drug experience? The key here is that an unexpected adverse drug experience is not listed on the current labeling for the drug or an unexpected adverse event may be much more severe or specific than a related event that is listed on the labeling.

(Slide.)

I have highlighted serious unexpected adverse events because those are the ones that must be reported by sponsors within 15 working days of receiving a report from a consumer or veterinarian.

(Slide.)

Other adverse drug experiences, those that do not qualify as serious and unexpected, must be reported in periodic drug experience reports. These are submitted every six months for the first two years after approval and then yearly thereafter. Note that consumers have no legal obligation to report adverse drug experiences. Only the drug sponsor has such an obligation.

(Slide.)

What happens when a drug product raises safety concerns? FDA has a number of different things that it can do. In some cases, FDA can request a recall under

the regulations. Alternatively, the firm may initiate a recall also under the regulations. Short of that, FDA would first try to do smaller steps. For instance, working with the sponsor on labeling and/or manufacturing changes. Fort Dodge for instance has worked closely with CVM on several labeling changes intended to make the drug safe for use. If none of these things work, FDA may issue an order withdrawing the approval of the product. Such an order would be issued based on certain findings by the Secretary. Such a finding may be that experience or scientific data show that the drug is unsafe for use under the conditions of use upon which the application was approved. That would be one of the possible grounds. Or such a finding might be that new evidence not contained in the application or not available to the Secretary until after the application was approved evaluated together with evidence available when it was approved show the drug is not shown to be safe for use under the conditions for which it was approved. These findings would follow notice to the sponsor and an opportunity for a hearing. This is the legal framework within which CVM operates.

FDA/CVM Adverse Event Reporting

Dr. Margarita Brown

DR. BROWN: Good morning, everybody. I am

pleased to have the opportunity to share with you our adverse drug event procedure here at FDA Center for Veterinary Medicine. I'm one of the four veterinarians initially recruited by CVM for the sole purpose of reviewing these adverse drug events and entering them into our database. We now have seven veterinarians working at this job part time. The rest of the week six of these seven practice veterinary medicine here in Maryland and in Virginia.

(Slide.)

As you can see, we all have strong clinical backgrounds, which is really critical in understanding and evaluating these reports. Every one of us knows what it is like to be the person responsible for prescribing and administering any of these medications, and we also know the many differentials that must be considered when things start to go wrong.

(Slide.)

Our job is to review and evaluate the drug events that are sent to our office from the drug sponsors as well as from veterinarians and pet owners. We do this because there are inherent limitations in the pre-approval process, and those can't guarantee then the absolute safety and effectiveness of the approved veterinary drugs.

(Slide.)

Now recognizing that we represent the clinical approaches of at least five different veterinary schools, it is very important that we have a way of making our review process objective. We use the Modified Kramer System. It's a good tool for promoting the consistent application of the same set of standards, regardless of personal opinion. We don't just grab a causality association out of the air. We have to get there the same way each time. There are six axes or criteria that are used. The first is previous experience. What is already known about this drug and its possible reactions? The second is an alternative etiologic candidate. That is, is there something else that could be contributing or causing this event? The third is timing. Is this a consistent timing to happen with this type of reaction in this type of patient? The fourth is, is there evidence of an overdose? The fifth is dechallenge, which is what happens when the drug is removed from the system; and the sixth is rechallenge, what happens when the drug is reintroduced.

(Slide.)

When we apply the algorithm to these events in the adverse reports we add up the scores to arrive at a causality assessment score. Here are the interpretations of

the ranges. Remotely drug related are those with the negative numbers, -1 to -6. Those that are possibly drug related are 0 to +2. Probably drug related are +3 to +5, and definitely drug related +6 to +7. For those of you who are familiar with our website where we post monthly the results of the causality assessment scores for our different drug events, you will know that the only scores and the only signs that show up on that website are those that are in the positive range. That is zero and higher. None of those with negative numbers are included in that analysis.

(Slide.)

Now when we get an adverse drug event we start by pulling up the label for that drug. We look at the species and the dose labeled for its use. We look at the labeled adverse events that are known to occur. We look at our database to see if similar reactions have been reported. We look at safety studies in the Freedom of Information Summary to see what kind of leeway has be documented before adverse events are precipitated at higher doses. We look at the pharmacodynamics to understand how the drug is processed in the body and when adverse events might be expected to occur. We can also refer to published articles in textbooks and journals. What we don't do is just think, "Well, you know, it seems like that could happen," and go on the

strength of our personal instincts. We have to use factual information.

Now if this is a newly-marketed drug we might not have a lot of information to work with as far as previous reactions are concerned. In that kind of instance we put our heads together, we discuss the information we do have, and we do our best to standardize the issues such as timing for labeled reactions. For reactions that are not labeled, the best we can do is to see if they show up at a time when the drug is at peak levels in the body.

(Slide.)

Okay. Let's take a look at a sample adverse drug event and apply the Modified Kramer Algorithm to it. So consider that we have a four-year-old mixed breed neutered dog. He comes into his veterinarian for his wellness care. He is good health on physical exam. He has a negative heartworm test. He is given his ProHeart 6 injection at the labeled dose, seems to be fine, but four days later he starts vomiting. So first I need to find out if the adverse event, vomiting, could be an expected reaction.

(Slide.)

So let's look at ProHeart 6's label. The labeled adverse events when it was first approved were

vomiting, diarrhea, listlessness, weight loss, seizures, injection site reaction such as itching or swelling, and fever. Okay. This complaint is for vomiting, and it is on the label.

(Slide.)

So I can clearly give this a plus one in the first axis of the algorithm, that for previous experience. It is generally recognized to occur in this species at this dose. It's on the label.

(Slide.)

Well, how about the second axis for alternative etiologic candidate? Is there absolutely nothing else that could cause this reaction? Might we expect this sort of reaction to occur spontaneously in this type of patient? Are any other drugs being given concurrently that can cause the same reaction? Is there a preexisting condition? You will notice that we need very firm evidence here to say that there is really no other candidate other than the administration of the drug. Often the strongest score we can give here is a zero. It might occur spontaneously or there might be an alternative candidate, but not a good one.

(Slide.)

We give it enough data to rule out the

possibility of a contributing factor. For example with vomiting. Well, have there been changes in the diet? Has this animal been thoroughly checked for parasites? Is there a history of vomiting in the past? Have blood values been checked and found normal?

(Slide.)

Now sometimes there has been a good physical exam, and excellent medical history and work-up are provided. In serious instances if we don't have that information we might call the sponsor or the reporting veterinarian for follow-up information. If we get that kind of complete information we might be able to score a +2 on that second axis. There is no good reason other than administration of the drug for the reaction to have occurred.

(Slide.)

But here in the real world I would like to represent a typical report and say we have no known dietary changes. We have one negative stool sample for parasites. There is no blood work. We can't really say for sure that something else is going on or isn't going on. We have to put a zero at that second position.

(Slide.)

The third component of the algorithm is

timing. Now we know from the pre-approval studies that PH 6 blood levels peak at seven to 14 days after injection. So the complaint is one of vomiting that started eight days after injection. I'm clearly able to give this a +1 at the third line for timing. It is consistent and expected.

(Slide.)

Now let's look at overdose. The way this is worded if I want to put a +1 in the position for overdose I need to know that this reaction is expected to occur in the species at this elevated dose. We will say we have safety studies showing that the drug was safely administered at three times and five times the regular dose. If there was a slightly highly dose given, but it is within that three-times to five-times range, then we cannot score anything stronger than a zero at this point in the algorithm. We are required to say that technically it was an overdose because it was higher than the approved label dose, but we do not score it as an overdose.

And let me add that we don't often score overdose for ProHeart 6 because it is given by medical professionals, either veterinarians or veterinary health technicians. It is not like you have the situation where the husband comes home early, he gives the dog its pill, then he rushes off to take the kids to their soccer game and

say an hour later the wife gets home. Oh, she dutifully remembers to give their dog their heartworm pill, and the dog has wound up with a double dose right in that instant. Or sometimes some of these medications are so delicious that the dogs will go ahead and gobble up a whole bottle full of them all by themselves. We don't usually see that happen with an injectable.

(Slide.)

Dechallenges is part of the algorithm, another one that doesn't really apply to ProHeart 6 because it refers to what happens when the drug is stopped, when it is removed from the system, or when its levels are reduced by decreasing the dose. With a six-month injectable, the drug stays in the animal's body for all that time. So it's difficult to say that when the vomiting stops in three weeks it is because the drug is no longer there. It is not like stopping a pill and seeing the vomiting stop in a few days. We can really only give this a zero in the dechallenge axis. Dechallenge is difficult, inappropriate, or impossible to assess.

(Slide.)

Rechallenge refers to what happens when the drug

is given again. This again usually gets a zero in the

ProHeart 6 reports. Well, there could be some instances where neither the owner nor the veterinarian suspects that the vomiting was caused by the injection until the same thing happens when the drug is given six months later. But unless that kind of follow-up information is given, the score here usually remains a zero for no rechallenge attempted. Again, compare this to seeing the vomiting occur several hours after every time a pill is given.

(Slide.)

So when we add up the scores assigned for this report of vomiting, which is on the label and happens during the time of peak concentration in the body, the strongest score we can give adds up to a +2, possibly drug related. I think you can see that usually this scoring system gives the benefit of the doubt to the drug. Now let's take a look at what happens with an event that is not on the label but starts showing up in the post-approval marketing, a complaint like anaphylaxis.

(Slide.)

Characterized by such things as sudden profuse vomiting and diarrhea, swollen head or face, hives, pale mucus membranes, or collapse.

(Slide.)

In many complaints as in this example,

ProHeart 6 was given along with routine vaccinations. So here you have a three-year-old small-breed dog. Again she comes in for her wellness visit to her veterinarian and is in good health on her physical exam. She has a negative heartworm test. She gets her ProHeart 6 injection at the label dose along with her annual distemper vaccination, and two hours later she breaks out in hives, her face swells up, and she collapses.

(Slide.)

Now because this reaction was not on the original label or in the Freedom of Information studies, we could only give it a zero in that first position for previous experience. How about an alternative candidate? Vaccinations are certainly known causes of anaphylactoid reactions. So we have to give a -1 score at that second axis to accommodate for the vaccination. In the third axis, timing, this was very closely associated with the injections and well within the time frame for this type of reaction. So a +1 can be assigned there. The regular dose was given, so this dose stays zero at overdose. Dechallenge and rechallenge not applicable in these reports, zero for each of those. So adding up the overall score we get a zero. That is possibly drug related.

(Slide.)

Now in some reports vaccines were not given at the same time, and neither was anything else such as a penicillin injection or a cortisone injection. We would put a zero then at that second position for alternative etiologic candidate, bringing up the total score to a +1, still possibly drug related. Such a large number of these types of reactions were reported that the label was changed in June of 2002 to include anaphylactoid reactions as adverse events. So we can now put a +1 at that first position for previous experience. Some of these dogs were closely observed after their injections, and we were thus able to put a +2 in that second position for no alternative etiologic candidate if the dog were kept inside and observed after the injection and insect exposure was unlikely. We did not have a circumstances where a dog had an anaphylactoid reaction and then was given a second dose of ProHeart 6. Again, overdose, dechallenge and rechallenge remain at zero. So a +4, probably drug related, is the highest score that could be assigned to many of these ProHeart 6 reports, and that demanded very complete reporting. No other medications administered, a patient closely monitored after administration to reach that score.

Now of course in many other circumstances you don't have a dog that is closely monitored after these

injections. Many people, they would just take their dog home and let him outside in the yard, and in that kind of circumstance in that second axis for alternative candidate we have to leave it at a zero. So for those again the highest score we could reach would be a +2, possibly drug related.

(Slide.)

So this level of information could rarely be provided for other complaints of illness, even if labeled and expected, such as the example of the vomiting dog I gave previously, and in addition we must keep in mind that these three components of the Modified Kramer Algorithm do not really apply to ProHeart 6. That is overdose since it is given by a health professional, dechallenge because the drug remains in the body, rechallenge because the drug is rarely given again if a reaction was recognized after the first administration. So most of these complaints can only be scored as possibly drug related, even if they are expected events that begin while ProHeart 6 is exerting its peak effect in the body. I hope this review of our scoring system will serve as a basis for understanding the rest of today's presentations. Thank you.

MS. SINDELAR: We are going to proceed with the agenda since we are moving along so well with Dr. Post.

ProHeart 6 ADEs/CVM

Dr. Lynn Post

DR. POST: Good morning. I am going to give an overview of the ProHeart 6 adverse drug events.

(Slide.)

The evaluation of adverse drug events falls under observational studies. In general, the advantages of observational studies are a larger and more diverse population and under actual conditions of use. The population at risk has differences in diet, genetics, breed, age, environment, and so on. In a diverse population there are many confounding factors, such as preexisting disease and concomitant medications. It is the variation in the population that makes it difficult to define a control group.

(Slide.)

Reporting rate is defined as the number of adverse drug events, the numerator, divided by the number of exposed patients, the denominator, over time. The ADE reporting rate is not an incidence rate for two reasons. First, ADEs are under-reported by the clinician because of such things as the adverse drug event may not be connected to the drug, there may be fear of litigation, just more

paperwork, and the clinician wishes to protect the client's privacy.

(Slide.)

Second, accurate data on the number of exposed patients, the denominator, is often lacking. It is only a guestimate.

(Slide.)

A reporting rate compared to the background incidents may provide a signal that there is a problem with a product. This is expected. But what happens if the reporting rate falls below background? Well, this does not prove that there is not an increased risk of the adverse drug event. The signal could still be valid. Furthermore, spontaneous ADE reports give uncertain numerators due to under-reporting with no denominator at all. The use of denominators only serves to compound the uncertainty of the numerator. Therefore, CVM has not used denominators in this presentation.

(Slide.)

Okay. Now I will go over a little of the pre-approval history. ProHeart 6 was approved in June of 2001. The laboratory studies revealed no serious adverse drug events in healthy dogs, but this does not prove that or mean that there will no adverse drug events in the post-

approval period. It only means that no adverse drug events were found in the pre-approval studies. Clinical field studies revealed several adverse drug reactions of vomiting, diarrhea, listlessness, weight loss, injection site pruritus, itching, and increased body temperature. In clinical field studies ProHeart 6 was used safely in conjunction with a variety of veterinary products, including vaccines.

(Slide.)

In the clinical field trials there were three deaths which resulted in the following precaution statement on the label: Use with caution in sick, debilitated, or underweight animals.

(Slide.)

The ProHeart 6 active ingredient, moxidectin, is also a macrocyclic lactone. Neurotoxic science for macrocyclic lactones may include seizures or convulsions. Seizures have been added to the post-approval safety information on several labels.

(Slide.)

There have been three label changes since product launch in June, 2002. Anaphylaxis/anaphylactoid reactions, depression, lethargy, urticaria -- that's hives -- and head and facial edema were added to the label. In

November of 2002, cardiopulmonary signs associated with the administration of the product in heartworm-positive dogs. ProHeart 6 was originally approved as safe in heartworm-positive dogs.

(Slide.)

The third label change was in July of 2003, and a client information sheet and the phrase "and rare reports of death" was added to the label. Two "Dear Doctor" letters were sent out by the sponsor describing the three label changes, on in June, 2002, and the other in June, 2003.

(Slide.)

The annual number of initial ProHeart 6 adverse study reports has not appreciably decreased. I am talking about the column under initial reports.

(Slide.)

The annual reports are further broken down by initial, follow-up, and total ADE reports. That initial is in red, follow-up is in black, and total is in green, and the X axis is calendar year and quarter. The reporting pattern shows a peak frequency in each of the second quarters corresponding with heartworm prevention season. Notice that the frequency has not appreciably decreased since product launch to September 1st, 2004. The

manufacturing changes indicated by an arrow in the third quarter of 2002, and the residual solvents were removed from the formulation. The minimal residual solvent lots were in use by the first quarter of 2004, the arrow marked MRS lots. Despite the manufacturing change, again there has been no appreciable decrease in frequency as of September 1st, 2004.

(Slide.)

Of the nearly 22,000 assessments for all the clinical manifestations, more than 19,000 of them, of the clinical manifestations, have a positive causality of possible, probably, and definite. Then 32 reports were categorized as definitely drug related, and all had causality assessment scores of +6 for heartworm ineffect. The top row marked definitely drug related.

(Slide.)

Time of onset refers to the duration between administration of ProHeart 6 and observation of clinical manifestation. All clinical manifestations had a positive causality assessment represented in this slide. Approximately one-half of the clinical manifestations were with concomitants. That is vaccines and drugs. Approximately one-third of the clinical manifestations were without concomitants, and approximately one-sixth were of unknown concomitant status. The majority of the clinical

manifestations, over 15,000 of them, occur in zero to 14 days.

(Slide.)

Time of onset coincides with peak serum concentrations of moxidectin from seven to 14 days.

(Slide.)

Clinical manifestations zero to 14 days.

(Slide.)

Peak serum concentrations of moxidectin seven to 14 days.

(Slide.)

Numbers of dogs with reported ADEs. The website numbers will be larger because of extra-label use. The ADEs on the website are listed by species and active ingredient, so a product labeled for a horse could end up under a dog. As you can see, we get a lot of adverse drug event reports for heartworm preventatives, including reports of ineffectiveness. Ineffectiveness seems to involve the entire class of macrocyclic lactones, and we addressed this concern of ineffectiveness at the American Heartworm Society Meeting in July of 2004. All of the products have ineffects for heartworms, but depending on the label indications one or more of the heartworm preventatives have ineffects for hookworms, roundworms, whipworms, fleas, ticks, and mites.

Selamectin since it is applied topically also includes a lot of application site reactions, things like local hair loss. CVM worked with the sponsor to conduct post-approval studies and implement an educational program for selamectin ADEs. That would include ineffects. As a result, ADEs decreased in frequency and severity.

(Slide.)

But when we addressed the frequency of series adverse drug events such as death, you can see that there are more assessments of death associated with ProHeart 6 compared to all the monthly heartworm preventatives combined. Dr. Brown will now outline some of these serious events in more detail. Thank you very much.

ProHeart 6 ADEs/CVM

Dr. Margarita Brown

DR. BROWN: So Dr. Post has just given you an overview of ProHeart 6. Let me now take you through some of our specific concerns. Let me move this back up until we get there. You remember that this is a spontaneous reporting system, meaning that someone has to take the time and effort to fill out a report. Large numbers of reports in relatively young, healthy dogs can be what we call a signal that something is going on. Now if we are talking about reports of side effects that are simply upsetting or

inconvenient we might not be so concerned. I am not going to waste your time with those. Instead let's take a look at some of the serious reports that have been submitted for the marketed heartworm preventatives other than the complaint of ineffectiveness. Now for all the tables that follow I am including only data for events with the highest-ranking morbidity and mortality with a causality assessment score of zero or higher. That is possibly, probably, or definitely drug related.

(Slide.)

Now I know you were all paying close attention during my earlier description of the Modified Kramer Algorithm, but just as a quick reminder, we use these six axes to arrive at the causality assessment score for each clinical manifestation in the adverse drug event reports that we receive. There are seven different reviewers, and we apply the same criteria to all the adverse drug report events sent to us.

(Slide.)

We use these interpretations for each score that is reached, and I am presenting only information that falls in the category of possibly, probably, or definitely drug related, and that is a score of zero or above. I think every pet owner's worst fear is death, so let's look at that

first.

(Slide.)

This table shows you that between the approval of ProHeart 6 in June, 2001, and its voluntary recall in September of 2004, there were more than twice as many deaths reported among dogs that received ProHeart 6 -- that is 485

-- than for all the other heartworm preventatives combined -- that is 219 -- even though ProHeart 6 sales represent approximately 24 percent of the market.

(Slide.)

One of our foremost concerns has been the number of anaphylactoid reactions associated with the use of ProHeart6, and as you know those refer to sudden shock events, swelling of the head and face, sudden profuse vomiting and diarrhea, even death. As you can see, there are almost 20 times the number of such events associated with ProHeart 6, 1,820, than for all the other heartworm preventatives combined, 97.

(Slide.)

These events are occurring very shortly after administration of ProHeart 6. This shows the distribution of the onset times for these anaphylactoid reactions. You can see that almost all of them, 80 percent of them, occur

within the first three hours. Remember these are dogs that came into their veterinarian for preventative care. Most of them were examined by their veterinarian and judged to be in good health, good physical condition, before ProHeart 6 was given.

(Slide.)

For these 1,820 episodes of anaphylactoid reactions, there reporting veterinarians indicated that at the time of ProHeart 6 administration the health status was good in 1,741 of them, fair in 69, poor in three, and unknown in seven; 54 of these dogs died.

(Slide.)

Some of these dogs had at least one vaccination given at the same time as ProHeart 6 injection since they were at the veterinarian for preventive care, or they might have been given some other drug such as cortisone or antibiotic. The label clearly states in well-controlled clinical studies ProHeart 6 was safely used in conjunction with a variety of veterinary products, including vaccines, anthelmintics, anti-parasitics, antibiotics, analgesics, steroids, non-steroidal anti-inflammatory drugs or NSAIDS, anesthetics, and flea control products. In 1,816 anaphylactoid episodes, dogs did not have any concomitant drug or vaccine given. In 731 episodes they did have a

concomitant drug or vaccine, and the concomitant status is unknown for the dogs in those 273 episodes.

(Slide.)

Another category with a lot of reported reactions concerns convulsions or seizures. These may be fairly minor or occur only once, or they may be so severe and protracted that the dog requires ongoing medication or even dies. Convulsions are a known possible side effect with the class of drugs it is used for, all the monthly heartworm preventatives and ProHeart 6, and convulsions or seizures are on the label for each of them. As you can see, each of the marketed heartworm preventatives except for the ProHeart or moxidectin tablets, which are not extensively used here in the United States, has more than 100 assessments for convulsions since the time of the approval until September of 2004. But ProHeart 6 accounts for more than half or 378 of the 630 for all the rest of them combined.

(Slide.)

Approximately half of these convulsions occurred within three days after the administration of ProHeart 6. As you can see, the distribution of the onset times falls well within the time of rising or peak levels of ProHeart 6 in the body. That is seven to 14 days.

(Slide.)

For these 378 episodes of the convulsions, the reporting veterinarians indicated that at the time of ProHeart 6 administration the health status of the dogs was good in 302 of them, fair in 64, poor in seven, and unknown in the remaining five; 61 of these dogs died.

(Slide.)

In 87 episodes, dogs did not have concomitant drugs or vaccines, and in 215 episodes they did. The concomitant status for dogs in the 76 episodes is not known.

(Slide.)

Let's look at liver problems next. There are many ways that liver problems can be manifested or diagnosed, so I have chosen to use the most specific markers in our database; elevations in an enzyme found in the blood called SGPT/ALT, and lesions found by pathologists on examination of biopsies of the liver or in the livers from dogs that died. Here again you see that the number of SGPT/ALT elevations and liver lesions reported for ProHeart 6 since in the first three years of its approval, at 192 and 65, surpass those reported for all the other marketed heartworm preventatives combined since 1987. That is 145 and 30.

(Slide.)

For the 192 SGPT/ALT elevations the reporting veterinarians indicated that at the time of Proheart 6 administration the health status of the dogs was good in 149 of them, fair in 36, poor in six, and unknown in one; 38 of these dogs died. Among the 65 dogs with liver lesions the reporting veterinarian said that at the time of administration the health status of these dogs was good in 50 of those 65, fair in 13, and unknown in two; 47 of these dogs died.

(Slide.)

Of the dogs with SGPT/ALT elevations, 50 of them did not receive a concomitant drug or vaccination, 112 of them did, and the concomitant status for these 30 is unknown. Of the dogs with liver lesions, 13 did not have concomitant drugs or vaccines and 44 had concomitance. The concomitant status for eight dogs is not known.

(Slide.)

Onset times for liver problems may be seen in the first three months after an insult. Here you see an interesting distribution pattern for these liver enzyme elevations represented in the light green of the bar charts. There is what may be an acute process after administration with episodes corresponding to rising or peak serum levels at up to 14 days. Then you get a second set of what may be

more latent reactions at one to three months after the administration. The onset times for the liver lesions is more difficult to interpret because of course with these lesions the onset time is considered to be the time that the lesion is -- that the biopsy or the histopath tissues are taken. And so it is difficult of course to retroactively decide when the actual onset was, but these are the times that they were determined.

(Slide.)

Another serious concern has been the number of dogs with hematologic or blood-related problems. Thrombocytopenia or low platelet count and anemia or red blood cell count were among the most commonly reported hematologic signs. In dogs low platelet count is frequently caused by the destruction of platelets by an immune response. Immune-mediated hemolytic anemia represented here as IMHA is a life-threatening condition that occurs with an immune response causes the destruction of red blood cells. Again, the assessments for these two problems in dogs receiving ProHeart 6 during the first three years of its approval exceed the assessments for all the other monthly heartworm preventatives combined for all marketed use. For low platelets there were 124 assessments for ProHeart 6, 86 for the other heartworm preventives. For hemolytic anemia

there were 67 assessments for ProHeart 6 and 51 for all the other preventives.

(Slide.)

The onset times for low platelets were similar to those for hemolytic anemia; 43 percent of the low platelets, represented here by the dark-brown bar graph, occurred between one week and one month following the ProHeart 6 administration. Approximately one-half of the hemolytic anemias, represented by the lighter-brown bar graph, occurred between one week and one month following the ProHeart 6 administration.

(Slide.)

For the 124 episodes of low platelets, the reporting veterinarians indicated that at the time of ProHeart 6 administration the health status of the dogs was good in 91, fair in 28, and poor in four. The health status for the dog in that one episode is not known; 45 of these 124 dogs died. For the 67 dogs with hemolytic anemia, the reporting veterinarians indicated their health status was good at the time of administration for 56 of them, fair in 10, and poor in one; 34 of these 67 dogs died.

(Slide.)

Looking at the concomitant status of the dogs with low platelets, in 26 episodes no concomitants were

given. In 76 episodes concomitant drugs or vaccines were given, and the concomitant status for 22 episodes is not known. Of the dogs with hemolytic anemia, 19 did not have concomitant drugs or vaccines, 34 did, and the concomitant status for 14 is unknown.

(Slide.)

I have outlined for you several categories of striking debilitating effects that we have assessed as being possibly associated with the administration of ProHeart 6 such as anaphylactoid reactions, convulsions, low platelets, hemolytic anemia, elevation of liver enzymes and the emergence of liver lesions. They are strongly associated with ProHeart 6 administration by their timing. These are the effects that have driven our concerns.

Dr. Post described the regulatory history of ProHeart 6 showing that the Center for Veterinary Medicine recognized problems and met with the sponsor about them. Label changes, "Dear Doctor" letters, and client information sheets were established. But despite these efforts, we have not seen an appreciable decrease in the numbers of reports received or of serious reactions if you will look at each marketed year from 2001, 2002, 2003, and 2004. The number of deaths possibly or probably related to ProHeart 6 has increased each year since the product was marketed

(Slide.)

The number of assessments for anaphylactoid reactions has decreased since the June, 2002 label change, but it still remains relatively high. The number of assessments for convulsions as we look at each marketed year is not appreciably different. The assessments for the other clinical manifestations involving liver changes and low platelets have increased over time. The assessments for hemolytic anemia appear to be unchanged over the past year.

(Slide.)

The sponsor of an animal drug product has the responsibility to demonstrate that the product is safe and effective prior to approval, but due to the limited size and controlled nature of pre-marketing studies only the most common adverse drug events are known before a new animal drug is marketed. The Center for Veterinary Medicine has a post-marketing system to detect adverse drug events that occur after marketing and when an animal drug is used in a larger and more diverse population. If we determine that a marketed animal drug is likely to be causing serious adverse drug effects, we must take action to prevent additional harm to the animals receiving the product.

(Slide.)

The frequency of ProHeart 6 adverse events,

the severity of these events, which include death, and the temporal association with the administration of ProHeart 6 correlating with established serum levels in dogs that are n good health at the time of administration all raise serious questions about the safety of this product. In working with Fort Dodge Animal Health to address the adverse events associated with ProHeart 6, the Center for Veterinary Medicine has requested three label revisions. Despite these changes, we have continued to receive a large number of serious adverse drug events related to ProHeart 6.

(Slide.)

ProHeart 6 is used to prevent disease in healthy dogs. The adverse drug events associated with ProHeart 6 are particularly striking when compared to other marketed heartworm preventive products. These other products have been on the market longer and have fewer reported serious adverse effects. These are the reasons that led the Center for Veterinary Medicine to request that Fort Dodge Animal Health stop marketing this product until we are satisfied that ProHeart 6 can be safely used in dogs.

Fort Dodge Animal Health will now have the opportunity to present their information on ProHeart 6. I would like to ask you to keep several points in mind while listening to their presentation.

(Slide.)

First of all, the toxicology data presented in Fort Dodge's narrative refers to the oral route of administration. Fort Dodge makes the statement that the toxicological profile of the oral route is relevant to the other routes of administration because of limited metabolism and the long terminal half life. But considering the large numbers of allergic assessments after injection and the possible association with immune-mediated diseases such as low platelets and hemolytic anemia seen in the post-marketing period, this is no longer an assumption that can be made.

(Slide.)

Fort Dodge's narrative states "Approximately 18 million doses of ProHeart 6 have been sold, with more than 12 million doses administered." Fort Dodge calculated reporting rates by taking the number of reports, divided by an estimate of doses sold to veterinarians for the same period. Well, this is problematic because only two-thirds of the doses sold were actually administered, and the doses were not necessarily administered in the same quarter in which they were sold. Also, a dose administered is an estimated dose. It is based on the average number of doses in a vial. Now if one practice sees many small dogs and

another one sees many large dogs, then one will have many more doses in a vial compared to the other. That might all even out in the wash, but it is still just a guesstimate.

It is also important to point out that the numbers calculated by Fort Dodge represent reporting rates, not incidence rates, and that a decline in reported events over time does not necessarily mean a decline in incidence. Reporting of adverse events is usually highest when the product is first marketed and declines over time, sometimes referred to as the Weber Effect.

(Slide.)

According to the Fort Dodge narrative, there were 1.26 allergy event reports per 10,000 doses sold. This reporting rate is two-and-a-half times higher than for Rabvac 3, Fort Dodges rabies vaccine, and 3.1 times higher than for Duramune Max 5L, their distemper-parvo-lepto combination vaccine. Additionally it is mentioned that only 37 percent of these allergy event reports had concomitant vaccine, meaning 63 percent did not have any other reason to react.

Of course many of us are not comfortable in the first place with comparing of biological products such as a vaccine that is supposed to stimulate the immune system, and that might just be expected to result in

allergic reactions, with a drug that has an entirely different purpose and mode of action for which we are not expecting allergic reactions at all. Keep in mind the label clearly states in well-controlled clinical studies ProHeart 6 was safely used in conjunction with a variety of veterinary products including vaccines, anthelmintics, anti-parasitics, antibiotics, analgesics, steroids, non-steroidal anti-inflammatory drugs, anesthetics and flea control products.

(Slide.)

According to the Fort Dodge narrative, there were 1.19 non-allergy event reports per 10,000 doses sold. This reporting rate is four times higher than for Duramune Max and 3.4 times higher than for Rabvac 3; 42 percent of these dogs had concomitant vaccines, leaving us with 58 percent that did not have any other known reason to react.

(Slide.)

Fort Dodge's narrative states "The adverse event case fatality rate associated with ProHeart 6 reports is lower than many Fort Dodge Animal Health harmaceuticals and similar to case fatality rates for the Fort Dodge Animal Health canine vaccine product lines, including Duramune Max 5/4L. Thus the incidence of death does not appear to be causally related to ProHeart 6 usage." Now this is a

difficult connection to make. What are these other Fort Dodge Animal Health pharmaceuticals, and under what circumstances are they be used? What is their target population? Are they injectables? If so, are they anesthetic agents such as Ketaset and Telazol? Are they non-steroidal anti-inflammatories like Ketofen? Does this included euthanasia products like Sleepaway? And how do case fatality rates for Fort Dodge vaccines compare to those for other manufacturers? That information is simply not available. We just cannot make this kind of statement.

(Slide.)

On page 49 of their narrative, Fort Dodge explains how it evaluated adverse event reports by body system, and this is a schematic based on the narrative. All the events were assigned to the medical association category of possible as a starting point. Events considered not likely to be associated with ProHeart 6 were excluded over here as unlikely. The possible group was further reviewed to distinguish between events that were potentially or probably related to specific body systems. The probable group included only those clinical signs that have a reasonable probability of being related to that body system. Events classified as allergic were excluded from the probable group. For neurologic, hematologic and hepatic

cases, only those in the probable category were submitted by Fort Dodge to the highly-esteemed experts for review.

I find this description thoroughly confusing. What is the formalized process for deciding on the categories of unlikely, possible, potential, probable? What is the standardized process for determining which reports go into which categories? What happens with signs like fever or death that aren't associated with any one body system? This all seems highly selective and very subjective. Furthermore, only those in this probable group are included in the calculated reaction rates. It is especially hard to understand why all the cases considered as allergic defined by Fort Dodge as those occurring with the first 48 hours of administration seem to have been excluded from the probable category. Is not the large number of allergic reactions to say nothing of the possibility of subsequent lasting after-effects one of our primary concerns?

(Slide.)

Finally we come to analysis from Banfield, the pet hospital. At first sight you may be impressed by the thought of the wealth of data here for the mining; more than 700,000 doses of ProHeart 6 administered across the country, over eight million patient records available for analysis. But as always, the analysis is really dependent

on the study design. One significant problem is selection bias. Fort Dodge Animal Health compares the number of events that occur among dogs that receive ProHeart 6 here, dogs that received an oral heartworm preventive one or an oral heartworm preventive two, and dogs that received no heartworm preventives at the time of their office visit. Keep that in mind. Both with and without the concomitant administration of vaccines.

Now you will notice that there are more than 5.5 million office visits where dogs received no heartworm preventives. Right away you know that many of these dogs must actually be on heartworm preventive of some kind. It just was not dispensed at that visit. Many owners buy six months supplies or even 12 months at a time. Many owners buy their supplies online or from catalog companies. Perhaps some of these dogs received ProHeart 6 a couple of months before their owners decided to go to Banfield. Also the dogs are not randomly allocated to these different treatment groups, and there is no evidence that these different groups of dogs are comparable, particularly with respect to health status. In fact, there is evidence to the contrary. The adverse event rate was highest for dogs that did not receive a heartworm preventive or a vaccine. And might the health status of these dogs be skewed by

participation in the Banfield Wellness Plan? So these are not in fact a control group, and neither can they be used as a normal baseline for incidence of background effect.

Now what about just comparing the different heartworm products? ProHeart 6 has a market share of about 24 percent in the United States. Among the heartworm preventive encounters at Banfield, 63 percent of them involve ProHeart 6. Consider also that dogs that received heartworm preventive one and two, the oral forms, may have been in poorer health to begin with than those that received ProHeart 6. The ProHeart 6 label states use with caution in sick, debilitated or underweight animals. Furthermore, in this study Fort Dodge assumed that these oral monthly heartworm preventives were administered on the same day that they were dispensed. They concluded that this assumption would result in an underestimate of adverse events. However the opposite may well be true. An owner that brings a sick dog into Banfield for treatment may also purchase a refill of their monthly heartworm medication during that same encounter.

Information bias or observation bias is defined as a flaw in measuring exposure or outcome data that results in different quality or accuracy of information between two comparison groups. It arises from a systematic

difference in the way that exposure or outcome is measured between compared groups. Well, we have already seen how exposure was assessed different, injection of one drug versus oral administration

or, excuse me, purchase perhaps, not necessarily administration that same day of another, versus none dispensed or injected at that particular visit. Another big limitation of this retrospective study is the follow-up of cases. Fort Dodge indicates that each encounter was evaluated for potential adverse events over the following 30 days. However, Fort Dodge does not state how follow-up was done and whether follow-up was similar among these different treatment groups.

Now Banfield has a quality assurance team, and I understand they make follow-up telephone calls after a pet has left their care. But does that continue for 30 days? What if the pet is fine at the three-day callback, but has a problem at day 15 and the owner just doesn't report it? We all know how frustrating it is to think a pet is doing well because the owner hasn't brought him in, and then we find out, oh, they didn't think it was something we should be troubled with, or they tried something suggested by the attendant at the health food store, or they couldn't afford care at the time, or even that they were so upset

with the treatment they received that they went somewhere else. Often when there is an after-hours emergency it is the emergency clinic staff that handles the diagnosis and the referral. Owners may be so upset and angry they never come back to their primary veterinarian. We may never find out what happened until we send that annual checkup reminder for the second or the third time; and of course there may be people who use Banfield for wellcare like vaccines and heartworm preventive, and use another veterinarian for more serious issues. Without an established, consistent method of follow-up for all patients you cannot say a reaction didn't happen just because the owner didn't come in.

Thank you very much for the attention you have given me today, and I will ask you to please keep these points in mind as you now turn that same attention to the representatives from Fort Dodge Animal Health.

MS. SINDELAR: Thank you, Margarita. We are moving along very well. Why don't we take a break now until 10 a.m. If you all will please reconvene at 10 a.m. in the room. Thank you.

(Whereupon, a brief break was taken.)

DR. SUNDLOF: Okay. We are missing our chair. Oh, there he is. Okay. We will reconvene, and you have heard from the Center for Veterinary Medicine. Now it

is my pleasure to have speakers from Fort Dodge Animal Health present their interpretation of the data. So we will go through these presentations and then hopefully we will have a little time, approximately a half-hour before lunch, so that we can start the discussion. We will ask the Advisory Committee to begin the discussion. You are free to ask any of the speakers any questions that you want clarification on, and then after lunch we will begin again. So the first speaker is Dr. Cobb from Fort Dodge.

ProHeart 6 ADEs/FDAH

Dr. Rami Cobb

DR. COBB: Good morning. My name is Rami Cobb. I am Vice President for Pharmaceutical Research and Development at Fort Dodge Animal Health, and I would like to thank the panel and I would like to thank the FDA for the opportunity for us to present the data which support the safety of ProHeart 6.

(Slide.)

Very quickly, moxidectin is the active ingredient in this product. It is a macrocyclic lactone and it is widely used in veterinary medicine as an antiparasitic for horses, dogs, cattle, sheep, swine, and a number of minor species in more than 70 countries around the world. This compound is also in co-development with the World

Health Organization for control of river blindness, onchocerciasis, in humans.

(Slide.)

It is an innovative product in that a single dose provides six months of protection from heartworm disease called by Dirofilaria immitis. In addition, it treats existing hookworms in treated dogs and it brings a singular advantage of overcoming the compliance failures that do exist when monthly products have to be administered to dogs by their owners.

(Slide.)

Reference has been made to the toxicology package which supports ProHeart 6. This is a very extensive toxicology package because this product is approved for use in food-producing animals. In addition to the core tox package, we have recently completely 60 receptor screens that showed no adverse potential for pharmacologic or toxicologic effects, and the data from these screens will be submitted to their CVM for the review as soon as the report is written. In terms of the relevance of the toxicology studies, we have studies of up to two years duration in mice and rats and of one year in dogs. There were no target organs in these studies. There were no histologic or biochemical effects on any organ system. So when we

consider the relevance of these oral toxicology studies to blood levels obtained from injection of ProHeart 6, we find that the exposure of dogs to moxidectin in these studies was 454-fold higher than would be obtained from being given two doses of ProHeart 6 over a one-year period. The two-year carcinogenicity studies showed no increase in tumors.

(Slide.)

In addition to the toxicology, we have conducted a large number of clinical safety studies. These studies demonstrate that the product, the formulated product ProHeart 6, has a wide margin of safety. It is safe to use in breeding animals, both female and male, and it is safe to use in unique canine populations such as ivermectin-sensitive

breeds of dogs and heartworm-positive dogs. In all of these studies at the commercial dose rate of ProHeart 6 there was 100 percent efficacy in controlling heartworm infection, and this occurred not just in laboratory strains of dogs, but in studies with a large number of breeds and crossbred dogs. In the US studies alone, a total of 770 dogs were evaluated, and there were additional studies conducted in international markets.

(Slide.)

If we look at the factors that limit

heartworm control in US dogs, we find that information can be difficult, but I would reference an American Heartworm Society survey conducted in 2001 which found that despite the widespread availability of monthly heartworm preventives there had not been a change in the infection rate of dogs with heartworm in the past 10 years. Some 240,000 dogs were reported testing for heartworm in the United States in 2001. In another survey of dog owners, one-fifth of the dog owners surveyed had missed giving one or more doses of a monthly product to their dogs and had stopped giving oral preventives altogether.

(Slide.)

If we look at our field experience with ProHeart 6, it has been approved and marketed in many countries where heartworm is endemic. The approval in the United States was in June, 2001, and I have listed the other countries where this product is approved and sold. In Australia a similar product, ProHeart SR 12, was approved in October, 2000. This product is used in dogs to provide 12 continuous months of protection against heartworm since the heartworm transmission season there is 12 months long. This product is administered to dogs and is three times the ProHeart 6 dose.

(Slide.)

Our experience with this product has been that there was rapid and broad acceptance by dog owners and veterinary professionals of these products. In the United States the product achieved 24 percent market share and in Australia 47 percent market share.

(Slide.)

If we look at that evolution we find that ProHeart 6 has shown a steady increase in acceptance from launch until the time of its removal from the US market, and similarly in Australia. This is in the face of either steady or declining usage of the monthly products. Almost half of all dogs in Australia that received preventives for heartworm are protected by ProHeart.

(Slide.)

If we look at our adverse event reporting experience recognizing all the deficiencies that go with passive reporting systems, we find that in Australia we, too, have sold significant numbers of doses. Something in excess of 2.2 million doses have been sold in Australia, and I have listed there for you the adverse event reporting rates split out by allergy and by death, areas that were classed as significant by the CVM. The reporting system in Australia is very similar to that in the US. It relies on voluntary reporting by veterinarians, pet owners and the

public, and mandatory reporting by companies.

(Slide.)

In September, 2004, Fort Dodge announced a voluntary recall of ProHeart 6 based on CVM's expressed concerns about the adverse events. These data, we obviously notified the regulatory agencies of other countries where these products are sold, and data were reviewed by the Canadian, Australian, European, and Japanese regulatory authorities. They reviewed not only their own country's post-marketing experience. They also reviewed the US post-marketing experience, and all of these countries confirmed our authorization to continue marketing the product.

(Slide.)

I would like to introduce the two speakers we will have to present our case, and I believe that they will certainly address all of the questions that have been raised by the CVM. Firstly, Dr. Larry Glickman from Purdue University. I think he is known to many of you through his publications. He is he professor of epidemiology and head of the section of clinical epidemiology at Purdue's School of Veterinary Medicine. He is a veterinarian and a Ph.D. in epidemiology. He is also the recipient of many awards and honors, and I would like to just highlight several of those. The Merck Award for Creative in Veterinary Education, the

Pfizer Research Award, the AKC Award for Outstanding Canine Research, and the Outstanding Alumni Award from the University of Pennsylvania. Dr. Glickman comes with excellent credentials.

He conducted a landmark epidemiological survey from a large independent nationwide database, and I want to express my thanks to Banfield, The Pet Hospital, for making that database available for the study, and it covers almost seven million encounters of office visits by dogs to veterinarians. The study evaluated ProHeart 6, two heartworm preventives and vaccines. The results of the study demonstrate no clinically significant increase in adverse events following ProHeart 6 treatment, and that the ProHeart 6 safety profile is similar to that of two monthly heartworm preventives.

Our second speaker is Dr. David Hustead of Fort Dodge Animal Health. In addition to working for Fort Dodge, Dr. Hustead is a member of the VICH Expert Working Group on Pharmacovigilance and is qualified to speak to this issue.

We did conduct a re-review of our database for adverse event reports following the September recall. In this we were assisted by independent experts with expertise in particular areas such as liver, hematology, and

neoplasia. Our conclusions following this review are that the overall reporting rate for ProHeart 6 is low. The reporting rate is declining, and we will specifically address that. Most adverse events appear to be allergic, mild, and self-limiting, that the assignment causality is confounded by concurrent vaccinations, and there is a very varied database of non-allergic adverse event reactions with no pattern that reflect diseases that are commonly seen in dogs.

So thank you. I would like to welcome our first speaker, Dr. Glickman.

A Controlled Epidemiological Study: The Safety Profile of ProHeart 6 and Two Monthly Heartworm Preventives in Dogs

Dr. Larry Glickman

DR. GLICKMAN: Thank you, Rami. I would like to take this opportunity to present to you the results of the controlled epidemiologic study that we conducted. We call it "The Safety Profile of ProHeart 6 and Two Monthly Heartworm Preventives in Dogs." Now as Rami says, it used the large Banfield database and support for development of the database to do this kind of study has been received from Fort Dodge Animal Health, the Centers for Disease Control, Center for Infectious Diseases, and the Food and Drug Administration Center for Veterinary Medicine. This report

will summarize the experience of approximately 900 Banfield veterinarians nationwide who at the time we did the study had administered greater than 700,000 doses of ProHeart 6 to dogs. Banfield practices are -- emphasize preventive medicine, and they are evidence based. Many of their dog owners do belong to the
Wellness Program, which then covers examinations, parasite testing twice a year.

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There are now over 400 Banfield hospitals located in 43 states in the United States, making them very representative geographically. All these hospitals follow similar protocols in the diagnosis, prevention, and treatment of illness. All drugs and vaccines are thoroughly evaluated by Banfield committees before they are adopted and used.

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Now what are some of the advantages of using a large database like this? You have heard from previous speakers the disadvantages of just receiving unfiltered passive reports about adverse events. So what advantage does using this database bring for post-marketing surveillance? First of all, Banfield veterinarians serve two percent or more of the US dog population and is

certainly representative with respect to breed and geography. What is really important to epidemiologic studies is all their medical records are standardized. They are computerized, and they are stored electrically in a central data warehouse. They do routine quality assurance of these records, and all dogs that died routinely review the case records to try and determine causality. You heard before that passive reporting lacks good numerators and good denominators. We think we have both. Good denominators because there is more complete ascertainment of adverse events, follow-up calls are made to all clients after each visit, and since all drugs and vaccines are warranted by the company owners are more likely to return if a problem arises or they perceive a problem.

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Now we were not selective in how we chose the Banfield dogs to include in this study. We took all dog encounters or dog visits over a two-year period from January 1st, 2002, to August 31st, '04, when the drug was voluntarily recalled. Each encounter was evaluated for potential adverse events over the subsequent 30 days, and I would like to emphasize all follow-ups were done the same way regardless of what drug or other treatment the animal may have received. We divided these office visits or

encounters into whether the animal, the dog, had received ProHeart or not, whether they got one of two monthly heartworm preventives which we are going to call heartworm one and heartworm two, whether they were vaccinated or not, or whether they received none of these products. We then calculated adverse events per 10,000 dog visit or encounters, and because of this I will explain in a few minutes the follow-ups weren't necessarily exactly 30 days. For example, when an animal dies. We also calculated the adverse event rate per 10,000 days at risk.

As has been alluded to previously, there are potentially many confounding factors when doing adverse event studies. Other drugs to be given, vaccines to be given. Dogs could have been treated with drugs for other reasons, for example steroidal anti-inflammatories. We took this into account in our final analysis by taking all these potential confounding factors into account.

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Now this first slide actually was shown to you earlier this morning. We looked at a total of almost seven million encounters over this two-year period of time. We broke these encounters down into whether the dogs had received ProHeart or not, heartworm preventive one or not, heartworm preventive two or not, or no treatment. That

included then all dogs seen at Banfield. Within each of those categories we subdivided them into whether they had received a vaccine or not, and that is shown on the website of this slide.

Now I would like to point out some interesting highlights here for you. You see three sets of numbers under each drug. For example, you see a large N, which are number of encounters in which that drug was given. So for ProHeart it would be a total of 735,000-plus. For heartworm preventive one vaccine, yes/no, heartworm preventive two vaccine, yes/no, and you also see then the number of animals in the category, the number of dogs. That's the N. The NA is the number of adverse events, and the rate which is the second column divided by the first column. So we are looking at incidence rates. We are not just counting events, and several things are striking from this.

First of all, if you look at the ProHeart and the heartworm one or the heartworm two, and they are in yellow there, if you look at the rates you can see that when animals receive this product, any of these products without vaccine, the rates are remarkably similar; 89.2 for ProHeart, 89.1 for heartworm preventive one, and 70 for heartworm preventive two. Now the rates are higher in the

last group, the animals that received no heartworm treatment, because those are probably sicker animals coming to the hospital for diagnosis. So for completeness we include them, but they are not really our primary comparison group. We are comparing events between the three heartworm preventives.

Within each of the heartworm preventive categories you can see if you look at vaccine yes and vaccine no there are approximately twice as many dogs that receive vaccine at the same time they receive ProHeart. Same for heartworm preventive two, approximately twice as many were vaccinated as not vaccinated, and the same for heartworm preventive two. Why is this important? Because we know vaccines are associated with adverse events themselves, and so you cannot ignore this heavy use of vaccine at the same time these preventives are given. Otherwise you get a biased outcome.

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Now this shows the use by Banfield veterinarians over time of ProHeart 6. There are two lines on the graph. The upper are dotted lines. It shows the number of animals that received ProHeart with vaccine. The bottom solid line are the number of dogs that had ProHeart without vaccine, and you can see it is roughly a two-to-one

ratio there. You can also see the seasonal pattern in the use of ProHeart with the peaks occurring each year during the peak of mosquito activity, usually from about April or May through September. The third thing is obvious that over this period of time there was increased use of ProHeart by Banfield veterinarians.

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I would like to walk you through our initial analysis where we looked at and calculated adverse event rates for animals receiving each of these products or divided into these eight groups. These eight groups are shown on the left. As we said, there are four possibilities -- ProHeart, heartworm one, heartworm two, or any vaccine -- and we show you then in the top row the animals that received none of these, and so there are no Ys in those boxes. The next one would be animals that received any vaccine, so it would have a Y under a vaccine, and then further down you see each of the heartworm preventives, both alone and with a vaccine. We looked at a variety of potential associated adverse event types. They are shown across the top: liver disease, neurologic disease, ocular disease, immune-mediated disease, and allergic reactions.

First let me focus your attention on ocular disease, for which there was a very low rate of adverse

events. Overall if you look in the any row, the bottom row, there was only 0.3 per 10,000 ocular events, and so it was hard to distinguish between drug types. For neurologic disease the rate was higher overall, 6.1, and the rates were fairly consistent between the three heartworm preventives. Immune-mediated the same, the overall rate is 5.1, and the comparisons between the three heartworm products did not point out any major differences. Allergic reactions are very interesting, and I will talk to them in a separate slide shortly. I would like to focus your attention here to liver disease, where if you look at the top row these are the animals we expected to be the sickest, and they had the highest adverse event rate per 10,000 at 61.6. If you look at vaccine alone, which would be the second row, the rate is 35.0. Then if you look at the three heartworm products going down with or without vaccine, you can see the rates are fairly similar. But in this analysis, which was unadjusted for any potential confounders like age or weight or use of other drugs like steroids, the ProHeart group, especially with vaccine, has the highest rate at 41.6 per 10,000.

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Now as I said, we also looked at adverse events when calculated per 10,000 days of risk. Why did we

do this? Because the way we follow it up in animals, an animal following a drug administration, for example ProHeart 6, we looked over the next 30 days to see if they had any adverse events. If they had for example an adverse liver event we counted that and then kept looking over the remaining part of the 39 days. However, if they are in the 30-day period an animal had received a vaccine -- let's say on day 14 following ProHeart, we would stop the follow-up with ProHeart at day 14 and then start a new 30-day follow-up associated with the vaccine. As a result, not all of the follow-up periods for all the products were exactly the same. In fact, they were slightly longer for ProHeart 6. Therefore, the importance of adjusting our rates per 10,000 days at risk, and if you look at this graph then you can see that the adverse event rate for the oral monthly heartworm preventives being 1.15 and 0.79 are not too different from what you see for ProHeart 6 when adjusting for days at risk. Again, the animals that received none had the highest rate, which we expected.

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Now let's look at some other potential adverse events in the same way. We have looked at death, cancer, cardiovascular disease and anaphylaxis. Now the rates for both -- for anaphylaxis were extremely low, a

total of 0.5 per 10,000, and were not very different between the products. The cardiovascular disease rate was slightly higher, overall 16.6, but also not different between the two monthlies and the ProHeart.

There are some striking findings though with respect to what we all agree is the most serious adverse outcome, which is death. When you look at the overall death rate, the last row under death and under rate, you can see that rate is 116.2 per 10,000. Then when you look further up now and look at the different products, the heartworm products of vaccines, you see that they are very similar except for one product. Heartworm one when given without any vaccine, the adverse event rate was the highest at 22.0 per 10,000.

The cancer rates I am going speak to separately. They also seem not to be similar between the groups in that the adverse event rates, meaning cancer, are slightly higher for the ProHeart 6 group both with and without vaccine, 6.1 and 4.2 per 10,000. We are going to get back to this and look at it in more detail.

Now I said I was going to get back to the allergic reactions because we've never had data like this to look at in terms of what products are associated with what reactions. But we look at the second row down, which is

vaccine, only vaccine, the adverse event rate was 44.3 per 10,000. But if you then look at heartworm two alone, heartworm one alone, or ProHeart alone, you get 51.8, 14.3, 54.3. Very similar but slightly higher than what we see for vaccine. So that was for the products given with vaccine.

When you look at the products give alone, heartworm two alone the rate is 18.7, heartworm one alone allergic reaction is 14.3, and ProHeart alone 18.4. Here we can really see the impact of vaccine when given with a heartworm product. It increased the rate by about two-and-a-half fold, once again suggesting you cannot ignore administration of concurrent vaccine with heartworm preventives when you are looking at adverse event reports.

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Once again to adjust for differences in the length of follow-up, this shows the relative rates of allergic reactions per 10,000, and you can see heartworm one, heartworm two, and ProHeart 6 are very comparable with vaccines clearly having the highest risk of allergic events.

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Now I said I would come back to cancer. We looked at three cancers -- lymphosarcoma, histiocytoma, and mast cell tumors -- because these are very common tumors in dogs, and previously we saw that ProHeart might be

associated with a high risk of cancer. Well, in fact, that increased risk is only found with mast cell tumor. If you look at the adverse event rate for heartworm one only it is 0.024, whereas for ProHeart 6 it is 0.072. So the important point here is the absolute rates are extremely small, but there is a slight increase with ProHeart 6 when it comes to mast cell tumor and it is also higher than you see with vaccine, but again the absolute difference is very small.

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As I said, it is important to adjust the potential confounding factors like age, like weight, when you are looking at the effects of the three heartworm preventives, and that is what we did in each of these models. So the results I am showing you are fully adjusted for everything else that we looked at, and the ones that I am going to show you are the only ones that came out statistically significant at P less than 0.05. So in the adverse event model for liver disease, which this one is, steroids increase the risk of liver disease by 25 percent. Which is not a surprising finding knowing what we do about the effect of steroids on the liver. In this fully-adjusted model now, ProHeart 6 is not associated with an increased risk of liver adverse events. Matter of fact, it suggests a decreased risk, and each additional dose of ProHeart given

further decreases the risk by eight percent. Now the reason this may be a little misleading is because of the bottom entry there. You see interaction of Proheart 6 and age, and the high significance level suggests that age is modifying the effect of ProHeart in terms of adverse events regarding the liver.

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So we plotted out what the age effect is. So on the X axis you see age in years, Y axis is the risk of liver disease, and you can see there is a relations. It is a straight line. But in dogs less than four years of age ProHeart is actually associated with a decreased risk of liver disease, while with older dogs, older than four, it is associated with an increased risk. But the overall net effect is no increased risk.

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Now we built a similar model for allergic reactions. We can go over this quickly because ProHeart, heartworm, and vaccine -- and this is heartworm one -- appear to all increase the risk of allergic reactions consistent with the previous findings. But vaccine has by far the greatest effect, increasing risk of allergic events by 151 percent. Now the two anti-inflammatory classes, non-steroidals and steroidals, also increased the risk of

allergic events, but it was theorized we are pretty sure this happens because steroids are actually used to treat allergic events. Once again each additional dose of ProHeart is actually a decreased risk of liver events. That is important. So the more ProHeart you give, you would not expect to see an increase in allergic event, but actually a decrease.

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Now this is the adjusted model looking at the adverse events associated for cancer. Lymphosarcoma and histiocytoma, there were no relationships between risk for those cancers and any of the heartworm preventive products. Steroids still increase the risk of lymphosarcoma, but that is because it is used to treat lymphosarcoma. Now with mast cell tumor we did confirm a slightly increased risk associated for ProHeart use, increased by 27 percent, and a very unexpected finding was an increased risk of mast cell tumor associated with non-steroidal anti-inflammatory use, and we need to explore this further.

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Of course death certainly is the most severe reaction, and in this fully-adjusted model heartworm one, the most commonly used monthly oral, appeared to increase the risk of death by 23 percent. Whereas ProHeart actually

decreased the risk by 71 percent, and each additional ProHeart further decreased the risk of death by nine percent.

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So what do we conclude from these analyses? I concluded that the safety profile of ProHeart is similar to two monthly heartworm preventives, the two orals, with two exceptions. One, there is an up-to-now biologically unexplained but very small increased risk of mast cell tumor following ProHeart 6 administration. Perhaps more important is the 23 percent increased risk of death following the use of the most common monthly heartworm preventive. In our study that is heartworm one. The other thing I think it is important to realize is that the adverse events probably were underestimated for the monthly heartworm preventative versus the injectables. Why? Because veterinarians are more likely to observe an adverse event when they give the product and the animal is actually in the office, whereas they are less likely to observe adverse events when the drug is given at home by the owner. Also we know and we have heard that many owners don't administer the oral medications when they are supposed to, and yet we are counting adverse events as if they were given. So again we are going to underestimate the rates with these products.

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I want to emphasize that these epidemiologic analyses adjusted for effects of concurrent vaccination and other potential confounding factors of which we found several, and it is hard to interpret results of adverse events without adjusting for these. Unlike passive reporting systems that are unable to calculate incidence rates, we can calculate incidence rates, and as important we can compare these incidence rates between the heartworm products. We utilize recorded medical events and not unfiltered reports from veterinarians or owners. We know there are biases associated with reports from owners and veterinarians, and certainly unreporting. We don't have that problem with our database. This database gave us an opportunity to test causal hypotheses that were generated through the FDA CVM passive reporting system, and I think this is the appropriate use of epidemiology, both in human medicine and veterinary medicine.

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My final conclusion, and I believe this based on the results I showed you and based on results I have not shown you for lack of time, that the safety profile of ProHeart 6 in controlled epidemiologic studies was definitely favorable compared with two monthly heartworm

preventatives. My own conclusion is that there appears to be no scientific rationale for the continued withdrawal of ProHeart 6 from the marketplace. Thank you.

FDAH Adverse Event Report Re-Analysis

Dr. David Hustead

DR. HUSTEAD: My name is Dave Hustead. I am a Senior Director at Fort Dodge Animal Health. My areas of responsibility are technical and regulatory affairs. I am going to present to you today a re-analysis of ProHeart 6 adverse events.

Before I start my prepared presentation though, I have been asked by the FDA to offer a subtle correction to Dr. Post's presentation. Dr. Post did show you a very nice three-line graph with three different colors for the numbers of adverse drug experience reports received by the CVM. While the graph he presented was correct, his verbal description of the legends for the three lines was incorrect. So we would ask that you look at that graph carefully and interpret it appropriately. The graph does show that the number of initial adverse drug experience reports are declining to the CVM.

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At Fort Dodge Animal Health our Professional Services Department is responsible for adverse event

investigations. They are also responsible for the regulatory compliance associated with those investigations. They have additional responsibilities in technical support and professional customer service. We have 28 veterinarians in our Professional Services Department. They have extensive practical clinical experience prior to joining industry. In addition, we have three PhDs and seven veterinary technicians.

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All reports of suspected adverse events are investigated by Fort Dodge Animal Health staff. To improve the quality of the data that we collect during those investigations, Fort Dodge Animal Health routinely pays for diagnostic services, including referrals to specialists. All reports received, regardless of causality and regardless of scientific plausibility, are recorded and submitted to the CVM per our regulations 21 CFR Chapter 514.8.

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To add in the analysis of adverse event reports, Fort Dodge places those reports into four categories. Those categories are injection site reports, allergy reports, non-allergic systemic reports, and lack of efficacy reports.

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We conduct medical association assessments based on VICH-approved draft guidelines. VICH is an international group of regulators and industry attempting to standardize and harmonize the differing regulations involved with adverse event reporting. I am proud to be a member of that group. As recommended by VICH, Fort Dodge Animal Health assesses each event as a whole. This is in contrast to the CVM practice of assessing each causality assessment individually and in isolation. We use three categories of the VICH system: possible, unlikely, and probable. All events are placed into the possible category. Possible means that the drug of concern is one of equally plausible explanations.

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If during our investigation we obtain sufficient information to determine that the event is not likely to be associated with the product or there are other more plausible explanations, the event is then placed in the unlikely association category. For an event to be placed in the association probable category all the following must be met. There must be a reasonable association in time; the adverse event should be reasonable given what is known about the pharmacology of the drug and the toxicology of the drug; and there should be no other equally plausible explanations.

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Now the CVM has said to you that ProHeart 6 has a very large number of adverse event reports associated with this use, and that this number of adverse event reports compares very unfavorably to monthly heartworm preventatives, and that this then supports a conclusion about the safety performance of ProHeart 6. Fort Dodge Animal Health believes that to make valid comparisons between products you must resolve a host of data inconsistencies, and often these comparisons are difficult if not impossible. Two primary areas of data inconsistencies are in the products themselves and then the users' expectations of those products, and then of the differing adverse event collection systems used to record adverse events for the different products. Product differences with ProHeart 6 as compared to monthly preventatives are that most monthly preventatives are given at home as a treat. There is a common belief among owners that medications given at home in this manner are not really drugs. If they are not really drugs then adverse clinical signs which are seen in the post-administration period may draw no association from the owner to product administration. If no association to the product is ever made, then no adverse event report is created. These

products, the monthly preventatives, are rarely given by veterinarians, and they are rarely given in conjunction with injectable products. These products have radically different sales, and sales differences do impact the numbers of adverse event reports which are received. Finally, the differing companies in this instance have differing adverse event collection systems. These systems collect, investigate, quantify, and then submit adverse event reports differently, and this creates substantial bias within the datasets for review. Unless these differing issues can be resolved, valid conclusions and comparisons are difficult if not impossible.

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ProHeart 6 has a substantial over-reporting bias associated with its use as compared to monthly heartworm preventatives, and these over-reporting biases become extremely valid if what you want to do is compare the rate of reporting of one product to another. ProHeart 6 is an innovative, sustained-released product. It was recently released on the marketplace. Early in its use veterinarians lacked an effective frame of reference to make reasonable conclusions about clinical signs they see in the post-administration period, drawing questions as to whether those clinical signs are or are not due to the drug which they

have just given. These questions then stimulate calls to our Customer Service Department because they know there is a wide range of veterinarians there with expertise to answer their questions. The product is a sustained-release drug. It is now plausible for a veterinarian to think that a set of clinical signs they see months post-administration just might be related to products used, again generating a call to the company.

Concurrent use with vaccine is common. Dr. Glickman has shown to you that vaccine use dramatically impacts adverse event reports. The CVM considers these events where ProHeart 6 and vaccine were used together as ProHeart 6 adverse events with concomitant vaccine use. It is equally valid to say the event is a vaccine adverse event with ProHeart 6 concomitant use. ProHeart 6 is injected by veterinarians. Injected drugs are viewed as powerful medications by the users and the clients. Veterinarians know exactly when the product was given because such is documented in the patient's record. If the animal subsequently has signs, the veterinarian easily sees in his record when ProHeart 6 was given.

Fort Dodge Animal Health has sent out two "Dear Doctor" letters during the time the product was on the market. These discussed safety issues associated with the

product. It is not unreasonable to think that these letters have created a bias amongst veterinarians to be concerned about clinical signs they would see in the post-administration period. Finally, there have been a large number and widely disseminated news reports and website postings critical of ProHeart 6. I can assure you if the veterinarians themselves have not seen these their clients have, and they have drawn these to the attention of their veterinarian. Clearly ProHeart 6 is subject to reporting biases that would not apply to monthly heartworm preventative products.

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Let me give you an example of how this over-reporting bias works. The practitioner is presented with a dog who has anemia and lethargy. When presented with a diagnostic dilemma the veterinarian will ask the owner questions about the dog's medical history. It is my experience based on decades now of adverse event reporting that veterinarians don't ask "When was your dog given his last heartworm preventative?" If this question is never asked then the veterinarian never draws an association to the clinical signs they are observing and the product that was given in the previous period. If they don't make that connection and adverse event report is never generated.

ProHeart 6 is very different. The veterinarian knows when ProHeart was given. He is then very likely to make a temporal association between the use of the product and the clinical signs being seen. As we have an effective Technical Services Department, this leads to a telephone call which basically goes, "This is what I've seen. What you guys think?" At that instant an adverse event report has been created, and that adverse event report, regardless of what we find in our investigation, will be submitted to the CVM.

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We believe we need to take a much closer look at the numbers of adverse event reports that the CVM has presented to you, and especially as how they compare the monthly heartworm preventatives to ProHeart 6. This is information that Fort Dodge was able to obtain from the CVM based on the Freedom of Information request. This is information not freely available. What I want you to see is to look carefully at the year 2003 and compare it to 2002, and notice for the monthly heartworm preventatives there is a dramatic increase in reporting between 2002 and 2003. Now Fort Dodge is not going to speculate about why this change exists. It is not germane to the issue that we have come here to discuss today, but it is important for you to notice

the difference in the pattern of reporting. It is also important for you to know that we have reviewed the pattern of reporting prior to 2001, and the low level that is seen in 2001 and 2002 continues in the previous history of these products.

Based on this data, Fort Dodge believes that it is inappropriate to sum the number of adverse event reports for the monthly heartworm preventatives and to conclude that the low number of adverse event reports associated with those monthly preventatives somehow supports a conclusion about the safety of ProHeart 6. It is very much apples and oranges. We believe that the differences in the numbers of adverse event reports much more clearly are an effect of the system involved in reporting those adverse event reports than the biological behavior of any of the products.

I would now draw your attention to the ProHeart 6 adverse event numbers. In 2001 we had 677 adverse event reports. This is a relatively low number compared to 2002, but this is completely explainable as the launch of ProHeart 6 was in June of 2001, well past when most veterinarians are administering their annually-based heartworm preventative programs. So therefore the amount of ProHeart 6 that was actually used in dogs in 2001 is

relatively small. 2002 was the first year where we had the product on the market for a full heartworm season, and so we saw a large increase in the amount of product use. This brings about an increase in adverse event reports, as would be expected. In 2003 you will notice that this number drops, and we believe this is important and significant as veterinarians grow accustomed to products the adverse event reports typically do drop.

In addition, we would like to draw your attention to the market share information provided in the final column. This is Fort Dodge's best estimate of the relative market shares of these three products, and this information is obtained from an outside source. If you assume for just a moment that all three of these products have the exact same biological behavior, and if you assume for the moment that all three products have identical adverse event reporting systems, then you would assume that the number of adverse event reports would follow the ranks that the products are sold in the marketplace. This is exactly what you see. The product with the highest market share has the highest number of adverse event reports. The product with the lowest market share has the lowest number of adverse event reports, and the product in the middle is in the middle for the number of adverse event reports.

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This is the same information which I just provided, but it excludes inefficacy reports. In general when we are using passive surveillance systems you have two issues that you are interested in. One is safety. The other is efficacy. If your question is safety then it is more important to drop out the lack of efficacy reports so you can just look at those reports which imply a safety concern about the product. I will not go into detail in looking at this slide because what you need to know is everything I told you about the previous slide applies to this slide as well. Therefore, Fort Dodge concludes that the number of adverse event reports associated with ProHeart 6 in 2003 compares favorably to other heartworm preventative products, and that any comparison of adverse event numbers from periods before 2003 is inaccurate.

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This is the number of adverse event reports that Fort Dodge Animal Health has received associated with ProHeart 6 from launch to recall by quarter. There are just a few interesting take-home messages here. You will see a peak in the second and third quarters of the year 2002. This is with the same peak that I showed you in adverse event reporting numbers in the graph that I just showed you.

This is certainly to be expected. You will also notice that there are three peaks in this graph, each of them associated with the second and third quarter of each year. This corresponds to increased use of the product in the spring and summer as would be expected with a heartworm preventative in the United States. You should also notice that these peaks go down each year with subsequent use of the product. We believe these decreased are significant.

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Now we do use reporting rates as an analysis tool. We believe that while these are not perfect assessments, they do offer some advantages to just looking at gross reporting numbers. The primary problem with gross reporting numbers is that they fail to provide any estimate at all of an incidence rate. We completely agree that reporting rates are not incidence rates. No one has ever made such a claim. In addition, gross numbers fail to account for changes in products used, and so reporting rates are a valuable tool as long as you understand what they are and you understand their deficiencies. Reporting rates are calculated by dividing the number of adverse event reports you get by the doses of product which are sold in that same period of time.

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This is the same data that I showed you in the previous graph looking at gross numbers of adverse event reports, but corrected for reporting rate. What you see here again is the peak in 2002. I have addressed this. The reason for the rise in the numerator number that represents this peak. But the reason this peak is so high in this analysis is because the denominator number or the sales number has been artificially reduced. The reason for that artificial reduction is that as I said before ProHeart 6 was launched late in 2001. We sold a lot of product in 2001 that didn't get used. That product was then used in 2002. If the product is used in 2002 but not sold in 2002 then it doesn't get into the 2002 calculation. In addition, much of the product that we sold in 2001 was short dated. This required veterinarians to return the product to us in exchange for product with better dating. These exchanges don't show up in our sales figures. So therefore the large peak here in incidence rate is an artificial elevation based on increasing numbers of adverse event report rates, balanced off at actual decreases in sales when looked at in this analysis method. After the peak, though, that is seen in 2002, you will notice that the product rapidly falls and establishes a steady stayed graph, which is what we expect when we look at incidence rates calculations over time.

The annualized reporting rate of ProHeart 6 in June, 2001, through May, 2002, was 2.45 reports for 10,000 doses sold. For the next calendar year, June, '02 to June, '03, it's 4.3 per 10,000 doses sold. But following that period it then reduces to 2.13 for 10,000 doses sold. It is clear that looking at ProHeart 6 either from a reporting numbers standpoint or a reporting rate standpoint that following a peak in early 2002 that the reporting for ProHeart 6 is decreasing.

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The CVM has previously presented to you that there are 485 deaths which are at least possibly related to ProHeart 6 and that this number compares very unfavorably to the numbers of death which have been associated with other monthly heartworm preventative products. I have addressed earlier in my presentation the reasons why these comparisons are inappropriate. They are inappropriate for total numbers of adverse event reports as they are inappropriate for the numbers of death. There are no differences.

There are additional issues, though, with the numbers, with the death reports that we would like to discuss with you. Fort Dodge was able to obtain 353 adverse event reports from the CVM from a Freedom of Information request. We then took a look at those causality assessments

conducted by the CVM and simply graphed them on a chart.

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You will see that five percent of the death reports have been characterized by the CVM as probably related to ProHeart 6. This compares to 77 percent of those assessments which are possibly related to ProHeart 6. There has been some indication this morning that the Kramer Modified Algorithm is an unbiased and objective way to review causality assessments. This is not the opinion of the VICH Working Group. They don't think -- the do not recommend the Kramer assessment to be used. In addition, while the Kramer system appears to be unbiased and objective, we believe -- I believe that is because it produces a number, and we as people are always predisposed to treat numbers as an objective and unbiased assessment of something. But if you look at the Kramer Algorithm what you see is that each of its components asks an extremely subjective question subject to all sorts of biases. A question like "Were there other reasonable alternative candidates?" Well, whether there are other reasonable alternative candidates depends on how far you look. So these are subjective questions producing an objective answer.

We would like to point out that the single

highest category of assessments on this graph is the zero causality score. It compromises -- or comprises, excuse me, 37 percent of the causality assessments given. If during the causality assessment conducted by the CVM if just one of the questions in the causality component scoring had come up with one less number in it, all of those causality assessments would have fallen to the other side of that black line, and now suddenly 55 percent of the adverse event reports are now remotely associated with ProHeart 6.

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So to summarize, the CVM themselves have assessed five percent of these events as probable -- these death reports as probably related to ProHeart 6. The CVM has assessed 77 percent of them to be possibly related to ProHeart 6. We would ask should all of these greater than possibly assessed adverse events be treated equally in an analysis of the safety performance of the product? We would say the answer to that is no. Also we would ask should market withdrawals be supported on events whose assessments are possibly related to ProHeart 6.

(Slide.)

Fort Dodge Animal Health believes there are other significant issues involved with the death assessments which have been performed by the CVM. From our review of

the cases that we have been able to look at closely, we believe there is a large number of scientifically implausible cases still within the clinical assessments of possible or above. These begin with concurrent vaccination. It is my opinion that when vaccines and ProHeart 6 is given that any assessment to which product is causality associated with the product is impossible. There are events in the database where cancers have been reported in patients, and these cancers have been reported less than six weeks after ProHeart 6 administration. We believe there is no scientific data to support the speculation that a medically-reasonable product can be given to a patient and induce clinically-observable cancers in less than six weeks.

I have already discussed with you the reasons for being concerned about causality assessments of zero. If these events are not removed from the database, any conclusion about the seriousness of ProHeart 6 based on the numbers of death reports is an exaggeration.

(Slide.)

Additionally, we have concerns simply about how the causality assessments were done all by themselves. Fort Dodge Animal Health again has reviewed a subset of the death events it could get. We reviewed 29. In one-third of these events we found that the FDA had assessed the death as

possibly related to ProHeart 6. Fort Dodge Animal Health using the Kramer scoring system as the CVM recommends assessed these events are remotely related to ProHeart 6.

Let me give you two examples. A dog with a hemorrhagic episode is presented a few days after administration of ProHeart 6. The dog dies. An necropsy is conducted. During the analysis of the information clinically significant levels of rat poison are found in the dog's liver. All this information is provided to the CVM, but regardless they score the case as possibly related to ProHeart 6.

Another case, a dog is presented with pain its abdomen four months after administration of ProHeart 6. The dog dies. A necropsy is conducted. A hemangiosarcoma is found in the dog's liver. This information is provided to the CVM. Regardless, this case is assessed as probably related to ProHeart 5.

MR. : --- five minutes.

DR. HUSTEAD: Yes. Thank you.

(Slide.)

We believe that the numbers of death reports need to be placed in their proper context. Even if you take the number of adverse -- of deaths associated with adverse events which the CVM has stated, which is approximately 500,

you need to compare that rate of dating with the expected mortality rate in a large number of dogs. If you do the math on the 500 assessments of the CVM divided by the number of dogs exposed over time, you will see that approximately 20 dogs per million have been reported associated with death associated with the use of ProHeart 6. The obvious question is what is the mortality rate in the canine population. I wish I knew. We have scoured the literature to try to determine what the established amount of death and mortality is in dogs, but we don't know. Various sources give various different information. We believe that very conservatively we have assessed this to be five percent. We would point out that a peer-reviewed journal article will show up in the peer-reviewed press very quickly showing that this rate is actually eight percent.

If you use five percent as your assessment and divide that by time, you will find that if you give any medication at all to one million dogs that approximately 50,000 of those dogs would be expected to die over the next one year. What we are saying here is that the numbers of death reports associated with ProHeart 6 when looked at amongst the numbers of dogs which have been presented, that rate cannot be extracted from the background of mortality in the dog population.

(Slide.)

Fort Dodge does place its adverse event reports into categories. Two of those categories are allergic reports and non-allergic systemic reports. Our allergic category are the largest events that we see, but only slightly thus so. The signs in this category are typical for what you would expect in a dog with allergy occurring within 48 hours. The systemic non-allergy reports involve any body system that is not typical of an allergy. We would point out that many of the events in this category overlap into the allergic category, but they are just not stereotypical enough to be called allergy.

(Slide.)

The rate of adverse reporting with allergy is low at the rate that has been previously told to you at 1.26 reports per 10,000 doses sold. The vast majority of 80 percent of these events are self-limiting and the dog does return to normal. The relative frequency of these allergy events are decreasing over time with no breed predilection. We have stated that the rate of these reports is similar. We have never said that they are identical, and what we have said is that given the limitations in the systems, trying to measure biologically complicated systems, these reporting rates are similar to Fort Dodge Animal Health vaccines.

(Slide.)

Now the CVM has expressed to you a concern about some unknown toxic mechanism that seems to be involving a wide variety of systemic responses in the dog. We believe that it is widely recognized that when an approved medicinal product causes toxicity that this toxicity would be expected to be seen in a small number of target organs. In contrast, the wide variety of suspected adverse event syndromes assigned to ProHeart 6 by the CVM is consistent with these standards.

(Slide.)

Fort Dodge has conducted a complete re-analysis of all of its non-allergy adverse event reports. To assist us in this analysis we did obtain the expertise of outside consultants who are extremely well recognized. We had the neurological cases reviewed by Dr. DeLahunta, Diplomat of Internal Medicine, specialty in neurology. The hepatic and hematologic events were reviewed by Dr. Alan Rebar, Diplomat of Veterinary Pathologists with a specialty in clinical pathology. The neoplasia cases were reviewed by Dr. Phillip Bergman, Diplomat of American College of Internal Medicine, specialty in oncology.

(Slide.)

It is the opinion of these independent

experts and Fort Dodge Animal Health that the majority of the adverse events are not causally related to ProHeart 6 and reflect the normal range of diseases occurring in the dog population.

(Slide.)

To summarize, Moxidectin-based products are used in a variety of animal species in over 70 countries around the world. There is an extensive toxicology study conducted in mice, rats, and dogs to support the approval of moxidectin for use in food animals, and this food animal approval is important. The food animal, the regulations to get a food animal drug approved are much higher than a domestic animal. So therefore the amount of information we have associated with moxidectin use in animals is much higher than would be associated with most domestic animal approvals. I have three more slides.

In a one-year dog toxicology study, the daily dose of moxidectin resulting in a monthly moxidectin exposure that is 454 times greater than the doses administered that are recommended with ProHeart 6 resulted in no toxicologically-significant findings.

(Slide.)

The rate of submission of initial adverse drug experience reports to the CVM has decreased in 2002 and

-- excuse me, 2003 and 2004 as compared to 2002. ProHeart 6 is subjected to substantial over-reporting bias. Even with this over-reporting bias and when corrected for market share, the numbers of adverse events associated with ProHeart 6 is similar to major competitors.

DR. CRAIGMILL: Dr. Hustead, I am very sorry, but we are out of time. You have exhausted your hour plus a few minutes and we must move on. If you could skip to your last slides please very quickly. Most people on the panel have the handouts and can review them.

DR. HUSTEAD: My last slide is based on this analysis. Fort Dodge Animal Health concludes that ProHeart 6 is a safe and effective product for prevention of canine heartworm disease.

DR. SUNDLOF: Okay. We are skipping ahead in our agenda to a clarification of VMAC questions, and at this time we are going to ask the VMAC committee members to ask questions of any of the speakers that have presented today and begin the discussion. I am going to ask Dr. Dan McChesney who is our Director of the Office of Surveillance and Compliance in CVM to go over the questions which we will ask for a committee response to later on this afternoon. Dr. McChesney.

Clarification of VMAC Questions

DR. McCHESNEY: Thank you. As you can see up on the slide there, we have really two questions. The first question we would like to ask the committee is "Based on the presentations and information provided, is ProHeart 6 safe for use in dogs?" We would like a yes or no answer to that. We would also like to know, "If there are remaining safety concerns with ProHeart 6, what additional avenues of research could be explored to mitigate and/or prevent the adverse events?" So we would believe there should be discussion on that. Thank you, and turn it over to the committee now.

DR. CRAIGMILL: Thank you very much. With that I would like to open up for questions from the committee to the people who have made presentations this morning. Lauren.

DR. TREPANIER: I have a question for Dr. Glickman. I would like better clarification of the way the Banfield study was done. I'm not really clear on how the adverse event was defined and what time frame. It says 30 days, but in what time frame were clients called? That seems a little unclear to me.

DR. GLICKMAN: Okay. As part of normal -- maybe I will let someone from Banfield address the question

of when are clients called first before then I will answer your question.

DR. CAMPBELL: I'm Scott Campbell. I'm a veterinarian ---.

(Adjusting equipment.)

DR. CAMPBELL: Okay. My name is Scott Campbell. I'm a veterinarian and CEO of Banfield, and what we do is we call all of our clients three days after they have been in the hospital. We also cover reactions at no cost to the clients, and they get a warranty when they leave that says that. So they all know that, and our clients on average come in about three-and-a-half times a year. So we see them very, very frequently, and of our clients about 94 percent come back for all their future care and service. So whenever we get a reaction we are very confident we get it reported because we pay for it, and that is one of the reasons we do it, because we want our patients to get the very best care.

DR. TREPANIER: Are you open for emergencies?

DR. CAMPBELL: Most of our hospitals are open seven days a week and we refer. We have relationships with emergency clinics, you know, in the area, and then those clinics of course refer back to us in the morning, or at least we get the report and any reports are followed up on

by telephone that day.

DR. TREPANIER: But if a patient was seen in an emergency clinic that wasn't associated with Banfield you wouldn't necessarily know about it?

DR. CAMPBELL: I suppose it's possible, but emergency clinics generally -- you know, we have a relationship with a clinic that we refer to, and we give the clients the number of that emergency clinic when we are not closed. Those clinics, you know, prepare a report for us the next day.

DR. GLICKMAN: I will answer the second part then. I believe it was how do we define adverse events? Is that the second part? What we did is we looked at the list of adverse events that had been reported on the website from FDA CVM and reports that Fort Dodge has received. Then we classified them into neurologic disease, liver disease, et cetera. Mostly it is by system and also allergic reactions and anaphylaxis. Then we go to experts in the field and say what would constitute a legitimate or accurate diagnosis, and we go into the database then from Banfield and pull out all the codes. The consist primarily of two types, clinically diagnosed abnormalities, like hepatitis, and then laboratory abnormalities. In the case of liver disease it would consist of three enzymes and bilirubin, and so we look

for abnormalities in laboratory values, clinical diagnosis, and in different combinations of the two.

MS. : A slide is up there is you want to.

DR. GLICKMAN: Okay. There's a slide. This is actually -- it was too busy to show, but it's a detailed breakdown for each class of adverse event, what went into defining an animal with that event.

DR. TREPANIER: So how does the diagnosis get coded? So let's say an animal is seen and then a week later calls and speaks to a veterinarian and the animal is vomiting. Does that get coded as a diagnosis in the record, or is it only a diagnosis if it gets coded associated with a visit?

DR. GLICKMAN: No, it can get coded either way. It gets into the medical record either as a code if there is a corresponding code in the Banfield database or as medical notes, which are also computerized and are searched. So we can do it either way, but it does get into the record when it is reported back to the Banfield clinic.

DR. MEALEY: Thank you. Going back to -- this is for you again, Dr. Glickman.

DR. GLICKMAN: Good.

DR. MEALEY: You had a slide up there and the

slides in here, I didn't think I was getting old, but I couldn't see the print in here. So I am going back to the original that you guys sent us. For anaphylaxis, you know, you broke down allergic reactions and things like that, but for anaphylaxis you didn't further break down the rates of ProHeart, you know, with vaccine, and heartworm one with and without vaccine. And I think if I remember right, your conclusion was that the rate was low for anaphylaxis?

DR. GLICKMAN: Yes. The rates as we showed, overall rate, was 0.5 per 10,000 for anaphylaxis, and the rates then within the different categories, the highest one was actually 1.7, which would have been heartworm preventive two with the vaccine. The rest were somewhat lower for the other products without vaccine.

DR. MEALEY: But if you look at the heartworm preventives alone -- tell me if I am looking at this correctly. ProHeart by itself was more than twice -- had more than twice the rate of anaphylaxis than any of the other heartworm preventives, is that correct?

DR. GLICKMAN: That's correct. The 0.7 versus roughly 0.2, and when we looked at those -- and I didn't show you all the models we developed. When we looked at the risk factors or the associated factors for anaphylaxis they do not come out. None of the heartworm

preventive products come out in the multivariant models. That is why there was no multivariant model to show with significant findings, and because the rates are so low those models are more unstable than would be the models for let's say liver events, which are more common. But we didn't find any significant risk effects for any of the heartworm products for anaphylaxis.

DR. MEALEY: Okay. Thank you.

DR. McGLONE: Dr. Glickman, you are very popular today. I was struck by the difference in the rate of death of dogs in the FDA data and in your model, and also in the raw data it appeared that there were -- it was a higher rate of death among dogs vaccinated and treated with the product in question. But in your multivariant model near the end of your presentation, the risk for death was actually decreased. So I am wondering what was in that multivariant model that accounted for the differences that when they weren't in the model.

DR. GLICKMAN: Right. I don't remember specifically for that model, but we did further analysis of every model. We put all potential interactions into the model, all potential two-way interactions, and the variable that seemed to have the greatest impact on most of these models in terms of changing the appearance from the initial

analysis to the adjusted was age of the animal. For example, we know that liver disease and death are highly correlated with age. The older the animal, the more likely they are to experience this. So in answer in general, age appeared to be the largest confounding factor. That is why I would almost rather rely rather on the absolute rates, the adjusted models, to come up with the true independent impact of these products.

DR. McGLONE: Right. Were any of the variables in model correlated with heartworm use, and were they also included?

DR. GLICKMAN: Yes. All the variant models --

DR. McGLONE: Heartworm medication.

DR. GLICKMAN: Yeah. I mean frequency of use or what product is used. We tried to look at the factors that could be either associated with the use or the product or the adverse events we were looking at and put them in the model, and not discriminate and actually put them in all models. There are a lot of relationships between the variables in the models like age and weight obviously and those things, and you can't anticipate all of them. It's nice we have the luxury with such a large data set to be able to put all the potential confounders in the model and

still come up with stable estimates, and that's what we've done.

DR. McGLONE: But doesn't including correlated variables remove the effect of the correlated variable? In other words, if the product is given more to older dogs than younger dogs for example, and then age is in the model, then doesn't the age effect sort of seem to account for the effect that might also be the product?

DR. GLICKMAN: It is a little more -- that is true, but it's a little more complicated because for age to be a confounder in one of these looking for associations it would have to be both associated with the use of the product, but also associated with the outcome that you are looking at.

DR. McGLONE: Well, age would be a --.

DR. GLICKMAN: And age is, yeah. It's just the most obvious one. But then of course age and weight are highly correlated in these databases.

DR. McGLONE: Thank you.

DR. LUSTER: I had a couple of clarifications, one for Dr. Brown and one for Dr. Glickman. On the FDA data, does the anaphylactic responses that are measured, are the reported? Maybe I missed the data, but I saw that you look at concomitants with all disease, but is

there concomitant vaccination data particularly with anaphylaxis that you have available? And secondly, do you have any data that would suggest that ProHeart 6 is used when anaphylaxis is observed which seems to be very high incidence that there is -- that that occurs after the first use or after multiple uses?

DR. CRAIGMILL: Dr. Luster, is that a question for Dr. Brown?

DR. LUSTER: Dr. Brown, yeah.

DR. BROWN: I'm not sure that I heard the first part of the question. I'm sorry. If you --

DR. LUSTER: Okay. The first question was whether the data from the ADEs indicated that there was concomitant, specifically concomitant vaccination with the anaphylactic responses.

DR. BROWN: Yes. We have for the anaphylactic reactions that approximately half or a little less than half of them also had concomitant vaccinations with drugs.

DR. LUSTER: Okay. You mentioned that with the whole, all the pathologies. Is that specifically for vaccination for anaphylaxis as well?

DR. BROWN: It would not necessarily be only vaccinations. It could be some other injection or tablet at

the same time.

DR. LUSTER: So you don't have that information then. Do you have information on the incidence of anaphylaxis -- not the incidence, but when anaphylaxis occurs whether it is after the initial first time the drug is used or after multiple uses with ProHeart?

DR. BROWN: There are instances were a dog might not react with the first injection of ProHeart 6, but subsequently have a reaction after say the second or the third. It seems that those reactions tend to be more involving say the liver signs or sometimes possibly the hemolytic anemias. In other words, there wouldn't necessarily be a full-blown anaphylactoid reaction, but could include some of those other signs as well. Typically if there were an anaphylactoid reaction the first time you wouldn't get a subsequent injection, but there are dogs that have had two or three, or some of them more than that, injections of ProHeart 6 and we are not seeing the reactions until say the fourth injection.

DR. CRAIGMILL: Essentially your ADEs do distinguish that?

DR. BROWN: Yes, they do. We do write that down in reports and take a look at that.

DR. CRAIGMILL: And one quick question for

Dr. Glickman. I was a little confused on how does diagnosis differentiate between anaphylaxis, allergy, and immune-medicated specifically?

DR. GLICKMAN: I think I'll pass that question on to Dr. --- perhaps or Will.

DR. NOVAK: So could you repeat the question?

DR. CRAIGMILL: What are the specific differences in the diagnosis between immune-mediated, allergy, and anaphylaxis?

DR. NOVAK: As far as the database system we would look for both anything that is clinical signs as well as any laboratory findings that are tracked. And so as far as what Dr. Glickman's work did on analyzing all of that, he was -- my understanding is that he was searching through the database for anything that was in the medical notes as well as any laboratory findings as well as any clinical signs that were associated. Is that correct, Larry?

DR. GLICKMAN: Yes. We really only used medical notes as backup. So it was not part of our original search. But codes are up here. The actual codes that were used to describe each of those. Now if you are asking how does the clinician distinguish when they write down auto-immune hemolytic anemia, that would be based on Banfield

diagnostic protocols. They do have protocols that they shared with me for an auto-immune hemolytic anemia.

DR. CRAIGMILL: I am still a little confused, because I mean an immune hemolytic anemia would be relatively straightforward diagnosis, but allergy, I am not sure what that might -- how that was specifically addressed.

DR. GLICKMAN: Okay. That is a good question. I said we used medical notes as a backup. So for example when there was a diagnosis of allergic event vaccine associate or allergic event drug associated, we took a sample, a very large subsample of the medical notes to go in and characterize what they are calling the allergic events, and it parallels what you see in the veterinary textbook as a description of allergy. Facial swelling, pruritus, urticaria, and vomiting were the major ones.

DR. NELSON: A different avenue I want to approach here. In the paper that we got from Fort Dodge there are talking about the heartworm-positive dogs in trials, and on page 26 there were two safety studies that are quoted and one of these -- well, first of all, are these experimentally-infected animals or naturally-infected animals?

DR. COBB: There were two types of studies conducted, one in which heartworm-positive dogs were

determined by circulating microfilaria. There was a second study that was conducted at the request of the Center that involved implanting adult heartworms into the dog so that the actual age of the adult heartworm was known and when the infection was established was known. So there were two types of studies done.

DR. NELSON: So one experimental and one naturally infected?

DR. COBB: Right.

DR. NELSON: Okay. The other thing, on page 22 when you were testing for efficacy against three- and four-month-old heartworms there is talk about now effective it is. There weren't any reactions noted during that time period on the three-month and four-month-old heartworms.

DR. COBB: I would ask Dr. Rock to comment on that one.

DR. ROCK: My name is David Rock. I am Director of New Product Development for Fort Dodge Animal Health, and could I just hear the question one more time as far as the three- and four-month infection retroactive studies?

DR. NELSON: Right. On page 22 of your report there is talk about the efficacy against three- and four-month-old heartworms post-infection.

DR. ROCK: Correct.

DR. NELSON: The question is was there any reactions noted when this was -- when the drug was given to these dogs? It talks about efficacy but nothing about any reactions.

DR. ROCK: Okay. There were no adverse reactions to the dogs. There was no adulticidal activity of the drug in those experiments. You will see that these worms were classified as abnormal but still alive. So the rate of kill again as an adulticide was not very fast and did not cause an adverse reaction, no.

DR. NELSON: Next one. When you were testing the product, because -- you know, partly the heartworm label was added later about, you know, if adverse effects were seen in heartworm-positive dogs. And just from, you know, kind of doing some review, you know, Veterinarians VIN, we see some Veterinarians Report no cases, and some veterinarians report multiple cases. Has anybody tested or seen what happens to this product, you know, just for example theoretically, if a technician drew it up with the 18 or 20 gauge but then try to force it through a 22 gauge needle? Do the microspheres break up? Would it cause an increased dosage of moxidectin release, or has that even been looked at?

DR. COBB: What we do see, the product is designed to go through a 21 gauge needle or larger. What can happen if you use a finer gauge needle is that sometimes you may get a blockage in the needle and the product is difficult to force through. That is the only information I can provide you. It is impossible to push them through very, very fine needles because they are particles that are suspended in the carrier.

DR. NELSON: Now if the product sits like where you have from the time it is mixed up there is, what, a 30-day? If it sits for two months is the moxidectin released in the vehicle?

DR. COBB: We have tested this quite extensively after three months post-reconstitution, and moxidectin is not significantly acceleratedly released upon storage. The vehicle is specifically designed to maintain suspension of the microspheres and it does not draw out the moxidectin selectively. So we do recommend that the product is used only with the appropriate vehicle. It should not be resuspended in saline for example where the microspheres could settle fairly quickly.

DR. NELSON: One other thing I noticed in reviewing the 36 cases that were given to us by the CVM, about 22 of those 36 cases there was no heartworm status

provided, whether they were negative, positive. Any previous heartworm preventative, one particular dog had had one injection, two years later had another injection, but no mention of what was given in between or any preventive history.

DR. HUSTEAD: That is a reflection of the data that you can get from veterinarians. You can ask the questions and you get the answers that you get. We recognize the deficiency in the information.

DR. CRAIGMILL: Dr. Nelson, we can continue this after lunch. I am informed that we must break now. Ms. Sindelar has some information before we do so. We will reconvene at 12:30.

MS. SINDELAR: All right. Thank you very much. There is a restaurant downstairs. There are also local restaurants in the area which you can walk to, and if the members and consultants will stay for just a minute so that we can all have lunch together, and we will reconvene here at 12:30. Thank you.

(Whereupon, a luncheon recess was taken at 11:30 a.m.)

A F T E R N O O N S E S S I O N

(12:30 p.m.)

MS. SINDELAR: Thank you, everyone. Please take your seats and we will restart the meeting. Because we have so many questions still to the panel members we would

like to continue for the next 30 minutes, from 12:30 until 1:00, entertaining questions to those who have presented today. At 1:00 we will begin with the open public hearing as originally planned. So, Art, you can take it from here. Thank you.

DR. CRAIGMILL: With that I would like to open up questions again for both representatives from CVM and from Fort Dodge. Panel members? Yes, Corrie, Dr. Brown.

DR. C. BROWN: I have a question for Dr. Cobb and Dr. Brown. We heard a lot of numbers this morning about the numbers of animals that were affected by various clinical syndromes and the numbers that died. However I didn't see much in the way of pathologic reports. What is the correlation for instance of 378 dogs with convulsions, 61 died. How many of those was a necropsy performed, and what were the histopathologic findings? I see that there is sort of -- I haven't quite seen a biological correlation between adverse events and death.

DR. BROWN: Let me address that, a portion of that for you. I can't give you any exact consistent type of necropsy finding because necropsies aren't always done. For the necropsies that were done, the reports would vary very much. For example, sometimes you might have

encephalomylacia with hemorrhage in the brain. You might have hemorrhage or lesions in other organs in the body with the comment consistent with anaphylaxis. With some of them the lesions might be consistent with severe protracted seizures. It depended very much on the type of death that occurred.

DR. C. BROWN: So in how many of these 485 deaths do we have necropsy data?

DR. BROWN: I can't say exactly. I would say probably in a third or less.

DR. C. BROWN: Well, a third would be a lot to look at, and that would be very helpful, and we have 192 -- 257 dogs with liver problems; 85 died. Did those 85 die due to liver problems? It is not clear from the report and Dr. Cobb from the Fort Dodge information, all I saw was that there were 15 livers examined histologically. Is that the sum total of what was looked at from your perspective?

DR. COBB: I would like to answer that question in a little bit more detail by asking Dr. Rebar to comment. He did the expert evaluation of all the liver reports that we believed could possibly be related to ProHeart 6, and they did include liver reports that did have either pathology or clinical pathology liver enzyme, and I would ask Dr. Rebar if he would describe what he did.

DR. REBAR: So I will focus specifically on the hepatic adverse event reports.

DR. C. BROWN: Yes. You know, Dr. Rebar, I have read the report so I know about all the -- you know, the liver enzymes. I want to know about the anatomic pathology.

DR. REBAR: Well, in that case I might defer to Keith Harris who actually did the pathology.

(Laughter.)

DR. HARRIS: Thanks. Thanks, Dr. Brown. That is a good question and we did only look at 15 cases, and those were selected based on the cases that we actually felt confident -- were graded as confident that were added cases. We were looking at ones that we were trying to look for a pattern to see if we had a common -- morphologic changes that would suggest a common mechanism for any toxicity we might see. So we selected the more severe cases to look at. You know, it has been brought up before there is not a lot of full post-mortem cases. They weren't done in a systematic way. Some are more thorough than others, but that is the reason we chose this subset.

DR. C. BROWN: Okay. So 485 cases. If you think there are necropsy results on a third, well, that's what, 150? And of that looking at it in this context in a

controlled systematic way, there were a total of 15 livers examined?

DR. HARRIS: That is all we examined that we could identify clear-cut cases with liver signs.

DR. C. BROWN: And CVM didn't consult with any other pathologist to look at this series of cases?

DR. BROWN: The liver lesions that we are looking at are not necessarily of course the same ones that Fort Dodge has looked at, and the pathology reports would have come in from across the country. The reason for pathology, the types of lesions found in histopath are not any one specific type of lesion. They are not all hepaticellular necrosis for example. Some of them could have been that. Some of them could have been consistent with allergic type reactions or hemolytic anemia. It depended very -- we don't have any one consistent type of lesion across the board.

DR. REBAR: Dr. Brown, if I could make one comment that may expands a little bit what Dr. Harris was saying. I actually examined the case studies from about 251 animals, and of those there were 15 that had histopathology of the liver. I think that those were the cadre of 15 that were actually examined by Dr. Harris.

DR. C. BROWN: So no one looked at the

pathology reports with an idea in mind about what moxidectin might cause pathologically?

DR. COBB: We examined all the histopathology reports that were available to us, and they numbered 15. We did ask for them to be looked at by Dr. Harris. In addition, we did identify a number in excess of 200 reports that had diagnoses that were either liver or were hematologic; and for those, although they did not necessarily have histopath reports, they may have had clinical reports, they may have had autopsy reports, and those we referred to Dr. Rebar since he has expertise both on hematology and on liver. So, yes, we made a very extensive effort to evaluate in excess of 250 of those cases that met the case definition of possibly related. Thank you.

DR. CRAIGMILL: Other members of the panel? Yes, please go ahead.

DR. GROSECLOSE: Question for either Dr. Post or Dr. Brown. What is the FDA policy on follow-ups once you receive a report?

DR. BROWN: It is usual for the drug company, the sponsor, to perform follow-ups on adverse events and send them in subsequently to the initial report if there is any further information to be gathered. If we are able to

and we feel that we really need to have further information, we might inquire back to the sponsor if further information is available, and if not could they please find out if it is and if so submit it to us. Sometimes we might call the veterinarian for clarification.

DR. GROSECLOSE: You mentioned that your report mentioned that 99 percent of most adverse events are reported from the sponsor. In this particular case, what was the proportion of adverse events that were reported from the sponsor versus from the general public or veterinarians directly, and did that change over time?

DR. BROWN: I think that with ProHeart 6 as with all the other drugs really the large, the vast majority, are the ones that are submitted by the sponsor. We will have reports also submitted directly from the public, and as you might expect those numbers of reports increase significantly after increased publicity. But we have not included any of the reports coming in from the public since the voluntary recall.

DR. GROSECLOSE: Among the seven veterinarians who review the adverse events, have you ever -- do you do a single classification, or do you have numerous observers classify the cases to see whether different observers would classify them similarly?

DR. BROWN: Usually it is one person doing each report. But if someone is having trouble really trying to understand the information in the medical record or if there are a lot of factors to be considered we might say, "Hey, could you take a look at this report and run it through the algorithm and see what you come up with?"

DR. GROSECLOSE: Okay. Thank you. Dr. Glickman, could you talk a little bit about the risk window that you talked about, and for example if a dog is treated with heartworm preventive there was the three-day follow-up. But when you looked at that dog's experience over time and following the treatment, how long was the typical follow-up to capture any adverse events that might have occurred? And also any treatment, for example the steroids, and how did that enter into your multivariant analysis?

DR. GLICKMAN: Okay. I think there are a couple of questions there. With respect to the callbacks, that was not part of any of our research. That was a normal part of Banfield practice. The information captured from those callbacks gets into the medical record. We go only with what was in the medical record. Our follow-ups were intended to be 30 days for each exposure, whether it was ProHeart or one of the monthlies. Our intent was to follow those animals for 30 days to see what happened in that 30

day window. The only time we cut it short, we would have terminated of course if the animal died, or if during the 30-day window for example an animal that had previously gotten ProHeart and we were following then received a vaccine we would stop the 30-day window with ProHeart at the time of the vaccine and then start a new 30-day period for the vaccine and so on. So it turns out that of course not every animal was followed for 30 days unless they fall in for ProHeart, but the average length of time is 29.2 days. So it is pretty close, and for heartworm one, which is the major product oral, it was 27.2 days. So we are pretty close at 30.

Now you can arbitrarily say 60 days or 90 days. Of course you can get more and more being cut off when you go that far, and it is pretty standard in human vaccine and drug studies to use the 30-day window. Why I am not quite sure. What we do know though from the 30-day window is that the first three days will capture about 90 percent of the allergic reactions. Day seven to about 21 will capture most of the immune-mediated like hemolytic anemia and ITP, and then the other events it is hard to tell. They are scattered throughout the window. So that was our approach. I agree with it could have been 60 days. I certainly wouldn't want it to be less than 30 days for

most of these events.

DR. GROSECLOSE: So any steroids that would have been administered within a 30-day period would have showed up in the model as well, and they may not have been administered at the time of the ProHeart administration.

DR. GLICKMAN: That is correct, and we felt it important to look especially at steroids because of course we have very little quantifiable information about what they do, and for the non-steroidals that is also true as it was up until a little while ago in human medicine. So we felt we had to improve. While we could have picked other classes of drug, you know, where do you stop? So we decided to at least with drugs use the steroidals and the non-steroidals, especially knowing about the effect of the steroidals on the risk of liver disease.

DR. GROSECLOSE: While I am hogging the mic, one question about did you look at the group of dogs that during this time period received only one ProHeart administration versus those who received two or more to see what the model might have looked like in that?

DR. GLICKMAN: Yes. Every time we found a significant relationship between ProHeart and an adverse event we followed up with a days at risk analysis, but we also followed up with a dose response analysis. So we went

back in the record to see whether this was the first, second, third, fourth, fifth time. The most we had was five, but given every six months and we did it for two-and-a-half years, that is all we would expect. So when possible we looked for a dose response relationship. Now a little bit of caution. I mean, it is possible that an animal had gone previously to another vet, a non-Banfield veterinarian, and received ProHeart. We would have not known about that. But, yes, we always look for a dose response relationship and did not find it.

DR. GROSECLOSE: Thank you.

DR. PAPICH: Dr. Brown, when you were talking about the elevations in liver enzymes, are the elevations that are assessed by comparing one measurement to another? Or were these simply liver enzymes that were above normal as a single measurement.

DR. BROWN: These would have been liver enzymes that were above normal as reported by the individual veterinarian according to their laboratories that they used.

DR. PAPICH: So is it possible then that these could have been liver enzymes above normal that the animal had prior to any drug administration?

DR. BROWN: That's always possible. Now sometimes of course we were fortunate and there it was based

on blood work drawn before, and in those circumstances then of course we could assign a higher score.

DR. PAPICH: Relating to the liver enzymes, Dr. Glickman, when you talked about in your evaluation liver disease, are you talking about elevations in liver enzymes or is this documented liver disease in those animals?

DR. GLICKMAN: A comment about liver enzymes first. We had the benefit that Banfield submits virtually all of their laboratory work to one laboratory nationwide, and that is Antech. So that built in some sort of degree of consistency on the results for liver enzymes. We collaborated with Al Rebar to tell us what the conservative cutoff levels are for each enzyme, and in fact originally I just took what was in the Banfield databases as being normal or abnormal. When Dr. Rebar looked at that he says, "No, I'd rather be more conservative and more specific." So he set the enzyme levels. Then what we did was we looked at either any abnormal laboratory value of the enzymes, any clinical diagnosis of liver disease or combinations of those -- meaning having both a clinical and a laboratory finding or either one of those. We looked at it all different ways, and it really didn't change any of the relationships. So we went with what I showed you was primarily a liver disease diagnosis plus a laboratory abnormality.

DR. PAPICH: I would like to ask a couple of questions about the pharmacokinetics of the drug. In this slow-release preparation in the graphs that were shown to us today it shows a peak of about seven to 10 days in the picture that we saw. It is in the handouts that we have. It shows a nice average plasma concentration. For anyone at Fort Dodge that is familiar with the kinetics, I don't know who that would be, if they could answer this. The picture that we have seen representing average concentrations, just how variable are those concentrations? Like what is reality in other words when we talk about a peak of seven to 10 days? Is that highly variable or is that consistent? Can somebody comment about that?

DR. COBB: There is individual dog-to-dog variability, and we did run pharmacokinetic studies in laboratory beagles which generally gave more uniform results than in the crossbred dogs that we looked at. The window of peak blood levels appears to range from about five days to 12 days in individual dogs. We do not see gross, huge variabilities or peaks at 30 days or later. It generally is a pretty indicative value to say that the product peaks between seven and 10 days.

DR. PAPICH: Relating again to the nature of the formulation, could somebody from Fort Dodge fill us in a

little bit about the nature of the formulation? I'm not sure that everybody around the table understands the -- just what makes this formulation slow release versus something else so that we can better understand how this drug is released over such a long period.

DR. COBB: I would be very pleased to answer that, Dr. Papich. It's in two parts. One relates to the inherent characteristics of the molecule. Moxidectin is a very highly

--- molecule with a very long half life in dogs, approximately eight days. So it particularly does lend itself to a sustained release formulation. It also has a very large volume of distribution regardless of whether it is applied topically or orally or by injection. So it penetrates into the fatty tissues of the body. It makes it very suitable for sustained release. We put this molecule into a microsphere that is based on glyceryl tristearate.

So when the product is presented to the veterinarian it comes in two vials. One vial has the microspheres, glyceryl tristearate containing 10 percent moxidectin. The micropheres are manufactured to very, very strict size criteria so that the surface area is very uniform and the release of moxidectin from these microspheres occurs in a very uniform manner. The second

bottle contains the diluent, and the diluent is formulated to a very specific viscosity to maintain the microspheres in suspension after the product is reconstituted. Because in order to get a uniform dose it is very important that the microspheres remain uniformly distributed through that vehicle. So that is just a thumbnail sketch of what the product is and why it does work in the way that it does work.

DR. PAPICH: Are there studies that you have done in dogs where either the diluent and/or the material in he microsphere minus the moxidectin has been injected into dogs?

DR. COBB: We have indeed. In our investigations of allergic events we ran a great many tests looking both at complete product and looking at every component within the product including the preservatives that are used because they are not ---. We were not able to consistently demonstrate allergic reactions in dogs to any of the components or the finished product. We could on occasion by intradermal skin allergy testing see a wheel or a flare with either moxidectin or the moxidectin microsphere, but that was not repeatable and not consistent. We did try to reinduce allergic infection -- reactions in dogs that had reacted to ProHeart.

We were not successful in doing that with either the complete product or with any of the components, and through the University of Wisconsin we ran a large-scale study where more than 7,000 dogs were treated with ProHeart 6. They concurrently received vaccines, either five antigen, seven antigen, or nine antigen parenteral vaccines. They also received kennel cough vaccines, some of which were intranasal and some were parenteral. What we were trying to do was to identify reactive dogs so that we could look at investigating the problem further.

With these 7,000 dogs we were able to identify one dog that showed facial swelling on treatment with ProHeart. We have subsequently retreated that dog twice with ProHeart and have been unable to reproduce any clinical manifestations at all. So it does appear to be idiosyncratic.

DR. PAPICH: Thank you.

DR. RIDDELL: I have got a couple of questions relative to reporting for Dr. Brown, and also a question for Dr. Hustead. Dr. Brown, relative to the suggestion that there is under-reporting, when I looked through the FDA packet all the reference are human. So my questions are what general comments do you have supporting the under-reporting phenomenon, two, specific to ProHeart 6,

and the third, what would be your response to Dr. Hustead's comment that there may actually be over-reporting of ProHeart 6?

DR. BROWN: I think that when we are talking about the reports that come in we have to consider that they come in from the same kinds of people, that is veterinarians and from owners, and they come in from all across the country and they come into the drug companies who then submit them to us. As far as comparing under-reporting in veterinary medicine with under-reporting in human medicine, I don't know that I could make that kind of comparison. I do know that we are far more limited in veterinary medicine as far as being able to have patient information available and to look prospectively particularly at any kinds of reaction to reporting.

With ProHeart6 as far as claiming that that might be over-reported, I think that if you are looking to a relation to media interest and public interest such as the websites for example, those really started to kick in early in the spring of last year. But as you can see from our slides that we've shown you before, we already had a great many reports coming in before any public interest was stimulated.

DR. RIDDELL: Thank you. Dr. Hustead, the

Modified Kramer System may actually have been a benefit for ProHeart 6 because the dechallenge and rechallenge really wouldn't be totaled into the score. But you say with your familiarity with VICH that they don't recommend that system. Does the system that VICH recommends have some added objectivity to it as far as grading adverse events?

DR. HUSTEAD: Let me try to address both your questions about under-reporting and about VICH and the Modified Kramer System. I don't think there is any question that adverse events in general are under-reported. I would think every expert in the world would say that as a general rule of thumb all adverse events are under-reported. The point that I was trying to make is that if you are going to compare two products that you have to look at the relative issues between those two products and determine if the same level of under-reporting exists. It was my point that in a comparison that the reporting biases are different with the two products. So I hope that was clear.

Versus the Modified Kramer System, I think you can argue the advantages and disadvantages of the Kramer System for a couple of days, as you can with the VICH system for a couple of days; and we have done so, haven't we, on VICH? Numerous times. There is no objective information that would say which system is better or not. At the end of

the day, it was VICH's interpretation that both systems are subjective, and that with the Kramer System you get a number and that makes people have some confidence that that's objective. But at the end of the day all you are doing is asking an educated person "Do you think timing is positively or negatively correlated with the event? Do you think the pharmacology and toxicology of the event are positively or negatively associated with the event? Do you think there are alternative explanations positive or negative associated with the event?" And then you make an assessment at the bottom.

DR. RIDDELL: Thank you.

Open Public Hearing

Aleta Sindelar

DR. CRAIGMILL: Thanks very much keep those questions. We will be coming back. At this time we are gong to move to the public comment section of the program. You are not off the hot seats yet, folks. Lots more to come. Ms. Sindelar will lead this discussion, but before we begin with the public hearing I am going to read this statement into the record about the open public hearing.

"Both the Food and Drug Administration, FDA, and the public believe in a transparent process for information gathering and decision making. To insure such

transparency at the open pubic hearing session of the Advisory Committee meeting FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with any company or any group that is likely to be impacted by the topic of this meeting. For example, the financial information may include the company's or a group's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you at the beginning of your statement to advise the Committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking." Ms. Sindelar.

MS. SINDELAR: Thank you very much. To begin the open public hearing let's begin with Tom Stafford. Please remain standing at the mic for your entire presentation, and you have five minutes.

MR. STAFFORD: Well, anyway, I have no financial reason to be here. I'm financially poor. I drove myself from Texas and spent the night in my van. My daughter wrote you all something. I wrote about three or

four different speeches, and after reading hers the night before I left I threw mine away. She was five years old when we got Bear. At his death she was 13. I have a son 17 and a wife.

She starts out, "To the makers of ProHeart 6, to my knowledge my dad and I took our dog, Bear, and our two other dogs, Angel and Mickey, to the vet as we did every year to get a checkup. As my dad waited for the vet to call us in he noticed that they had come out with a new shot, a six-month heartworm shot. So he decided to look into it, asked the vet about it. Everybody thought it was okay, even though Bear had had 15 seizures just three months prior. Three of our other dogs got the same shot on the date of May 9th, 2002. Not two days after that my nine-pound Pekinese had a seizure."

At that point I really thought my kids were overreacting or just looking at the dog seeing our other dog having seizures just -- I didn't believe it to be quite honest until after everything else happened. Anyway, back.

"Poor Bear had his first reported seizure on 11/13 of '01, not long after my dad stayed up all night with Bear watching over him and taking care of him because in the night total Bear had 15 seizures. I woke up the next day to my mom taking me to school, and I come out of my room and

saw that Bear was having another seizure. I was very horrified. I was sad, scared, confused all at once. It hurt me to see him, and I went to school so disturbed I could hardly focus.

"Over a period of time Bear had three more shots of this ProHeart 6 and a lot more seizures, and my family and I helped him through them all. It was really heartbreaking. On the day of September 14, 2004, five months after his last shot, my dad and I had helped him through a little seizure before we left. We put him in a wire cage, kennel-type, very large. We put a blanket in there to comfort him in case he started banging around like he normally does. We went to load some furniture that we had bought. We loaded it, came back home."

She got the keys from me and unlocked the door to the house. "I went inside and looked at Bear. I said after I walked by him putting my stuff down I thought at first my best friend of eight years, long, loving years, was just sleeping. Then I bent down to pet him in his cage calling his name trying to wake him up. After a little while of trying to wake him up I finally realized my best friend in the whole wide world was dead. The look on his face, his teeth were bared, his eyes were wide open. I broke out in tears. Just ran outside hysterical trying to

get it out that Bear was dead. My dad realized what happened, ran inside, a couple of seconds later came out crying. I'll never forget that look in his eyes. I don't think I could ever forget seeing it. That is one of the things. I found him, Bear, myself. I was the one. I'll never love another dog like I loved him and there'll never be another dog like him. He was the sweetest dog you'd ever meet, a 90-pound solid black German Shepherd. He knew when you were upset, and he would always come in my room and whine and sit right down by me, comfort me. He was the best dog ever. Because of the makers of ProHeart 6 I will never see him again."

MS. SINDELAR: Tom, thank you very much for your testimony. Our second speaker is Dr. Scott Campbell.

DR. CAMPBELL: Okay. Thank you very much for giving us the opportunity to speak. My colleagues and I are here today. We are the purchasers of many pharmaceuticals and from many of the folks here in the room, and our practice is a general practice, and so we buy a lot of stuff. Fort Dodge has picked up our hotel bills for being -- as one of the things -- as the only thing for being here.

A couple of things I want to tell about our practice in the next slide. I guess the next slide.

(Slide.)

Our practice is an evidence-based practice. We make all of our decisions based on evidence, and we are continually trying to find new evidence every day. Pets are certainly a part of the family unit for our three-and-a-half million clients, and so that is the standard that we hold ourselves to. Really providing those pets the same care that we want for ourselves. We do that in a lot of different ways, and if we had more time I could go into those. But it is a very high standard that we hold ourselves to.

Products that are on our formulary, our criteria, you know, are many, but certainly the top ones are it has to be safe. That's a go/no-go for us. We believe every product on our formulary is safe, and we'll take it off the formulary immediately if we believe that it's not.

The second thing is, you know, does the patient receive it? You know, is it in a formulation where the client, you know, is actually going to give the medication; and then it has to be effective, and the effectiveness is a combination of how good is the chemical or the molecule as well as is the client going to give it.

We can, you know, certainly show anybody that we have the same case mix as most traditional practices. As I said, 1,016 veterinarians and 443 hospitals.

DR. NOVAK: Next slide.

(Slide.)

I'm Dr. Will Novak. I'm the chief medical officer for Banfield, and one of my responsibilities is managing our surveillance system. This was mentioned earlier. We have a quality assurance team which is about a dozen people that are tracking a number of different things on quality client service, medical records to making sure that the documentation is accurate, and then our surveillance system. So we are tracking the incidence of disease, and we compare that to rate of reactions that may be seen with vaccines, with antibiotics, with any of the drugs. And we are constantly using this to do a national risk assessment on each component of the products that we're using. Next slide.

(Slide.)

So we track medication reaction rate and it is on a national reporting system, and so this is not a passive system. It is an active system. Anytime that there is a report of any problems from a client or it is noted during the healthcare visit that is automatically put into our reporting and tracking system. So that is required as a practice standard. So as such we are constantly reviewing that data, running statistical analysis against it, and the

analysis that we have done has shown that whenever we compare our medical record details back to our reporting system we find that there is a very, very high, statistically-significant correlation. So as such we got a lot of confidence in the information that we've got. Next slide.

(Slide.)

We do approximately 2.7 million doses of vaccine annually, and that rate is going up every year. So one of the things that we believe is that we do have a really good understanding of how preventative care works based on the science of large numbers. All of our vaccines are warranted, including the vaccine reactions as was mentioned earlier today. So that is another reason that we have good information on having really excellent follow-up care when it comes to any patients having problems. Overall reaction rates on our reporting system for anaphylaxis is 1.8 per 10,000 doses, and that is not purchased or delivered. That is what was actually given to the patient. So this is one of the few cases where we have got data that really says what did the patient get, what was the reaction rates that we are seeing. We also have a peer-review process that anytime that there is a adverse event we do a full medical case review with a group of boarded

specialists, and we go through all the different components or do follow-up laboratory work as needed to make certain that we know what is going on with that case. Next slide.

(Slide.)

So I will turn it over to Dr. Lewis.

DR. LEWIS: I'm Hugh Lewis, and I'm a veterinarian and in charge of new knowledge business called Data Savant. This slide is a simple one that just shows the acceptance over a period of a few years of moxidectin in our hospitals. At the time it was taken from the market, about 90 percent of the pets that we were seeing were being given the six-month treatment. Next.

(Slide.)

This is our incidence of adverse reactions using our internal system, and when we became aware of the concern that the FDA had about adverse effects we immediately reviewed our database. This is just some of the combinations of vaccines and other treatments just to put it into perspective, and you can see from just ProHeart 6 alone next to the end there we had 109 dogs that received only that and 4.4 cases per 10,000 adverse effects. The adverse effects are delineated on the bottom right-hand corner, and 0.8 per 10,000 of anaphylactic reactions. So this is very much within the range both qualitatively and quantitatively

that we see with vaccines, and for us this puts a great deal of perspective on the product and it seemed to be as safe as vaccines.

MS. SINDELAR: Thank you very much, gentlemen.

DR. : Last slide? There is one more.

DR. CRAIGMILL: I am afraid the time has expired, sir.

MS. SINDELAR: Thank you. Our next speaker is Lauren Simpson.

MS. SIMPSON: Hi. My name is Lauren Simpson. I have no financial gain with any organization or any group. I would like to thank everybody for allowing me to speak today. Let me clarify I am not any kind of scientist, vet, or in any medical field. But as a --- I have started collecting information regarding this drug, especially after my Pug had a reaction to ProHeart 6 back in April of '03. Very minor compared to what you guys see and hear about today. She was only getting this injection because the vet was conveniently out of her normal preventative. Later I found out it was suggested that vets carry only one preventative so as not to confuse the consumer with choices.

I stand before you today, though, not just as an individual, but for thousands of caregivers that feel

their companion is part of their family and not just a dog. When they were told this product was safe, "There's no reactions. It's better than monthlies," they thought they were doing the right thing for their dog. Then to watch them suffer and possibly die spending hundreds, thousands of dollars trying to save them, all the time being told by their professionals, "No, it cannot possibly be ProHeart 6 because that is safe," or being the reaction is too soon or too late, or that this type of reaction "Has never been reported to us before." The guilt we have all felt because we not only okay'd this drug, we paid for it and blamed ourselves for not researching it.

I recommended "Rainbow Bridge" more times than I could ever think possible, but I've been told recently we have a ProHeart 6 bridge now. But we are here to discuss the safety of ProHeart 6 with our pets. Safety seems to have been sidelined for our pets either for the almighty dollar or something bigger. There are two parts of ProHeart 6 to consider, moxidectin and also the delivery system. Microspheres are new in the vet world. They are also new in the human world where they are being used for females with uterine fibroids. They are described as little golf balls that emit moxidectin. They are supposedly fragile. Directions say shake to mix, but then once it has

been stored you only roll it gently. I can't help but wonder what happens to these microspheres after an injection if the dog is roughhousing or playing and that injection site gets hit. Remember, we are talking everyday dogs, not dogs kept in a cage.

Moxidectin is used in horses, cattle, sheep, and many other animals. It has been tested on fish, tortoises, humans. It's administered by gels, porons, orally, injections, and time-released injections. In 2000, ProHeart 12, also known as SR 12, was approved in Australia as a one-year preventative, just nine months before the approval here in the United States. Australia may not have the adverse reaction reporting system as we do here, but they do have one, although little known to the public, and they do have reports that have already been evaluated as probable and possibly related.

The manufacturer has stated repeatedly in the last three to four years that ProHeart 6 is not effective against adult worms, that it is not effective for microfilaria clearance, but that circulating microfilaria may decrease. Yet in 2000 the World Health Organization say the single treatment produces slow death of adult worms in dogs. Not effective for microfilaria clearance, but on page 30 of the document you have before you they admit

microfilaria counts were reduced to almost zero three weeks after treatment. I have no doubt that the manufacturer presented testing that was required by the FDA CVM at that time, yet I wonder was it ever taken into consideration that being innovative maybe more testing should have been done.

Alabama did testing for heartworm-positive dogs; 20 dogs were in the test, 10 were in control, 10 dogs received ProHeart 6, but only at three times the regular dose, and they were sacrificed only after 28 days. Texas did testing for repeated doses. The tests lasted three years according to FOI summary, but look deeper and apparently only four dogs received a regular dose of ProHeart 6 every six months for three years. Extensive testing.

In field trials, FOI summary in the document before you it states 200 dogs received regular doses of ProHeart 6 for a year and that three died. Then a press release to Chicago and Boston CVS in February of '03 they stated that 330 started this trial, receiving ProHeart 6, and only 280 finished. That is a difference of 50 dogs. In document they present to you on page 27 it states that in an 18-month study 12 dogs died or were euthanized, and apparently after the manufacturer's review their deaths could not be attributed to ProHeart 6. I wonder what it was

attributed to? Old age? Heart failure? Liver failure? Kidney problems? Or maybe while crossing a street they had a seizure and were hit by a car.

We all know what the label states, so I won't repeat it here. Give to healthy dogs. Use with caution on sick dogs. How much caution can you use with a six-month time-released formula with no antidote except not to use it? According to charts I found suggested ages to start geriatric screening can be as early as four years of age for a larger breed. Were there any warnings for this?

MS. SINDELAR: Thank you, Lauren. But please remain standing because our next speaker, Ingrid Zorge, who registered --

MS. SIMPSON: Ingrid Zorge is not here today.

MS. SINDELAR: Correct, and she requested that Lauren Simpson please read her submission. Thank you.

MS. SIMPSON: She wrote it. She sent it to me. She wanted me to introduce you to Tigger and to Mac. Her name is Ingrid Zorge and she is a legally blind Canadian citizen, and she would like to offer apologies for not being personally present to give her statement. But the priority had to be taken care of, her dying dog which passed away yesterday.

"I would like to state that all the

information in this statement are my personal opinions only and conversations I recall to the best of my knowledge. On May 27th, 2004, I made a decision that would forever change my life. I agree to allow my vet to give a ProHeart 6 injection to all three of my dogs. One of those dogs was my lifeline, my seeing eye dog named Tigger, a 10-year-old Golden Retriever. I had raised Tigger from a sickly six-week-old puppy into a happy, healthy, and extremely intelligent friend who later was privately trained to become my sight. During the course of his duties as a service dog Tigger saved my life twice in traffic. I cannot begin to explain the bond that we shared or the depth of my feelings for this extraordinary animal who is my best friend.

"Within a few hours of receiving ProHeart 6 Tigger developed diarrhea, vomiting. He became lethargic, depressed, weak, lost his appetite. At times he would collapse on the floor too weak to stand. These symptoms continued, and after three weeks of supportive vet care an ultrasound revealed tumors on his spleen. His spleen was removed and during the surgery it was discovered that he had many more on his liver and his abdominal cavity was full of blood. Tigger did not improve from the surgery, and after about a week he died a painful, horrible death, vomiting blood, suffering through his back legs.

"He diagnosis was hemangiosarcoma, a canine cancer. This cancer did not develop nor did it end by normal standards. He was healthy, happy, and energetic prior to this injection. This cancer is usually diagnosed by ultrasound only after the dog has shown signs of weakness and collapse. Several studies suggest the average time until diagnosis is eight weeks. Usually the spleen is removed, the dog makes a positive recovery, and the average life expectancy is three months.

"My second dog to receive ProHeart 6 on the same day was Mac, my seven-year-old Rotty. Mac also vomited several hours after receiving the shot, but he appeared to return to normal in a day or two. In July and August, about six to eight weeks after the shot, Mac began vomiting, lethargic, had a fever. His symptoms increased. In November, '04, he had an ultrasound which showed tumors on his spleen and liver. Diagnosis, same as Tigger. Again, Mac was happy, healthy, very energetic prior to receiving the ProHeart 6 shot. Yesterday, January 30, Mac collapsed again and began vomiting. I was forced to make the painful decision to have him put down by our vet. This beautiful, courageous animal fought for his life to the very last minutes, struggling to rise even though he was heavily sedated. I will carry this disturbing image for a long

time.

"Three days ago, January 28th, my third dog who had received ProHeart6 on the same day collapsed, vomited, many pools of blood and bloody diarrhea. Rain is a one-year-old Border Collie mix and has had intermittent vomiting and diarrhea for the past six months. We are waiting for the test results now.

"There are approximately 1,000 diseases that can affect dogs. The mathematical probability of all three dogs developing the same cancer within this time period would be about one in 160 million. Think about it. Three breeds of dogs, three different ages, three different diets, only one common denominator. Do I believe that ProHeart 6 is safe for my dogs? Absolutely not.

"Drug companies are powerful entities. I am sure we would all agree to that, but with power comes responsibility and accountability. Fort Dodge, a division of Wyeth, manufactures ProHeart 6 in the United States. These vials of ProHeart 6 are then shipped to Canada and distributed to Canada vets by Wyeth Animal Hospital. In the US there have been recalls for ProHeart 6 due to varying factors. I believe this recall was to be international in May, yet there was no actual recall done in Canada. In the United States there have been three label revisions, new

package insert, Dear Doctor letters issued to US vets due to reported adverse drug reactions. Why was this information withheld from Canadian vets and consumers? Why did Fort Dodge, the sole manufacturer of ProHeart 6, only make three label revisions for vials of ProHeart 6 sold in the US? Why did Fort Dodge not send Dear Doctor letters warning of adverse reactions to ProHeart 6? Why would representatives of Wyeth Animal Health here in Canada not feel responsibility to inform Canadian vets and consumers of reported adverse reactions including deaths?

"My vet or myself would never have allowed my seeing-eye dog nor my companion dogs to receive this had we been informed of the possible dangers. Two different executives here in Canada have told me that they are not required to distribute this important information to Canadian vets or consumers. Why not? Are we as Canadian consumers not entitled to make informed decisions? Obviously not. In Canada our veterinary drugs are approved and regulated by the VDD similar to the CVM in the United States. The VDD is a division of the Health Canada system. I have questioned the VDD several times --."

MS. SINDELAR: Thank you very much.

MS. SIMPSON: Okay. Thank you.

MS. SINDELAR: Our next speaker is Laurie

Rentas.

MS. RENTAS: My name is Laurie Rentas. I have no financial relationship here with anyone, and in fact the only financial relationship I have had was with the vets that I paid to have my dog die anyway. I am here today because on February 5th of '04 ProHeart 6 destroyed a member of our family, our Yorkie Murphy, after a nine-month agonizing and ultimately losing battle. My initial intention was to focus my time on her loss, but based on the other tragic stories that came to my attention and showed me that the impact of ProHeart was much worse and much bigger than Murphy's case, I chose to address that.

We didn't want her sacrificed so that other dogs could be saved. We didn't want our lives changed forever, and we most certainly didn't want to end up a statistic of an unsafe drug and a pharmaceutical company that seemed to be ambivalent however we are. And because we are, I want this panel to know even more the horror stories regarding

ProHeart 6. I want to say right now that at no time have I ever or will I ever claim to be a scientist, a statistician, or an expert regarding the knowledge I have of ProHeart 6.

The totally voluntary and unsolicited data I am about to share with you came from a website called CAPS.

The president of CAPS created and made available a ProHeart 6 complaint form because she knew of people who suffered at the hands of ProHeart and wanted to see who else was out there and going through the same thing. Complaints rolled in on almost a daily basis. Keep in mind that at no time did anyone go out looking for these people. They found CAPS because they were looking for answers, but they found as did we that there was no going back once this poison was put in your dog's body.

There are far more deaths than anyone was lead to believe, all which came as a result of a product that was supposed to offer safety against heartworm, and the veterinarians lead us guardians literally to slaughter by misleading us as to the safety of ProHeart as the new, convenient alternative to the monthly drug. But in reality, it was an unsafe heartworm prevention promoted over the perfectly effective products that had been on the market for years. We went to these veterinarians because we trusted them to know more than we did regarding heartworm prevention, and we accepted their recommendations.

There seems to be a denial factor here in these vets. Out of all these reports that came in through this CAPS website, only 10 positive comments were made by the guardians that their vet even tried to help them or was

at least empathetic and open to the possibility that ProHeart could be causing the problem. Most vets wouldn't even engage in conversation regarding the possibility. Guardians basically hit brick walls trying to fix what was happening to their pets, and the brick walls were Fort Dodge and the vets that we trusted in the first place.

I won't even address the thousands of dollars we have thrown away as a direct result of ProHeart. There was a test for every symptom, and all it took was a credit card from the guardian to carry it out. Yet definitive answers as to those problems were never forthcoming.

So were the vets lied to? Who lied to them and convinced them of the effectiveness and safety of this product? All of us in this room were informed that the purpose of the hearing is to determine the safety of ProHeart 6. ProHeart 6 is not safe. The comparisons against all of the monthly tablets prove that. The numbers show unequivocally that there are not the same degree of adverse reactions in the monthly prevention drugs.

Unfortunately there are still people out there who are in the midst of fighting what Proheart 6 is doing to their dog since it has only been five months that it has been off of the market. So we know that there are still dogs with this in their system. There was never the

degree of effort stopping the use of ProHeart that there was in couching us all to use it. In fact, there are reports of dogs receiving this after the recall.

Of over 60 adverse reactions, they came from over 35 states. There was no rhyme or reason to the drug's effect on size, sex, or age. There's practically equal numbers of both male and female. There are dogs from age 15 down to puppies six-months old. Seven-years old was the most common age reported for death in what we collected, with four-years old being second. We have complaints from Chihuahuas and Yorkies to Great Danes and to St. Bernards. 70 of the 174 guardians, which translates to over 40 percent, responded that on that day the only thing administered to their dog was ProHeart 6, 40 percent. But the most disturbing fact to come of all these statistics is this: Out of the 174 voluntary reports, 80 of these dogs have died so far. Think about it, 46 percent.

If Fort Dodge truly feels their product is so safe then I question why a company of your magnitude would offer thousands and thousands of dollars in hush money if you have nothing at all to hide. One and only one common denominator among all of this data? Right, ProHeart 6.

MS. SINDELAR: Thank you. Our next speaker, Janice Storey.

MS. STOREY: My name is Janice Storey, and my dog died in October of 2002. Two-and-a-half years I've been waiting for this product to be recalled. Many thousands of dogs have been affected. I have in my possession two other dog owners have asked me to cite the conclusions that veterinary specialists after determining, after thorough examinations and extensive testing, how ProHeart affected their dogs, and the case numbers have been presented to the FDA and Wyeth. One of them is in California, an attorney, and that case number is 80840-05. The other one is a -- the name of the dog is Pickles. The other one is case number 200402016, Rusty, a six-year-old champion Doberman in Dallas.

Also my dog, four vets, not one, not a single on vet would ever admit -- the product had only been on the market one year -- that my dog could possibly have been harmed -- actually I was told could never be possibly harmed by ProHeart 6. However, my new personal vet, I submitted his x-rays which had a huge amount of spots on them, to him. He submitted it to an utmost heartworm specialist. I can't say names here, but he appears on the Wyeth front page of your website, so you would know who that would be, and he is at Auburn University. So you all can all figure it out. He looked at my x-rays and he said that it is difficult for

vets sometimes to look at these x-rays and determine if it is in fact heartworms or if in fact it is cancer. So he looked at my x-rays and he determined as told to my personal vet that it was pulmonary thromboembolisms. Furthermore, my own dog's testing, the very first vet that I took him to, he had written down PTE remarkable. I had no idea what PTE is. I later found out it means pulmonary thromboembolisms.

My dog had hidden heartworms, and he had tested 11 years due to being on Heartguard Plus. Any monthly preventative out there is capable of making the female worm sterile with prolonged use. The testing is inaccurate on low female worm burdens. Therefore any dog that receives a ProHeart 6 is at risk. I have documentation whereby the dog in Dallas, it cleared the adult heartworms in 33 days and the microfilaria in 45. Has Wyeth ever contacted this specialist? No. Furthermore, the personal vet of that same dog, Rusty, heard from Wyeth one time. They have yet to have ever been paid, and that was a year-and-a-half ago. But Wyeth will pay the vets that don't speak out against ProHeart, and that is the problem the public has. We can't convince our vets if they are brainwashed by Wyeth. They are afraid of Wyeth. They buy products from Wyeth. It is very difficult for us to prove to you. Furthermore, any of you vets here know that in the

clearance of microfilaria that it can create IMHA. You also know -- I have a study here from Japan, a clinical research data, a published veterinary journal. It shows what happened to microfilaria-positive dogs.

So, yes, I'm emotional about this. I'm mad about this. I am not going to read to you everything. You can read it. You have the case numbers. You can read what the vets concluded. I'm tired of the vets that promote the product like Banfield who is going to acquire a lot of money because we come in every six months and spend our money. This product -- and I'm mad at the FDA. They should have never approved this product. There was not enough research done. Only 200 dogs in Australia for microspheres, but that was extensive testing. It was in two veterinary clinics and students were overseeing it. Why don't you all investigate the microspheres?

Why don't you investigate what's really going on here? They are obtaining research on our dogs, and they are using it to further their vaccines in my opinion, and that testing can be tied to the fact that in October of '03 they had a first injection for humans that they announced. Okay? And in March of '04 they announced their affiliation with TR and World Health Organization. So this isn't about just a heartworm shot. You vets have been mislead. You are

being used as a tool to inject the dogs, and they pay for the tests and they win. We lose. Our dogs die. We can spend thousands of dollars to protect them. So I'm angry. I'm sorry, but I am angry.

MS. SINDELAR: Thank you for your comments.

MS. STOREY: So -- thanks.

MS. SINDELAR: Our next speaker is Jean Brudd.

MS. BRUDD: Good afternoon, Ladies and gentlemen. Let me first state that I do not have a financial interest or relationship with any group or company or whatever. I paid all my travel expenses to get here. I jut want to say that I am here today on behalf of my two diseased dogs, Tasha and Nicki. They died during the peak period of 2002 due to one shot of ProHeart 6. My survivor dog, Casey, is on the low end of normal. Again, two-and-a-half years later, and his immune system was compromised.

However, I am not speaking here today on behalf of my dogs. It's still too painful for me to talk about two-and-a-half years later. Slow down here. I just want to say that most of the people speaking this hour are not a bunch of fanatics on the internet as we have sometimes been called. We are here because we have been victims of ProHeart 6. Our dogs took ill. Many of them like my dog

died. Some may say that these are just dogs that can be easily replaced, but not for us. These dogs were and are our family members. For some of us our dogs are the children we never had and never will have.

I am sure each of you in this room has bonded with a child. Perhaps it is one of your own. Your love for this child is so great you cannot imagine your life without him. Imagine a drug you agree to be given to this child to keep him in good heath. Imagine this child adversely reacting to this drug and there is no known antidote to counteract its adverse effects. Imagine this child having to suffer through the adverse effects for many months until the drug passes from his body, if his body can live that long. Imagine the horror of watching day after day your child seizing on the floor, or walking into walls, or not being able to eat or drink, or urinating or defecating on himself, or blood coming out of every orifice of his body, he is crying out in pain, and there you sit powerless not able to do a thing to help him. All you can do is turn over your child to the doctors, the so-called experts, and hope the doctors can figure out how to treat him, because they sure as heck don't know what is wrong with him, and it sure as heck cannot be the drug that they administered to your child.

Your doctor won't admit it if he thinks it is the drug because he doesn't want to be slapped with a lawsuit, and the manufacturer won't admit it because they don't want to be slapped with lawsuits. Meanwhile, you sit in desperation and pray that God fixes it all, brings you the miracle you are so desperately praying for, but the miracle never comes. You are faced with quality of life issues for your child who is never going to eat or drink on his own, walk, talk, play again. So what do you do? Do you let him suffer, or do you play God and pull the plug? Either way your child dies, and all you can do is blame yourself because it was you who trusted your doctor when he said this product was safe. But you played a part in killing your own child. How do you live with yourself for the rest of your life?

Welcome to our world. This is our own private living hell, the world of thousands of us guardians who have our dogs, our family members, adversely effected and even killed by ProHeart 6. If this happened to your child would you sit idly by? We think not. This product is not safe. You know it and we know it. The manufacturer will say that less than one percent of dogs are affected, that it benefits more dogs than it hurts. But when all the dogs in your household are affected by their product that is

100 percent, and it was 100 percent in my household.

Fort Dodge, we want you to stop experimenting on our children. Stop the killing. Stop this poison for profit. Members of the Committee, please tell them to leave our family alone. Look into your hearts and do the right thing by us and by our innocent, loving, animal companions. Please, do the right thing. Thank you.

MS. SINDELAR: Thank you four your comments. The next speaker is Dr. Martindale.

DR. MARTINDALE: Thank you. Other than purchasing Fort Dodge products I have no financial connection with the company. I am a practitioner in Denison, Texas. I own and operate a clinic for the past 36 years. It's a companion animal practice, and we did start using ProHeart 6 when it came out in 2001 and have progressively moved towards this drug as our primary heartworm prevention. Since the beginning we have experienced better compliance from our clients. It does fit well into our wellness program where we see the pet twice a year. It is readily accepted by the client, and we've had a marked decrease in the heartworm incidents over the past two years, ranging between 45 and 55 percent, depending on the year. Compliance was increased by sometimes as much as 60 percent in the two years that we have used it. So in our

experience it's been a very effective heartworm prevention without any serious side effects or any disease entity that we could directly attribute to its use.

We did have one small dog within 45 days after ProHeart 6 and vaccinations with immune hemolytic anemia. Interesting enough, though, that was the only case that we saw during the year. Whereas in previous years we historically would se anywhere from three to five cases of this disease.

Also I have had the opportunity to visit with many colleagues. My local colleagues, colleagues in Oklahoma, Texas, and Louisiana over the past few months before and after withdrawal. Every veterinarian that I've talked to said they have not experienced bad side effects with the use of the drug, and these veterinarians were giving anywhere from less than 500 doses to one veterinarian that had given 10,000 doses in Louisiana. So my experience has been good. I think if this drug is handled, stored, and administered correctly that it is a very effective means of preventing heartworm disease. Thank you.

MS. SINDELAR: Thank you very much. Our next speaker is Dr. John Gay.

DR. GAY: Good afternoon. Dr. John Gay, a faculty member at Washington State University. I am

veterinarian and have a PhD in epidemiology. I am the epidemiology representative on the American Veterinary Medical Association's Counsel on Biologic and Therapeutic Agents. My comments have been reviewed by fellow council members, and the Clinical Practitioners Advisory Committee. The AVMA paid for my travel. I have no financial interest in Fort Dodge Animal Health, and I am not engaged in clinical practice.

The AVMA is a national association recognized as the primary voice of the veterinary profession. We have some 70,000 members, which is 86 percent of all veterinarians. The AVMA's mission is to advance the art and science of veterinary medicine in all aspects, from clinical practice to food safety, to regulatory medicine to wildlife. We commend the FDA for holding this meeting and thank you for the opportunity to participate.

First, we believe a strong, science-based, transparent, systematic, post-market surveillance system is critical to our patients, to our clients, and to our profession. It provides important information that our profession needs to maximize the benefits and to minimize the risks for patients under our care. Our patients, ranging from finches to elephants, and Pekingese to Great Danes, present with a wide range of individual

characteristics and live in a wide range of environment. Because of this diversity we recognize that clinical trials required for new drug approval cannot be expected to detect all combination of circumstances and may lead to adverse drug experiences. We also recognize we cannot avoid all risk, that virtually all drugs and biologics have inherent risk as a consequence of their effectiveness. We recognize that to minimize this risk we must continually strive to improve our understanding of these and the conditions under which they occur.

A strong system reduces two general types of errors. First, it has sufficient sensitivity to provide early, clear detection of associations between particular drugs and adverse effects in particular segments of our patient population. In the long run, this is required to maintain the profession's confidence in the drugs we use and our clients' confidence in us. Second, it has sufficient specificity to reduce problems with spurious false association between particular drugs and adverse events in animals' lives. Again, this is required to maintain the profession's confidence in and access to these drugs.

Critical to a strong surveillance system and thus to reducing these errors is sufficient information. Increasing computerization of patient records and internet

access may provide several opportunities to increase reporting. One opportunity may be as simply as including URLs for direct adverse event reporting on every FDA approved drug insert. Another may be developing procedures to upload event information being routinely captured in electronic patient records, particularly in large corporate systems. This is already happening with HMOs and other care organizations in human medicine. Third, because the USDA is launching a surveillance system for adverse vaccine reactions, sharing of data between the USDA and FDA would improve the depth of comparative risk information for both agencies. As drugs, biologics, and pesticides are often used in combination, interagency collaboration including the EPA would enhance the detection of adverse effects resulting from particular combinations. Fourth, enhancements in the timely feedback of clinically relevant information to practitioners would help communicate the importance of reporting. Finally, it may be necessary for professional organizations to further inform the members on the critical importance of reporting adverse drug experience information.

To be as strongly science-based as possible, a pharmacovigilance system should incorporate all of the steps for logically assessing the strength of evidence for causality. The first step is using statistical analysis to

objectively determine the likelihood that any observed associations are due to chance rather than due to cause. Unfortunately, subjective assessment of count data for trends and clusters is fraught with danger. Statistical procedures to determine how likely apparent trends in counts or clustering events are due to random chance are well established. Quantifying risk is an important component of this process. However, reliably establishing and comparing risk requires sound exposure data, which is not routinely captured in the current system.

Finally, to retain trust and to maximize cooperation, the system must be sufficiently transparent to all stakeholders. Obviously the identity of individual patients and clients must be strictly protected. That marketing data providing for proprietary advantage must remain confidential. But if any party loses trust or reduces cooperation, animal health and ultimately the profession suffers. Again, I commend the FDA for holding this meeting, and I thank you for the opportunity to participate and to comment.

MS. SINDELAR: Thank you for your comments. Our next speaker is Connie Dominy.

MS. DOMINY: Good afternoon. My name is Connie. I am from Georgia. I went through snow, sleet, and

pure hell to get here, and the mic just came off the thing, but that's fine. I can improvise in five-minute period of time. Let me say first that I am here of my own accord. I do not represent any group, not have I received any monies from any group here. I paid my own way. I am here to represent --

MS. SINDELAR: --- slide presentation?

MS. DOMINY: Pardon?

MS. SINDELAR: Do you have a slide presentation?

MS. DOMINY: No, ma'am. I don't, and this is not at my five minutes, okay?

(Laughter.)

MS. SINDELAR: We will give you your time for it.

MS. DOMINY: Okay. That's fine. I'm sorry. Would you please restart the clock?

MS. SINDELAR: We will give you credit.

MS. DOMINY: Thank you. You know who I am, you know why I'm here, and you know that I do not gain financially from any of this whatsoever. I don't even own stock in pharmaceutical companies because I don't trust them today, even though they are a big business and I'm sure I would have monetary gains if I did.

By profession I am a psychotherapist and I have been in this field in private practice for over 20 years. I have been able to be familiar with product development and marketing statistics -- or tactics, I'm sorry, and post-approval safety data collection. My goal today is to challenge the FDA and the Advisory Committee to simply do your job. You are consumer advocates. The consumers are the animals, and they can't speak for themselves. You are charged to do this to the best of your ability and to not let politics, power, or greed intimidate your decisions. You are to hold the manufacturers of animal products accountable for their safety. I encourage you to look deeper than your soul and make the right decision regarding ProHeart 6.

I have a comment about Banfield that I have heard today. Let me just tell me that I went into our Banfield in Macon, Georgia six weeks after the product had been recalled voluntarily. They still had the advertisements up. That is not accountability. I'm sorry.

I remain firm in my belief that the symptoms my dog, Ready, who received the ProHeart 6 injection who is an Italian Greyhound and a champion, he received it and six months -- over the whole six months he exhibited symptoms, and I believe they were related to ProHeart 6. Fort Dodge

remains firm in its belief that their product is safe and science will prevail. Well, ladies and gentlemen, I am telling you here today that I believe that this product is not safe and science will prevail.

I have read the FDA report. I am appalled to think that Fort Dodge would interfere in the reports sent in by veterinarians as being -- referred to them as being over-reactive and biased. I believe veterinarians under-report adverse reactions. I believe that veterinarians are grossly mislead by Fort Dodge and their sales representatives. You ask about necropsy. By the time our animals get to that point we have spent major megabucks, and that is the last thing on our mind.

When looking at all of this with a scientific perspective, I question the validity of the initial studies presented to the FDA for product approval. To have a valid study the sample groups should represent the treatment time that this product is intended to work for. That at less than 180 days does not represent the study validity or reliability. The sample size was inadequate based on the projected population size and the dosages that Fort Dodge projected to sell, nor was it representative of a cross-section of the subjects that would receive this medication.

Another concern is the glaring absence of

longitudinal studies of significant sample size. It is interesting to note that the laboratory trial subjects were destroyed. This is otherwise known as destroying the evidence. In some areas this is a criminal activity. It is my opinion that Fort Dodge has been negligent in their job to provide a safe product. They have also failed in their job of apparently addressing the issues, the data collected post-approval indicated. They have categorically denied that the symptoms seen are not related to ProHeart 6. Denial of Fort Dodge is similar to that exhibited by the parent company when they denied what Phen-Fen was doing to our population, and we all know what happened with that.

So is this a systemic problem within this company? Maybe so. Is it a trend? Maybe so. It certainly brings me and I hope the FDA and the Advisory Committee to question Fort Dodge's integrity and their ability to provide unbiased information to the FDA and consumers. After all, the bottom line is profit, not safety or concern for our family members. This creates the biggest bias reported here today, profits.

As late as October, 2004, Fort Dodge was still denying that my dog's adverse reactions were due to ProHeart 6. I talked to the Fort Dodge Representative. They told me that they had contacted my vet and they had

been told that his case had been closed because he exhibited no other symptoms. Well, my little dog for seven months exhibited symptoms. They didn't contact. They didn't talk to my vet. I talked to the vet. The vet told me the same thing. Would you believe that? That vomiting and diarrhea are not side effects of ProHeart 6. It's on your brochure. I had tests done by ---. I had upper GI done. I had all kinds of stuff done to try to rule out ProHeart 6 at my own expense, ladies and gentlemen. Never did you contact. But yet you continue to deny, saying that because his symptoms, his primary symptoms, occurred on the 11th day -- I've heard seven to 14 days, ladies and gentlemen. I have a copy of his documentation with me. I encourage you to insist that more comprehensive studies be done on existing data and surviving subjects. Ready is alive. Let him be your champion.

One final parting thought. Until one has loved an animal a part of one's soul remains unawakened.

MS. SINDELAR: Thank you very much for your comments. Our next speaker is Georgene Paulauski.

MS. PAULAUSKI: My name is Georgene Paulauski. I'm a clinical specialist at St. Anthony Medical Center. I'm a clinical educator for Indiana University, and I --- college. I have no financial gain. I filed an

adverse reaction report in December of 2003 after Cletius received a ProHeart 6 injection. I was contacted by CBS-2 News in regards to what happened to my dog. The segment aired. Fort Dodge gave their account of what happened and published this both on the internet and through mailings to your peer vets throughout the United States.

I would like to read to you an excerpt of what Fort Dodge printed about my dog. "Initial testing identifies some abnormalities. Hemolytic anemia was a possible diagnosis. He was placed on antibiotics and corticosteroids. The dog's steroid dose was decreased. Shortly thereafter he presented not acting right again. After increasing the dosage, the dog's condition improved."

Now I would like to show you and let you see in reality during the seven months. These are the real facts, not what was published. Cletius received ProHeart 6 on September 27, 2003. No other injection. Immediately he developed a hot spot. Within weeks anorexia and became lethargic.

(Slide.)

Looking at the first slide I have up, in Fort Dodge's word there were some abnormalities noted. Anybody that knows a basic CBC, these are not some abnormalities. There are grotesque. These are panic value levels. This is

the case of Cletius and hemolytic anemia. He is in your packets. That's his number.

(Slide.)

Medical visits, we went through 45 office visits, two separate visits in ICU stays at Purdue University, multiple emergency visits, surgery.

(Slide.)

He had 102 lab draws, multiple types and cross-matches, multiple cultures including blood, urine, gastric, blood gas analysis, and ABGs.

(Slide.)

He had two ultrasounds, abdominal scans, numerous x-rays.

(Slide.)

This next page is hideous. These are the drugs it took to keep my dog alive during his hemolytic anemia. I am not going to go through the numbers. You can look at them and gasp.

(Slide.)

The fluids to keep him alive. Multiple keep opens, 0.9 normal saline, lactated Ringers, Hespan, blood transfusion, Oxyglobin, potassium chloride, Hetastarch.

(Slide.)

Due to all this multiple complications

resulted. You can't imagine anything worse on a hemolytic anemia than a dog starting to hemorrhage. That is exactly what took place. The dog started hemorrhaging, vomiting blood, tarry stools. At this time he also had grossly elevated liver enzymes. My dog's appearance became grotesque. Pot belly, enlarged liver, muscle wasting, the inability to walk, foot flop, swayed spine.

(Slide.)

Numerous attempts were made to try to wean Cletius from his immunosuppressants while the ProHeart 6 was in his system. Every attempt failed, and a lot of those attempts resulting in having to increase doses of Pred.

(Slide.)

Eventually he became over-suppressed and leukopenic. I then had to deal with bladder, bowel, and gastric infections, cystocentesis, diarrhea, numerous antifungals, antibiotics, LONOX were added. Little did we realize his over-suppression would finally become a turning point.

(Slide.)

After a lengthy conversation with Purdue and our vet, the debated on whether to decrease the dose of the immunosuppressant or finally withdraw it. The comment was made, "If it is truly the ProHeart 6, we should be able to

remove all meds and this dog should do perfectly fine."

(Slide.)

After him living on over 100-and-some medications weekly, on 6/2/2004 all meds were DC'd. I spent the entire summer rehabbing Cletius, walking, swimming, rebuilding his muscles.

(Slide.)

He is since now symptom free and drug free for 209 days. He has gone back to Interceptor without any incident. I am one of the fortunate ones here today He is healthy, happy, and extremely active.

(Slide.)

As a point of interest, my dog did have mild skin allergies. This was not his first injection. If you go back and look at your data, along with the ProHeart 6 when I went to the vet he said, "Is your dog itching?" If he was they gave him a shot of Depo-Medrol. Did that save him from a previous reaction? Absolutely. The steroid protected him.

(Slide.)

The long-term effects of all the meds to keep Cletius alive are yet to be seen, but what my family and this dog went through were pure hell. It consumed seven-and-a-half months of our lives. I can't begin to tell you

the bills, the time lost from work, without a single dollar recovered.

(Slide.)

It is very disheartening to know after seeing the clinical trial data after the fact I would have never have injected my dog with this knowing what you have published as an adverse reaction. Can I just give a closing comment? I say to Fort Dodge stop making excuses. You printed fluff about my dog, not faxes. As for the paper, shame on you. The hell that my family went through and what my dog went through? You continue to create a facade. You put it out on your internet, published it --

MS. SINDELAR: Thank you very much.

MS. DOMINY: Thank you.

MS. SINDELAR: Our next speaker is Paul Marron.

DR. MARRON: I do not have any financial affiliation with Fort Dodge. I'm not a government employee. I have paid my own expenses to come to this meeting. Members of the Food and Drug Administration, members of the press, fellow veterinarians, fellow companion animal providers, pet owners, thank you for this opportunity to speak before you.

As was mentioned, my name is Paul Marron. I

am a veterinarian and a practice owner at Battlefield Animal Hospital in Manassas, Virginia. I graduated from Texas A&M University in 1985. I've been in practice for 20 years, four-and-a-half years with the Army Veterinary Corps and 16 years in private practice. We currently have five veterinarians in practice at Battlefield Animal Hospital. We provide veterinary care to almost 7,000 companion animals.

The veterinarians at Battlefield Animal Hospital have as their first and foremost concern providing safe and effective products to insure the health and well-being of our clients' pets. As such, we were excited when a product became available that would not only improve compliance for parasite prevention, but also significantly reduce parasite disease and exposure to pets and pet owners. In July, 2001, we began providing ProHeart injections to our clients. Since then we have given 2,357 injections with only two verifiable minor reactions to those injections. During this period we have not seen any evidence of any increase in disease conditions in the pets treated at our hospital. For our experience it speaks for itself. ProHeart in our hands has shown itself to be a safe product.

Before the introduction of ProHeart, our clients were faced with only one choice in heartworm and

intestinal parasite control. That was oral medication. Though oral medication is effective, compliance has always been a major issue. At our hospital, we remind our clients by phone, by regular mail, by email, and during hospital visits to be sure to give the oral medication to their pets. Even with our efforts and the good intentions of our clients, compliance among our clients was at best 30 percent. Only one out of three of our clients' dogs were consistently protected. That means a higher exposure potential for internal parasites for our clients and their children.

As you know, transfer of parasites from our pets to us and our children has become a very real concern, not only for the veterinary profession, but to those of you in the regulatory professions. The Center for Disease Control in a recent survey of animal shelters revealed that almost 36 percent of dogs nationwide and 52 percent of dogs from southern states harbor intestinal parasites. At least 3,000 to 4,000 serum specimens from human patients are submitted to the CDC, state public health labs, or private labs for sero-diagnostic confirmation of intestinal parasite disease. The CDC further recommends that practicing veterinarians can provide an important public service by recommending fecal examinations twice yearly and providing

well-timed --- treatments. The Companion Animal Parasite Control Council recommends that fecal exams on companion animals be conducted two to four times per year.

Ladies and gentlemen, the reason I provide these statistics is to inform you that the use of ProHeart at our hospital has been one of the most effective means in helping to follow the guidelines for preventing internal parasitism in our pets and transmission to our clients and their children. In our practice and with the use of ProHeart 6 injections done every six months, fecal exams are now availably done twice yearly. In addition, it has helped to greatly improve compliance for internal parasite exams and treatments. As a result of utilizing ProHeart 6, our compliance for intestinal parasite exams, heartworm tests and prevention has increased from 30 percent to over 80 percent. That, ladies and gentlemen, is a significant improvement in protection for our pets, our clients, and their children.

Members of the FDA, it is my opinion that the current risk assessment strategy being utilized is flawed. The unfiltered reporting system utilized to evaluate the safety and ultimate recall of ProHeart 6 has to create confusion with pet owners, veterinarians, and the public in general. On the one hand, we have thousands of

veterinarians nationwide who have provided tens of millions of doses of ProHeart with few complications. And on the other hand, we have claims of a potentially deadly drug. On the one side, I speak to my clients about the safety and efficacy of a safe, convenient, and effective drug. On the other side, they hear media reports and internet hype, opinion, and conjecture of serious complications.

I encourage a revision of the current reporting system to insure that review of drug safety is done by factually, scientific, examined discourse and weight of evidence. Not with conclusions and actions being taken as a result of the seriousness of the charges. It greatly concerns me as a veterinarian that I have been told that there are those in regulatory agencies who believe that, quote, "Veterinarians cannot be trusted to report accurately the adverse reactions to ProHeart because they are simply trying to protect their own interests and are seriously under-reporting the adverse reactions associated with ProHeart." Unquote.

I hope that these reports are not true. First, this type of self-promoting talk is grossly inaccurate and unprofessional. It is does not encourage cooperation and communication. Second, it seeks to promote an attitude of distrust between veterinarians and their

clients. Finally, I would like to restate that the veterinarians I personally know have as their first and foremost concern for the providing of safe and effective products for our clients and their pets. The goal of our profession is to improve the quality of lives of our pets and improve the client-pet bond while at the same time reducing the risk of disease being transmitted from pets to owners and their children. As a member of one of the greatest professions I again thank you for this opportunity to address this Council.

MS. SINDELAR: Thank you for your comments. Our next speaker is Dr. Bob Rogers.

DR. ROGERS: I'm Bob Rogers. I am a private practitioner in Houston, Texas. I have no conflict of interest, financial or otherwise. I want to applaud the FDA for the action they have taken to product the public by the withdrawal of ProHeart 6. The adverse reactions that I witnessed in my practice fall into three categories; neuro-toxicity manifesting in the form of seizures, pulmonary symptoms including massive pulmonary thromboembolisms resulting in death, allergic reactions including hemorrhagic gastroenteritis progressing to disseminated intravascular coagulation and death.

The following questions need to be answered

before this drug is returned to the market. Are these problems due to an inherent problem with the drug moxidectin, instability of the microspheres, allergy to the microsphere coating, or are they due to mishandling of the drug by veterinarians or perhaps some of both?

If ProHeart 6 is injected through too small of a gauge needle or if the bottle is reconstituted and then shaken vigorously after several nights of refrigeration instead of swirled, could this cause disruption of the microspheres? Could disruption of microspheres cause premature release of the moxidectin, moxidectin overdose, and resulting seizures? Or could this be an intermittent manufacturing problem?

We know moxidectin is a more potent filaracide than ivermectin or milbemycin. In a letter I have from another veterinarian dated February, 2002, she says that her patient died from a pulmonary thromboembolism as an adverse reaction to ProHeart 6. She states that Dr. La Roch at Fort Dodge told her they knew ProHeart 6 could kill L4 and L5 larvae. Fort Dodge did not send out a Dear Doctor letter to warn veterinarians not to give heartworm to heartworm-infected dogs until November of that year, nine months later. Does the death of L4 and L5 newly-emerged, young adult larvae and possibly the death of migrating

intestinal worm larvae, all of which cannot be detected by available testing methods, post a fatal risk to our patients? How can this risk be avoided?

How does ProHeart 6 cause hemorrhagic gastroenteritis? Is this due to the death of migrating larvae, or is this a manifestation of allergic reaction?

What is the cause of mast cell degranulation? Are dogs allergic to the hydroxypropyl methylcellulose? Do these anaphylactic reactions result in DIC? Is there a hapten somewhere in this formula that we don't know about as was the case with diethycarbamizine? What is the cause of the auto-immune reactions?

If microspheres are injected into a dog, do some of them enter the circulation? What is the impact of circulating microspheres on the kidneys, liver, and lungs? Studies have shown in other species that microspheres can cause pulmonary hypertension.

Looking at the ADEs it seems a number of product failure reports and end effects increased with time. Is this due to laxity of testing on the part of veterinarians?

Finally I have a suggestion which could increase product safety. Unit dosing has been widely mandated for human drugs. If this product is returned to

the market, unit dosing would help to prevent many of the mishandling and storage errors.

I want to express dismay at the method in which this product was marketed. Please help me to understand why a company would choose a person whose presentations involve so much profanity? Dr. Whitford is not a board-certified cardiologist, not a parasitologist or pharmacologist. He has no qualifications. In his presentation he focused on one point. Veterinarians will go broke due to competition from Pet Med Express if they don't switch their clients to this product. He stated that allergic reactions could be treated with Benadryl. Since when is Benadryl the standard of care for DIC? He repeatedly said that all of the adverse drug experiences reported to the FDA are not due to ProHeart 6. For a company to deny all FDA ADEs is not responsible. He did nothing to emphasize the need to handle the drug carefully and the consequences of not following the label directions.

In my humble opinion, Fort Dodge is responsible for this mishandling of this drug by veterinarians and the death of pets that have resulted because they not only failed to warn veterinarians about the side effects, they denied them, and the failed to adequately inform veterinarians on the proper handling of their drug.

This lack of responsibility is no in the best interest of Fort Dodge, it is not in the best interest of our patients, and it is not in the best interest of the veterinary profession.

If this drug is returned to the market, the FDA needs to mandate that Fort Dodge implement a thorough training program to insure clients are warned and to insure that veterinarians are instructed on the safe use of the drug. FDA mandated programs have proven very effective increasing safety of drugs in past like Tilcomycin and Revolution.

Now Banfield has an excellent employee training program and --

MS. SINDELAR: Dr. Rogers?

DR. ROGERS: Yes.

MS. SINDELAR: Thank you very much.

DR. ROGERS: Than you. Our next speaker is Stephanie Shain.

MS. SHAIN: Thank you. I'm Stephanie Shain. I'm here from the Humane Society of the United States, and on behalf of our over 8.5 million members and constituents, the majority of whom are pet owners I am here today. As a matter of course, the Humane Society does not offer our opinion on veterinary drugs. We choose rather to leave that

to the individual veterinarian and client relationship. We make an exception for ProHeart 6 for two reasons. Number one, the enormous number of animals that were adversely affected by this drug; and, number two, the fact that it is a preventative drug and not something to treat disease.

I am lucky as an individual pet owner of four very healthy dogs that we chose not to use ProHeart 6 when it was offered to us by our veterinarian, thinking rather our monthly works, we know it's safe, and a six-month injectable just seems too good to be true. We ask because this is a preventative and because there are many known safe other drugs that can prevent heartworm safely that this drug not be released back onto the market. We think to do so is just simply reckless and too great a risk for individual pets and their owners who will invariably suffer from it. Thank you.

MS. SINDELAR: Thank you for your comments. Our next speaker is Kerry Tuttle.

DR. TUTTLE: My name is Kerry Tuttle. I'm a veterinarian from Peoria, Illinois. I have been in practice for over 30 years and am the director of three hospitals in Peoria and Bloomington, Illinois. We have approximately nine veterinarians working for us, most of whom have been with us for over three years. In late 2002, being somewhat

of a cynic with all new drugs that come on the market because of problems that have later been found once they have been presented, we did not begin ProHeart 6 upon its initiation. Late 2002 we gave our first dose, and since that time we have given approximately 6,000 doses. It represents just over half of the heartworm prevention of the clients that we have in our practice.

We offered our clients the choice of the once-monthly heartworm medications and the ProHeart 6. In that time, since we began that, which is over two years until the time it was removed from the market, via three-day callbacks, the fact that we have three practices that are relatively small practices, three doctors per practice, we feel that we know our clientele reasonably well and our clientele knows us. If they have a problem they tell us. If we think that they have got a problem, we morally accept some responsibility to solve that issue, I think no different than most veterinarians.

In the two years that we have given ProHeart 6, the 6,000 doses, we have documented four adverse reactions. Of those two were transitory digestive upsets, one was facial swelling, and one was hair loss at an injection site. The only one that has maintained or has been a continued problem has been the hair loss at an

injection site. It didn't grow back and probably is the size of a half dollar at this point.

Our efficacy as far as the drug has been essentially 100 percent. Compliance on the part of the clients has been good. We do give them the choice. We have advised them that there have been adverse reactions. To each doctor they have their preference to their client as to which they may provide voice inflection or at least provide which they recommend. As I said, we are over 60 percent or slightly over half with ProHeart 6. Art the time of the recall we had approximately 5,000 doses in stock. We questioned whether or not to send it back. Shortly we decided that immediately we would send it back because it was the right thing to do. Since that time all we have heard from clients is, "Don't you have an extra shot of that around somewhere, Doc? We want it. It's great."

I empathize with the individuals here today who have had disastrous reactions. We have not seen those, and I empathize with your group in the FDA because you are getting certainly some diametrically opposed information here, and I don't know you decide what's right and what's wrong. Thank you.

MS. SINDELAR: Thank you very much for your comments. We have exceeded the time allotted for the open

public hearing. I would like to yield the floor to Dr. Art Craigmill. Thank you.

Committee Deliberations

Dr. Arthur Craigmill

DR. CRAIGMILL: Thank you, Aleta. We will spend another half hour until we take a break. I think one-half hour. Is that your plan? Until 3:00, so it is 45 minutes. I would like to at this time to return to asking the committee if they have questions, and I think maybe in the interest of efficiency we will simply start going around the table, and I will skip people who have already talked and then come back for clarification. So I would like to start with Dr. Aref please.

DR. AREF: I sort of have spread out questions from various places. On page 18 in your -- the document from Fort Dodge, it says that about the carcinogenicity studies that the mice and rats that had the two-year study that doses were lowered because mortality was increased. Then the last sentence is that there were not compound-related findings in hematology values, organ weights, or at macroscopic or microscopic examination. There was no evidence moxidectin-related target organ toxicity or tumorigenicity.

So for a lay person what does that mean?

That you -- I mean, you obviously saw higher mortality, but you didn't see any symptoms or any changes in the various -- ?

DR. ROBB: I will ask Dr. Blasak to respond to the toxicology questions.

DR. BLASAK: Yes. Thank you. My name is Dr. William Blasak. I'm with Wyeth Research, and the carcinogenicity studies were done in mice and rats as they are typically done to assess carcinogenic potential because it is a disease that tends to happen more in later years of life. Those species have very relatively short life spans of one to two years. So there are commonly used for that.

The way doses are typically chosen for those types of studies, they are typically chosen on what is called a maximum tolerated dose. So you feed -- in these particular examples you feed the animals a certain amount of the test article, in this case moxidectin, and you maintain them on that diet. Now if that dose is too high generally what you will see is you will see some kind of toxic effects. Okay? And the effects that we saw were very typical of what is seen with moxidectin, and that is they stop eating, okay, they begin to lose weight, and if you go on long enough, okay, you have mortality in that study. Now obviously you cannot study the carcinogenicity in animals

that are no longer there. Okay? So the reason of reducing those doses is that we were too high in those doses. Okay? And so as the studies were going on -- I think it was within about the first month or so we noticed these decreasing body weights in these animals versus control animals. Okay? So we reduced the dose of moxidectin in the diet.

DR. AREF: Okay. So this was just a carcinogenic study so that you were only interested if they got cancer?

DR. BALSAK: No. No, and at the end of these studies -- so once those doses -- once the animals, if you will, stabilize at the lower dose, okay, the study has gone on, the animals are monitored on a daily basis. Okay? Then at the end of the study hematologies are performed, clinical chemistries are typically performed, and a full histopathological analysis of all the organs and tissues is conducted. Okay? And the main reason to do that obviously is to look for tumors first of all, but you also will find any kind of systemic organ or target organ toxicity in those animals. So if there were liver lesions resulting from moxidectin you should find them, if there were kidney lesions, et cetera.

And if I could add, it is not in the package, but we did a series of pharmacokinetic studies to supplement

what Fort Dodge had done. Okay? And the reason we did the pharmacokinetic studies is we wanted to know by the diet route how much moxidectin those rats were actually being exposed to, because we weren't sure. We weren't sure how much would be absorbed through the diet. Okay? And so we put those studies on in November actually to help address some of these issues, and if you look at what the rat consumed over the two-year period versus what a dog would be given over a two-year period with ProHeart, that is four injections, and you look at the actual exposure in the blood of those animals to moxidectin -- not just how much you gave them, but the actual levels in the blood -- those rats received about 860-fold the amount of moxidectin that dogs receive in a two-year dosing regimen. That is how exaggerated the moxidectin levels were in that study.

DR. AREF: So what did cause -- I mean, that they didn't want to eat and the weight loss?

DR. BLASAK: Well, you know, it's not uncommon in these effects. It is not uncommon when an animal is taking in too much of anything. Okay? There can be CNS effects. There can be effects on a variety of all biological phenomenon where they will stop eating, and we know that there is CNS effects of this drug. We know that from a variety of different sources, let alone just the

macrocyclic. But it is the exposure of the animal to the drug that is really in question. Okay? So if they were getting 860-fold the amount of drug over two years, if they were getting more than that maybe that did cause some effects, but, you know, the exposure differential there is so large that its relevance to a clinical practice is really in question.

DR. AREF: But would a necropsy show anything?

DR. BLASAK: No.

DR. AREF: So if you do a necropsy on dogs who have gotten ProHeart 6 you wouldn't see anything either?

DR. BLASAK: That's correct, and the dog studies for example, we have done a whole series of studies in dogs. He longest term study was a one-year study. Now this is a study were dogs were given again in the diet moxidectin for one year. So they got to eat their chow every day with a certain amount of moxidectin in it for over one year. Okay? And at the end in those dogs, and absolutely a good case, they did not lose weight. There were no adverse findings in life, and upon necropsy they went through a very full necropsy, a very systematic necropsy where all the tissues and organs were examined, and hematology, clinical chemistries, all those sorts of things

were looked at, and they were actually perfectly normal. Okay? Now those dogs were exposed to 454-fold the amount of moxidectin that a dog would be exposed to over one year. That is how much the level was in those dogs. Okay?

Now in studies prior to that, you don't just start a one-year study cold. You have to have previous information about how much you can give dogs so that you don't go over certain amounts. Okay? So in studies prior to that one, one-month studies and three-month studies. In those studies indeed at doses even way above the dose we used for the 454 multiplication factor, you would have the dogs showing the same thing. They would stop eating. Okay? They would have tremors. Okay? They would become lethargic, a very similar picture. But upon necropsy in those animals you don't see any systemic effects at all.

DR. AREF: But so it is likely if a dog was already compromised if you gave that injection without knowing it was compromised for whatever reason, it would not take that injection very well.

DR. BLASAK: Well, I can't speak to that. The toxicology studies were done in very healthy animals and I can't speak to whether or not if it is given to a compromised animal. I think it would certainly depend upon what is wrong with that animal to start with about what

would happen to the animal. Sorry.

DR. AREF: I have another question. It's about a couple pages further on. There is a field study mentioned on page 26 where client-owned dogs were looked at. There were 374 dogs representing 84 breeds. 280 were ProHeart treated and ProHeart 6 treated, and the others were -- 94 were on ProHeart oral tablets. On the next page they said that there were 12 other dogs were euthanized or died during the 12-month study, and those were all from the ProHeart 6 population. It doesn't say anything about any dog from the ProHeart oral population of these dogs. If none of the ProHeart oral dogs died, there is actually a statistical significance in the two populations' mortality rates at five percent.

DR. COBB: Dr. Rock, would you address that please?

DR. ROCK: Yes. We are talking about the field studies in the studies that you are talking about, and in conducting these types of studies a number of things happen. These studies are 18-month studies. Sometimes, you know, dogs would get hit by cars. They are not in there. Dogs, we had dogs that were lost in hunting accidents. We had dogs that ate antifreeze, and a number of different things that happened throughout the conduct of the field

trial. The bottom line in the interpretation of the experiments, both by Fort Dodge and by the FDA reviewers, is that these deaths could not be attributed to the use of the product, either the ProHeart 6 or the ProHeart tablet. ProHeart tablets at a very, very low dose, three micrograms.

DR. AREF: Based on the clinical observation, but it is assumed that the populations are equal except for the drug that they got? They should have the same kind of mortality rate, shouldn't they?

DR. ROCK: We find that in the conduct of this type of study and in the interpretation of these cases as I said, some were hit by cars, some hunting accidents. There was antifreeze. We did have, you know, two geriatric dogs. We had one dog that had congenital diseases which was talked about already today. But it was the interpretation that these -- that in both populations that there was not a correlation to the use of the product.

DR. AREF: Right. But I am just saying that just from when you have two groups of dogs who receive different drugs, there must be geriatric dogs in the oral ProHeart medication group and there must have been those that potentially could have been hit by cars and stuff. Were there none of those that were?

DR. ROCK: Yes, there were. I mean, there --

DR. AREF: There were ---?

DR. ROCK: Both populations basically reacted the same.

DR. AREF: Okay. Just because you mentioned only the 12 on the Proheart 6 --

DR. ROCK: No. The incidence was basically the same for both treatments. Remember the design of the experiment is two-thirds of the dogs are on ProHeart 6 and one-third are on the ProHeart tablet.

DR. AREF: Yes. It just doesn't say anywhere how many of the other ones died. That is the only -- I mean, because you don't give any numbers for those in the oral group that died then I was thinking that none of them died.

DR. ROCK: Okay. I understood we were writing the report for ProHeart 6 to provide you information like that, but the two populations basically responded the same.

DR. AREF: Okay.

DR. CRAIGMILL: We will move on and come back if you have one further. Dr. Bennett, I would like you to have 10 minutes now.

DR. BENNETT: Right. Thank you very much. I want to actually focus a little bit on the Banfield study a

little bit. The way I look at it from the FDA report there is about 12 million administered doses of the drug, and the Banfield people said they have administered about 735,000 or basically about six percent of all doses. What my concern was, my question was of the 485 deaths that the FDA has that are reported through the adverse event reporting system, how many of them come directly from the Banfield program?

Then secondly in general with this nice adverse event reporting system the Banfield field program has set up electronically, how many of those adverse event reports from the Banfield system when straight down to the FDA and when the FDA goes through their adverse event reports came out of the Banfield system? So just some cross-correlation between what Banfield reports and what the FDA reviews.

DR. NOVAK: So two questions, is how many --

DR. CRAIGMILL: Please identify yourself for the record.

DR. NOVAK: Dr. Will Novak, Chief Medical Officer for Banfield. Question one was I believe how many patient deaths did we have that were attributed to ProHeart 6. We had zero. And the second question was how many of the adverse events do we have that we have reported in our own system are then reported to either the manufacturer or

to the Food and Drug Administration. We don't of course have a requirement to report that through the system, and so I don't have an exact number. There are a handful of the reports that we've had that would have been reported with FDA. Anything that was reported with FDA goes through the normal reporting process. I am sorry -- have been anything that we reported would have been reported to Fort Dodge Animal Health. They have of course a requirement then to go ahead and report it on up through the system. And so any of the reporting that we would have done would have been something that we thought was above and beyond unusual after our peer-review process medical record review and that sort of thing.

DR. BENNETT: See, the question I have is given these several Dear Doctor letters and these package insert changes and the threshold for reporting decreased over time as I understand from what people said because awareness came up. It seems that if the threshold decreased over time then the original reports we heard from the FDA was that people would report differently at different thresholds. It seems to me a little strange that as those thresholds came up that the Banfield system didn't activate any different way than it had before, even though as you said up front that there was an increased alertness,

increased concern that these things might be related. That initially they might be passed off and then --- it might not have been.

DR. NOVAK: Okay. I am not completely following the train of thought there, but maybe to go through our adverse reporting system the way that we have got it set up is it designed for an interim reporting system. So we are then statistically tracking any variables that we would see for each of the individual components of the vaccine versus ProHeart 6. So we wouldn't particularly change the reporting methodologies going from us to let's say Fort Dodge Animal Health, unless we saw a spike on some change.

Now another example would be is that we may see a spike or a change on a vaccine, a particular component of a vaccine. That would then instigate that we would get involved with Fort Dodge Animal Health. Example, looking for a batch of vaccine that maybe we think needs to be changed out. So, and I'm not -- the reporting system, I do have the same concerns about the general reporting system when it comes to everything that has been discussed today is that by nature if you send out a Dear Doctor letter one would have a heightened concern about some things. We have an internal medical advisory group that fields a lot of

those questions, and so we are -- we got a lot more interchange between board-certified experts at our main office and our doctors in the field. So, you know, we are constantly looking at this thing internally.

DR. BENNETT: Well, okay. I won't go belabor the point, but the last point I would make is that if you had a concern about the way the cases were adjudicated between what you saw or when you reviewed the FDA reports and there was concern that Fort Dodge didn't adjudicate them the same way as the FDA did when there were cases to be adjudicated. My question was why don't they look at the exact same cases that you have in your data set that the FDA has and adjudicate them to see if you get concordant or discordant reasons and discordant things. You could adjudicate those even with what they have by matching them up by state and dog size or something like that. There are some ways that --- but you are also going to report.

The last thing I wanted to bring up is the question that was brought up from one of these speakers, was the issue about the handling of the product. I think that is a point that I think when I look at the side effects of ITP, IMHA, anaphylaxis, it raises a concern to me again of the question of the single vial that somebody brought up as an issue as opposed to the repeat use vial. Any questions

about impurity related to not actually the product, the drug itself, but the vehicle and the stability? And I am wondering if the company has spent some energy to look at the stability in terms of multi use as opposed to single use and whether these adverse events that have been reported are associated with vials that have been potentially out there more with more environmental exposure than the other vials.

DR. COBB: I would be happy to address that question. Yes, the company has expended a great deal of time and effort looking at various aspects that you raise and they are very valid aspects. When we initially received reports after the product was launched we in fact did a number of practice surveys because we did notice a cluster effect in that a practice in one city may report several reports. Neighboring practices did not report any. And our first thinking was there may be something in the handling, the storage, or the administration of the product. In fact, people from our professional services and research groups went out and visited practices, spoke to the veterinarians, to the technicians who were involved in handling the product. They even spoke to some of the pet owners to try to understand if there was any identifiable predilection that would point us to something that precipitated a reaction. We were unable to identify any patterns.

We certainly have conducted extensive stability testing on the product, both in its primary presentation as two vials and also in its reconstituted presentation. That has involved repeat penetration of vials. It's involved storage of inverted vials versus upright vials. We find that the product can be stored under normal usage conditions according to the label without any detectible deterioration or change in the product. We certainly have looked at what happens to microspheres over time, whether there is different release of moxidectin as the microspheres age. We do not find that in our testing, and I think a comment was raised about the coating on the microspheres. I would stress we don't coat the microspheres. The microspheres are manufactured from a consistent granulation to insure a uniform distribution of moxidectin through the glyceryl tristearate matrix.

As far as the carrier, we did extensive testing on the hydroxypropyl methylcellulose. We sent quality assurance auditors into the manufacturing facility to see if there was any possibility that the product could be contaminated either during manufacture with something else that was being produced by that manufacturer. The quality audit was very favorable. All of our stability tests, sterility tests, have shown that the product when

used and stored according to label and under the rigors of normal commercial use appears to be very stable. We brought product back from the field. We tested it extensively, product where dogs had been treated with that particular vial and had reacted, and we could not determine any deterioration or change in the product that we could attribute to a reaction.

DR. CRAIGMILL: If I may just interject one question here. Thermal stability, did you test that? I'm sure you tested thermal stability of the preparation of the microspheres, and could you comment on thermal stability if perhaps something got a little too warm?

DR. COBB: Thermal stability is an issue, and at above 40 degrees centigrade there can be a change in the matrix of the glyceryl tristerate. Moxidectin also is temperature sensitive. It is a fermentation product and like many fermentation products is temperature sensitive, and temperatures above 60 degrees centigrade would be expected to cause some degradation of moxidectin. They were not temperatures that we encountered in our site visits to the practices. The products generally were stored according to directions. We found reconstituted products generally were stored in refrigeration or at worst sat on a bench top for several hours. They were not exposed to temperatures of

60 degrees centigrade that we could determine.

DR. CRAIGMILL: Okay. If I may follow it just a little bit more. So the microspheres may become unstable if they are heated greater than 40 degrees centigrade?

DR. COBB: The microspheres may actually change their physical form a little bit. The glyceryl tristerate has a critical temperature of 40 degrees C, and does change into a slightly different form and you may see clumping of the microspheres if they are heated to greater than 40 degrees. That was one of the first things we looked at when we did our field visits to see has this product been heat stressed, are the microspheres a conglomerate in the bottom of the vial rather than being free-flowing microspheres, and we did not find that.

DR. CRAIGMILL: So there is a visual representation that you can see. It is a very visual --

DR. COBB: It is very visual. They actually glue together in a big blob.

DR. CRAIGMILL: And so you can possibly give it if that had happened in shipping or anything like that?

DR. COBB: They would need to --- I think.

DR. CRAIGMILL: Okay. Thank you very much. That is what I was wondering. At this point, I would like

to move to another one of the people who has not spoken yet, Mr. Jaffe.

MR. JAFFE: Okay. Thank you very much. I have a question for Fort Dodge. The report that we were given that you had produced talked about incident rates of adverse incident reports in -- 10,000 doses sold. It was a rate as to 10,000 doses sold. I guess I would like to know whether you have some information about how many dogs were actually give ProHeart over the two-and-a-half years that it was marketed and whether you have done any calculations of sort of rate per 10,000 dogs for example. I know that some of these adverse incidents you would expect if they had multiple doses the chance of the likelihood of it happening to be decreasing and so forth. Allergies and so forth if they had gotten through the first dose without any adverse incidents. So I am curious if you can tell us what information you have in terms of how many dogs have actually been treated with ProHeart, how many dogs are repeat in terms of the number of doses per dog that have been gotten since the product has been on the market.

DR. HUSTEAD: You ask very interesting questions. The numbers of doses of ProHeart which have been sold are about 18 million. We estimate that about 12 million dogs have been dosed with the product. We get that

from interviews with our customers and analysis of marketing data which comes into the company. We have not calculated a rate of adverse event report per that number because the number is so highly skewed we don't know how to evaluate it. So as has been presented, you need to be very careful when you look at incidence rates so that you can draw any sorts of conclusions with them. One of the things you have to do is have consistent numbers, and the numbers of dogs is just not a number that we can get a hold of with any consistency.

MR. JAFFE: So the numbers that are in the report are done on the 18 million figure, not the 12 million figure?

DR. HUSTEAD: They are the number of doses sold. That's correct.

MR. JAFFE: Okay. Thank you.

DR. CRAIGMILL: Anything else, Greg?

MR. JAFFE: No.

DR. CRAIGMILL: Okay. Let's move then to Dr. Nolan.

DR. NOLAN: Hi. I wanted to ask Dr. Brown about the Fort Dodge assessment of -- how if you tried to reconcile what they found as remotely related to ProHeart to your possibly related.

DR. BROWN: Well, I didn't really participate

in training Fort Dodge in the use of the algorithm, so I'm not sure how consistently it was applied. But something that has to be considered is the initial categorization as to assigning something else as a possible etiologic agent. We apply that to the algorithm, which is weighted to take all of that into account. So that as you go dog by dog, drug by drug, clinical sign by clinical sign, you have the same consistent type of score that -- for a causality assessment that can be reached. If one considers only that there is something else that could be causing that and therefore you say it is unlikely or remote, then you don't apply that to the weighted algorithm. You simply take those out as unlikely and exclude them from the beginning.

DR. PETERSON: I have a question for Dr. Glickman. The study that you did with the Banfield, you set up three groups of dogs that were on heartworm preventive to include the ProHeart 6. Did you examine whether or not there were any differences in the basic demographics among those three groups? For example, age, breed, or gender?

DR. GLICKMAN: Qualitatively there were no differences. If you apply statistical testing to them, there are statistically significant differences, not surprising given the sheer number in some of those groups of 700,000 or 400,000. You get very significant P values, but

clinically no. You are talking about perhaps a percentage of females of 52 percent versus 50 percent, but they come out. You know, you traditionally look at it and say, "Oh, wow. Statistically significant." But I didn't see any clinical significance of that magnitude of difference.

DR. PETERSON: Okay. Thank you.

DR. SAMS: Thank you. The preparation of the formulation for injection involves a number of steps that are specified in the product insert, and those steps appear to me to be somewhat more involved than for the preparation of other parenteral formulations that are on the market. Therefore it seems to me that there are opportunities for error in the preparation, administration, storing and handling of the product. So my question is, have any studies been done involving the intentional mishandling in terms of either of the preparation, administration, storage, or administration of the product?

DR. COBB: In terms of the detailed instructions for reconstitution, they are there for a purpose because this product is a little different than a reconstituted solution or a reconstituted suspension that is used in a single treatment. We do have an approved shelf life of one month for reconstituted product in the US. So it was very important to us to write detailed instructions

to be sure that this product could be used safely and effectively within that time window. In some other markets are reconstituted shelf life has been adjudged to be two months.

We certainly looked at what happens if you do it differently. If you use too much diluent, and we do put a little overage of diluent in the vial to allow the veterinarian to express any air bubbles that he may draw into the syringe. You may a product that is marginally more dilute. If you lose half of your diluent, if it squirts out of your syringe, you may reconstitute a product that is somewhat more concentrated. But certainly our --- studies with ProHeart 12 show that three times the concentration can be administered and used with safety in dogs.

There were questions raised as to why do we recommend that the product be swirled after reconstitution, are the microspheres so fragile that if you shake the product after constitution is this a problem. The reason we saw swirl rather than shake is that if you shake it you end up with a lot of air bubbles in there, and it means then that you have to put the vial down and let it sit for perhaps 40 or 60 minutes to allow those air bubbles to release themselves from the formulation. That obviously

would be a significant irritation both to the client and the veterinarian. So we do recommend that you make sure that the microspheres are uniformly suspended by that gentle swirling. But, yes, the product has been fairly rigorously tested in terms of what we would expect to happen under normal field conditions where people do get the dilution rate wrong or they go to inject the dog and some of it squirts out and the dog is under-dosed. We've looked at that.

DR. SAMS: Can any of the adverse drug reactions be attributed to any mishandling of the product during its preparation, administration, or storage?

DR. COBB: We have looked very meticulously many times, and we have not been able to identify any adverse event related to drug mishandling or poor storage by veterinarians. No.

DR. SAMS: Does Banfield conduct training programs specifically directed toward the preparation of this product?

MR. : Will, did you hear that question?

DR. NOVAK: Yes. The question is do we have specific training programs; and, yes, we do.

DR SAMS: And is that program applied

uniformly across all of your sites?

DR. NOVAK: We believe so. As with 1,000 veterinarians you will always have a little variation.

DR. SAMS: But there is a formal program?

DR. NOVAK: Yes. We have a web-based training program as well as when we originally launched the product we did regional meetings. So we spent a fair amount of time making sure that all of the steps of the process were well trained against.

DR. SAMS: Thank you.

DR. CRAIGMILL: I guess it is my turn. I have a slide for Dr. Brown -- slide -- question for Dr. Brown. I would like to hear what the FDA knows about the Australian experience with the ProHeart 12 drug in terms of two major questions. One, is their adverse event reporting system similar to ours; and, two, what is there experience with that drug?

DR. BROWN: Well, it is my understanding that in the different countries around the world that the adverse event reporting systems are actually somewhat different in terms of their collection and the way that they are interpreted. Perhaps Dr. Post as Chairman of the VICH might be more prepared to answer that.

DR. POST: Well, I will beg off on the VICH

part, but it's just different. Different populations, different systems. It's about it.

DR. CRAIGMILL: Can you comment about what they have found, seen, or in terms of have they had a similar problem basically or any of the other countries where it is approved?

DR. POST: No, I can't really comment on different countries, what they have found or haven't found. I just know about what we found in the US.

DR. BROWN: I would just have to refer you to the websites for those countries and to take a look at the numbers of reports that have been received and what types of reports they are.

DR. CRAIGMILL: Just even one further question about obfuscation. Do you know is the formulation the same as -- it is a different formulation being used, right? Or is it a different carrier?

DR. BROWN: I would be happy to answer that. The formulation in fact is the same. We put three times as much mircospheres in the microsphere vial. We put the same amount of diluent in the diluent vial. So the product is administered at three times the does, three times the concentration, but at the same volume.

DR. CRAIGMILL: Yes, Dr. Hustead?

DR. HUSTEAD: Well, I am actively involved in the Australian adverse event regulatory arena as my area of responsibility is all countries around the world. And it is my assessment that the adverse event reporting system in Australia is actually very similar to the FDA's reporting system. There are of course always differences, but those differences are comparing vanilla ice cream and French vanilla ice cream. The similarities are much more similar than the differences. And as far as the adverse events that they have experienced, it is our review of the events in Australia and here that they are highly similar

DR. CRAIGMILL: Okay. Thank you. My second -- I have four questions, and we will take a break at 3:00. My second question has to do with we heard about the long-term studies that have been done with moxidectin per se. I would like to know what acute and chronic studies have been done with the actual formulations, multiple injections, one, three, five-X doses, et cetera, for ProHeart 6. Can we have someone to cover that?

DR. COBB: Yes. I will ask Dr. Rock to cover that.

DR. ROCK: The safety program for ProHeart 6 actually covered three types of studies. The first type of study is a safety study in the target animal. Okay? It's a

one, three, and five-X study, and there is a necropsy of high-dose and then controls. If there is something for us to look at, if there is a trend or something there, then we will go in and do the mid doses.

DR. CRAIGMILL: Can I clarify? Is that a single dose?

DR. ROCK: That's a single dose. Yes.

DR. CRAIGMILL: Thank you.

DR. ROCK: Okay. We have also done a study in ivermectin-sensitive Collies. In that study we choose Collies which are shown to be sensitive to 120 microgram dose of ivermectin. That's approximately a 1X dose for a 20 KG dog. We use a 1X, a 3X, and a 5X in that study, and we follow those dogs for two days. We are looking for typical signs of toxicity which would mainly be CNS effects. We follow those dogs in locomotion studies, and we also follow immediate reactions to those dogs, and in that study we saw none.

In a third study which was already talked about today, we identified dogs that are naturally infected with heartworms. We determine that by measuring the circulating levels of microfilaria. We then treat those dogs with a 3X dose, a single dose of ProHeart 6, and then we necropsy those dogs later on and look for abnormal

reactions. We are also looking for abnormal reactions immediately after treatment. If there is some of the toxic effects that one might expect if we were having a mass kill of adults, and allergic reaction or something to that nature, and in those studies we were -- we did not show any adverse reactions.

Just one step further in our discussion as part of -- and Dr. Cobb talked about it earlier today, as part of the ProHeart 12 program we did do a heartworm-positive study with dogs that had 20 adult heartworms inserted via the juggler vein, and looked at adverse reactions. In those dogs we let those worms equilibrate for a period of 60 days I believe, and then we treated them with a 3X of ProHeart 12, which was a 9X of ProHeart 6, and there were no adverse reactions in that experiment as well.

DR. CRAIGMILL: Do you have data from multiple injections of the ProHeart 6 in dogs?

DR. ROCK: We have a small, non-pivotal study in multiple injections. It was in -- it is in the FOI where we started out -- one of the concerns that we had at the beginning of the development program with ProHeart 6 was if we are going to have dogs on ProHeart 6, two injections a year for a period of seven, eight years or something to that nature, what is going to happen with each one of those

injection sites? So we set up a study which starts out with a fair number of dogs, but at each time point after six months, after 12 months, throughout a period of time, we will necropsy and excise those injection sites in a small number of dogs. Whether it is two or four, we will go left side, right side, both on the right side, and all different combinations. It ends up with a large number of dogs, but it ends up with a small number of dogs at each of the necropsy points if you are trying to cover all points. In that study we determined or we observed that there was no adverse reaction to multiple injections, nor was there any accumulation of the drug in the body.

DR. CRAIGMILL: Okay. Being a toxicologist, one more question. Did you run a test of the formulation using like a guinea pig, hypersensitization model, anything like that as part of the initial acute screen?

DR. ROCK: There were these types of studies way back in the discovery phase when we were dealing with moxi

-- with microspheres as a whole, and there was -- we did not identify any problem with the use of microspheres.

DR. CRAIGMILL: Okay. I will save my last two questions until after break. We will come back and recommence at 3:15. Sorry. Aleta has something for now.

MS. SINDELAR: I am sorry. Just for the purposes of transcription and for the record, Dr. Tuttle has agreed to just make some comments which he didn't make at the opening of his five minutes.

DR. TUTTLE: I apologize. I didn't announce. I have no financial interest with Fort Dodge, a general drug distributor who provides not only Fort Dodge products but all of our other products did pay my expenses here.

DR. SINDELAR: Thank you very much. Okay, 15 minutes please.

(Whereupon, a short break was taken.)

DR. CRAIGMILL: Okay. At this time I would like to ask Fort Dodge Animal Health people again and Dr. Cobb probably and who will probably refer it to somebody else again. It is a follow-up question to Dr. Papich's question about the pharmacokinetic values. You mentioned the Tmax, the time of maximal concentration was somewhat variable. The key point I believe five and 14 days? The Cmax, the actual concentration obtained, what type of variability did you see with that?

DR. COBB: The variability in the Cmax is not enormous. It ranges generally around the order of five nanograms per ml, but we do not see levels in excess of six. So it is quite tight Cmax, although the Tmax may vary a

little bit in individual dogs.

DR. CRAIGMILL: So you don't see why it swings in that, in the Cmax at all. Interesting. Thank you. Dr. Nelson, whom I cut off at lunch, now we will return with his questions.

DR. NELSON: Aa a clinician, I am more concerned about clinical cases, and I would kind of like to return to these cases that were presented to the committee as representative of some of the problems that were going on. I guess one, the liver, since Dr. Brown was bring about the pathology of the liver in these six cases, one of the things here, there is only one case that actually has a level of what the ALT was. Mostly it says it's elevated. Did you get actual, you know, values on these cases? Or the report just came in elevated ALT?

DR. BROWN: That would depend. In most of them I would say that we do have actual values, and there again they are considered elevated reported by the veterinarian who is attending clinical that patient and also referring to the baseline of the laboratory that that individual practitioner uses.

DR. NELSON: Then also in those cases two were necropsy, one had a biopsy. You were asking about pathology, and the third case we get a biopsy, and this done

like three or four days after the injection. The diagnosis came back as chronic active hepatitis?

DR. BROWN: Yes.

DR. NELSON: And then on another case, case number five, necropsy was approximately two weeks after injection, and in that one there was some mineralization in the kidney tubules, which is more of a chronic kidney problem? I guess one of the --- today with these clinical cases is the lack of information. In the neurological cases one of the things you had in here on case number six, you talked about a CSF tap and then you bring up a distemper titer of one to 80. Is that in CSF fluid or one to 80 in serum?

DR. BROWN: Oh. I believe that was in the CSF fluid.

DR. NELSON: Which positive titer and CSF fluid is pretty much indicative of distemper, right?

DR. BROWN: Well, the laboratory said that could indicate vaccination infection or exposure.

DR. NELSON: Did you have the titer of also serum?

DR. BROWN: No. That's the only titer we have.

DR. NELSON: Also there are some questions in

here about health status?

DR. BROWN: Yes.

DR. NELSON: I thought it was interesting that it listed health as good in a 40-pound Dachshund?

DR. BROWN: Oh. Yes, I found that rather interesting myself.

(Laughter.)

DR. BROWN: Actually in that circumstance obesity would be listed as a concomitant medical problem and for circumstances anything affected cardiology or the joints or the liver we would of course give that a -1 in the alternate agent category.

DR. NELSON: The other thing that is also not listed, and you talk about concomitant use of vaccinations, it just says distemper. It does not list whether it is distemper with lepto or without. Do you have any of that information?

DR. BROWN: Yes, usually we do have that information, and for almost all of these if it says it is distemper vaccine it is actually referring to distemper adnovirus parvovirus combination. Usually with lepto unless specified not.

DR. NELSON: So all the ones that say just distemper you had lepto included?

DR. BROWN: Yes. In some circumstances we have the actual names of the vaccinations used, and in others we don't.

DR. NELSON: And then also did you have, as I brought up earlier, any information about previous heartworm preventatives in a lot of these cases where there's gaps of two years?

DR. BROWN: In many of them we don't. Sometimes we have owners coming to practices with all their previous records in hand. Sometimes they will come and there is really no previous information available. If the reporting veterinarian has been able to ascertain that, that would be in the medical record, or we might call them and ask them for that information. But if they don't have it, then they just don't have it, and that does kind of obscure the possibility of has there been a repeated exposure or has there been the possibility of a cross-reaction across a class of the macrocyclic lactones. We are just not able to say in those circumstances.

DR. NELSON: Well, I hate beat a dead horse, but the whole issue of heartworm status is so important with these drugs. I mean, there is not one of these drugs that we have not seen reaction in a heartworm-positive dog, and then just the whole understanding of the pathogenesis of

heartworm disease. It was a little disturbing in going through the CVM's report referring back to the 1999 guidelines and about heartworms being found in the right atrium. When they break loose there it is supposed to be in the pulmonary artery they are found, and also the three-month disease cycle that we actually have two-inch worms in pulmonary arteries at 90 days. So it is extremely important that the heartworm status of these dogs and the prior preventative that has been administered be known if you are going to try to predict any type of anaphylactic reaction to --- filaria.

DR. BROWN: Yes. We really would like to have that information, and as I said many times we have called and asked please go back and try to find it. Often they will send the entire record that they have to us, and it is just not there. It really would be helpful if we had more complete reporting.

DR. CRAIGMILL: Other members? Dr. Brown.

DR. C. BROWN: I have a follow-on to that. Not to sound like a little dog at the end of a rag, but necropsy findings, histopathology, is there any further data on that to be presented?

DR. HARRIS: I'm Keith Harris. I'm head of pathology for Wyeth Research. I will try to talk loudly --

MR. : --- will get the microphone.

DR. HARRIS: Is that better? I'm Keith Harris. I'm head of pathology for drug safety in Wyeth Research, and I guess this goes back to your earlier question of how many necropsy and pathology reports we had in the Fort Dodge database, and there were -- out of the 616 animal in our database, there were 165 necropsies. Out of those we had eight -- there were 85 pathology reports, and to the best of my knowledge all the pathology reports went to the various consultants that were looking at liver, CNS, immune-mediated disease, and that's how we divvied them up. So I focused for example on liver, and I did look at a few heart cases as well. Does that answer your question?

DR. C. BROWN: So you read the reports, but you didn't review the series of slides?

DR. HARRIS: No. The only ones we read, the -- we looked at the reports, looked at -- in my case I looked at -- we all looked at the total package, but we looked at the reports, looked at what the individual diagnoses was made by the pathologist, then looked at their final comments. The only case that I looked at slides or did we look at slides was in two heart cases where I looked at sections from the animal in trying to figure out what was going on in the heart.

DR. C. BROWN: Thank you.

DR. GROSECLOSE: Just a question on the series of studies that were discussed just prior to the break. I had wondered whether those were done pre-marketing or post-marketing, and how many animals may have been included in those studies, and what was the power to detect any adverse events in those studies should there have been any?

DR. ROCK: The safety testing was done during the development program, and it is done to a standard design that was discussed with the Center for Veterinary Medicine prior to initiation of the development program.

DR. GROSECLOSE: Okay. Maybe I can then direct it at the Center for Veterinary Medicine. What power do those studies have based on the sample size that you require to detect adverse events prior to bringing these biologics to market?

DR. POST: We don't do a statistical analysis. It is all -- oh, are you talking about pre-market?

DR. GROSECLOSE: Pre-marketing, right.

DR. POST: I'm talking about post-marketing. I will defer that question to Dr. ---.

DR. BARTHOLOMEW: I will try to address it, and the answer to that --

MR. : Please identify yourself.

DR. BARTHOLOMEW: Mary Bartholomew from the Center for Veterinary Medicine. I'm in the biometrics group and we review target animal safety studies for the Center. The gentleman from Fort Dodge Animal Health is correct in that there is a fairly standard study design that has been used for companion animals, and the typical study size is four males and four females per treatment group in each of zero, one, a three, and a five-X study. The reason for using the exaggerated doses is typically because the studies are fairly small and we are trying elicit the toxic syndrome. So in terms of power we'd have to talk about what size difference for what variable, and we look at sometimes for including all the clinical chemistry, the hematology, necropsy variables, and some of the in-life measurements like weight and feed consumption. We look at probably 50 variables, so there is also a multiplicity issue there. But that is the typical size. Sometimes that varies, but that is the standard-sized study and I believe that's the size study that Fort Dodge did.

DR. GROSECLOSE: Okay. Thank you. Just two more questions. The microsphere technology, is that used in

any other of your biologics at Fort Dodge?

DR. COBB: No. We do not use that microsphere technology in any of our other products.

DR. GROSECLOSE: And a question for Dr. Glickman. Could you review the findings of your multivariant analysis of the association between ProHeart and allergic reaction? There seemed to be a statistical -- I mean an increased risk of allergic reactions in dogs that were administered

ProHeart 6, and you didn't mention it in your conclusions, and I --.

DR. GLICKMAN: Yes. In looking at the multivariant model, well, what we saw from just looking at rates was that there appeared to be an increased rate of allergic reactions in the dogs that got vaccine compared with the dogs that got any of the heartworm products. In fact, this came out in multivariant analysis. There was this 150 percent increase in the risk of allergic reaction in vaccinated dogs versus not vaccinated. Both ProHeart and heartworm one monthly also were associated with an increased risk of allergic reactions. In ProHeart it was increased 38 percent, and heartworm one 12 percent. We probably didn't see any increased risks for heartworm two because it is the more infrequently used product, so the sample size was much

lower. Had the sample size been bigger, we probably would have seen an increased risk rate as well. So we did see an increased risk of allergic reactions for basically all of the heartworm preventives we studied, of course as well as with steroids because of this use association.

But the interesting thing to me was then if you look at each additional dose of ProHeart, the risks do not go up further. In fact, it was marginally reduced.

DR. GROSECLOSE: Well, how did you account for say -- I don't want to belabor it, but, you know, a dog that had two versus three versus four in your model?

DR. GLICKMAN: Well, we put that in, in the model. One dose, this was ---. Zero would be no dose, then first dose, second dose, third dose, fourth dose, and it went in the model just that way; and there was no significant dose response relationship on the up side, and even on the down side. It was sort of a negligible change in risk with each additional dose.

DR. GROSECLOSE: Did you see any dogs that may have received one dose of ProHeart who then received -- went back to a monthly heartworm medication subsequent to the first dose?

DR. GLICKMAN: No, we didn't track longitudinally in this case and distinguish reactions to see

if a reaction on the first dose would be associated with a reaction on the third or fourth. It's interesting. We have done a large study in this database with vaccines, which appear to be more allergenic, and sort of the belief out there is, "Well, if a dog has an allergic reaction to our vaccine, either you shouldn't give it again or you have to pretreat or whatever." And using this database we have seen no larger risk with a second dose in a dog that had a reaction the first time than in a dog that did not have a reaction the first time. This is the first time we have been able to look at this scientifically, and pretty much we are finding similar things with ProHeart. It was a little harder with the oral monthlies because since they weren't given in the practice it is harder to track, and owners miss doses and you would probably not know about that if there is no way to track it.

DR. MEALEY: Okay. One question about the mast cell tumor, the increased risk that you found with mast cell tumors. Were any of those mast cell tumors found at the injection site?

DR. GLICKMAN: That's a good question. We have not gone back to look at two things, though clearly one should know whether it is at the injection site or not, and, two, whether perhaps histopathologically they differ, that

is mast cells in dogs that got ProHeart versus mast cells in dogs that did not get ProHeart. For example like we see with fibrosarcoma in --- when they occur at injection site they are much more aggressive, et cetera, than if they are not. That has not been done.

What we did do was to calculate how many dogs would we need in a prospective study. For example, to detect this increased rate that you see with let's say ProHeart with vaccine versus vaccine alone in the incidence of mast cell tumor, and it comes out to be 600 --- dogs per group, so it is clearly never going to be done.

But what you suggested is absolutely right. One should go back now and for those dogs who have histopathology, which most will, actually pull them out and compare them, and also try to get more information on the site of the tumor, which we did not do. Phil, do you want to say more about the medicine?

DR. BERGMAN: Yes. Dr. Mealey, in reference to your question, my name is Phil Bergman and the outside oncology consultant for FDAH. Of the 130 cases that we had available that I had available to review, there were three dogs with mast cell tumor, and none were associated at the injection site. Importantly, all three of those dogs actually had their tumors occur with three weeks of

injection of ProHeart 6. So suggesting that there was no association with ProHeart 6.

DR. MEALEY: Second question is there seems to be a concern, and I have some concern, that maybe moxidectin itself as the drug is maybe not a cause of these adverse events, but potentially the vehicle. And in the FDA documents that we got on page 11 there's a couple of statements in there about letters that were made from the FDA to Fort Dodge Animal Health about problems with manufacturing. There was sterilization problems I think and dissolution time point and GMP violations basically. I guess I want to know, is that a fairly common -- are those letters, citations, whatever they are, are they fairly common among manufacturing pharmaceutical industries, or is that kind of an unusual thing?

DR. : I don't know if I can answer how common they are, but it is these letters were not really directly connected with adverse drug events. They were just some manufacturing problems that were cited in an inspection.

DR. COBB: Perhaps I can comment on those issues. The first issue related to dissolution testing failure. Dissolution testing is conducted under laboratory conditions, and it measures the consistency of a product

release. We put the product into a laboratory media and we measure how much moxidectin is coming out at 1.0 hour, 1.5, 2.0, 2.5, and 4.0 hours. Every batch of ProHeart 6 that is released passes that dissolution test before it can be released.

On one occasion we did test some six month stability samples that had been stored for six months and had already been released, and we found that these two batches which were made from the one lot of microspheres marginally failed our dissolution specification at 2.0 hours and 2.5. The release specification was within specification at the 1.0 hour and 4.0 hour time limit. Despite that, it did not make specification. We recalled those batches from the market.

However I would say to you that this is a manufacturing consistency test. It tells you nothing about how the product releases in the dog, and certainly a dissolution test that showed a slightly slower release at two intermediate time points over a four-hour period would not be expected to have any clinical impact.

The second issue in relation to the plant inspection and the warning letter, I might ask Mr. Corcoran to comment on that. I believe that all of those issues have been resolved and much to the satisfaction of the FDA.

MR. CORCORAN: Yes. I'm Tom Corcoran with Fort Dodge Animal Health. Countering along with Dr. Post's comment, the warning letter we received is the first warning letter that we have received in at least over 10 years that I am aware of. Previous inspections have been absolutely spot on, very few observations. We were having an inspection in December of 2003. The observations were mostly administrative type of observations. We undertook a full retraining of our personnel, underwent an inspection in October of this year and got a complete bill of health from the FDA.

DR. LUSTER: A couple of quick questions. You talked about immunogenicity testing earlier and said you had done it, and I saw the post-clinical data presented in the document. But what preclinical immunogenicity testing were you referring to? You indicated you tested the moxidectin separately and the microspheres separately. Did you test the formula as it is used together?

DR. COBB: Yes. In our testing what we did was we ran a large number of tests. Tests were run on the complete product, on the microspheres containing moxidectin component, on the vehicle alone, on microspheres that did not contain moxidectin, and we ran it independently on various components of the vehicle. The vehicle carries

several preservatives,

--- and ---. They are preservatives that are commonly used in human and veterinary pharmaceuticals. We have looked at those. We have looked at the hydroxypropyl methylcellulose, and so that we did run tests on the individual components as well as the microsphere component and the total product as well.

DR. LUSTER: What was the test that you ran?

DR. COBB: We ran a number of tests. We looked at IGE and IGG levels in dogs that had reacted and could not find any evidence that these reactions were mediated by gammaglobulins. We did passive cutaneous hypersensitivity testing and had very mixed results and not repeatable. We did intradermal skin testing again with very mixed results and not repeatable.

DR. LUSTER: So this is preclinical dog studies that you are doing this immunogenicity testing on you are saying?

DR. COBB: These were actually done as a result of field reports of adverse events, but they were done in laboratory settings.

DR. LUSTER: And also a little bit of clarification, but regarding the -- I was a little confused because the FDA people were talking about an increase,

showed some data in their talk as an increase in anaphylactic responses after they were adjusting for market shares. Then you were talking about a decrease in anaphylactic responses, or equal amount of anaphylactic responses with ProHeart as there is with vaccine responses? Can you clarify that for me? Is it more or less? And this is data without obviously concomitant vaccine data.

DR. BROWN: Are you asking us initially?

DR. LUSTER: Yes. I would ask you first.

DR. BROWN: So you had wanted to know if we felt that there was an increase in reactions, anaphylactoid reactions after --

DR. LUSTER: Well, you indicated that there were -- after you adjusted. In your talk you adjusted for usage or for market share, and you said that the actual rate of increase in anaphylactic responses in dogs that took ProHeart without vaccination was three-fold or something like that? Is that -- did I get that number correct?

DR. BROWN: I think we might be talking about several different things. One reference I made was to adverse events, full anaphylactoid events over the marketing years, and we felt that there was a decrease in those number of events after the label change in June of 2002. Although we still do have a significant number of events. That was

one factor.

I think the other was in Dr. Post's slide when he was showing you the effect of was there a reduction in serious events after the minimum residue solvent lots were put into the market, and he was showing that in fact there were not. That we were continuing to receive high numbers of serious events, even after those lots with minimum residue solvents were in full market.

DR. LUSTER: I know you are being very careful and not saying any numbers, but you did mention numbers in your

-- at the conclusion of your talk.

DR. BROWN: Oh. That may have been when I was referring to the Fort Dodge document? Talking about anaphylactoid -- about allergic reactions with vaccines versus ProHeart 6?

DR. LUSTER: Right.

DR. BROWN: Okay. Yes, that was referring back to Fort Dodge's narrative that they submitted in which they showed that the reaction rate was I believe 1.16 -- 1.62 with -- sorry, 1.26 with ProHeart 6 versus 0.4 with the Duramune distemper vaccine or a 0.5 with the Rabvac 3 vaccine. Is that --?

DR. LUSTER: That's right.

DR. BROWN: Right. Which makes the reporting allergy event rate for ProHeart 6 two-and-a-half to three-and-a-half times higher.

DR. LUSTER: Well, that is how you got that number. Okay.

DR. BROWN: Right. That is on page 11.

DR. LUSTER: Okay.

DR. BROWN: That is on page 11 of my slides, but it is on page 37 to 38 of Fort Dodge's narrative.

DR. LUSTER: Okay. Now in the Banfield study, the Banfield spokesman said that you saw approximately the same amount of anaphylactic responses with ProHeart 6 as you did with vaccination. Is that true? Anaphylactic responses.

DR. GLICKMAN: Yes, the rates were extremely low, 0.7, 0.4 per 10,000. So they were extremely low for any of the products in terms of anaphylactoid. Not for allergic.

DR. LUSTER: Just that it is easy. As I indicated earlier, it was easy. It's easy to say this is allergy if a dog has a skin reaction and the dog has anaphylaxis. It is more likely to be reported I would assume, and it is quite a bit more obvious.

DR. GLICKMAN: Yes. I think in general

regardless of which, even the passive reporting, and certainly interactive review of the records. Reactions that occur within the first one, two, three days, are much more likely to be reported than reactions that occur later on because of this association in time between the event and the product. You know, just mentally one is less apt to associate the two. So there is much more complete reporting I think for early events than there is for later events.

Interesting, too, when you look at the -- you mention the allergic event rate of 1.26 that was calculated by Fort Dodge from passive reporting. In the Banfield database we calculate a rate that is roughly 18-fold higher, and that is the first time maybe where we have a comparison of -- or a basis for stating what the amount of under-reporting is in a passive system, and that is in a reaction that is more likely to be recognized. So under-reporting, yeah, it might be harder for the others that occur late.

DR. HUSTEAD: I would like to clarify as well that the number of adverse event reports in the allergy category are going down each year following 2002, and there relative frequency is also decreasing as well.

DR. NELSON: I have one more question. I skipped over this earlier. Dr. Cobb, you all talked about certainly

microfilaria were cleared approximately one week after injection, and you know the effect against three month and four month old. Do you have an data of actually how rapidly L3s, L4s, and L5s die?

DR. ROCK: In our heartworm-positive study which we conducted with naturally-infected dogs there was a 97.6 percent reduction in circulating mircofilaria at seven days, which increased to 98 at 14 and 99 from there on out through a 28-day study. One has to assume that if they are naturally infected dogs that those stages of larvae would be part of that population. If you look at the three- and four- and six-month-old infection study, the retroactive studies where these animals are being infected with microfilaria, the microfilaria are allowed to mature for three to six months. Some of those microfilaria, those larva stages are going to be the stages that you are concerned with, too, and there was no as we discussed previously in a previous question, there was no adverse reaction in those dogs as well.

DR. NELSON: I guess the question I am asking, do you know how long after the administration that you actually start to see like an L5 die?

DR. ROCK: I don't have that exact number. No, I don't.

DR. NELSON: I was just trying --- correlation with, you know, being a clinical science or not.

DR. ROCK: True.

DR. RIDDELL: I guess I have a couple of relatively disparate questions. Another thing that I do, I am involved with AVMA's Council on Biologic and Therapeutic Agents. Currently I am being chair of COBTA, and I appreciate Dr. Glickman's information about the relative reporting rates. That is something we have been looking for. COBTA has expended not a small amount of effort in the last couple of years to enhance adverse event reporting by the practitioner through the USP network and to FDA and also working with the Center for Biologics as far as vaccines. We have also been working with that National Animal Poison Control Center.

I guess I have and AVMA has always asked for a lot of these decisions to be made based upon science, and it is a little bit frustrating to me. We are having to ask people to make very weighty decisions with not a lot of science out there floating around. So I am very intrigued by the potential power in a database like Banfield's, and I had a question for I think probably Banfield.

Is when an adverse drug event is reported, there must be a team to evaluate it, and if so at what point

will a trigger point be reached that that would be reported to the sponsor, whereupon it would have to go to FDA?

DR. CAMPBELL: Any adverse event at all, you know, is reviewed by our internal group. If we believe that there is -- you know, it relates to the drug, then we report it.

DR. RIDDELL: But you don't have any specific trigger points, or it is just a feel for the instance?

DR. CAMPBELL: There are specific trigger points. My two colleagues, who would know that, you know, had a flight back to Portland this afternoon. But I know there are trigger points. I don't know particularly what they are. Larry might. Do you know? But I know a number of the -- you know, especially the anaphylaxis incidents and so forth, you know, that we had ProHeart. We reported it and, you know, rolled into Fort Dodge's data and then into the FDA data. Is that your question? We didn't have any deaths, so obviously we didn't report any.

DR. RIDDELL: Okay. Thank you. One other question to Dr. Cobb. You were pretty explicit in saying as far as the thermal stability of the microsphere was 40 degrees centigrade. Is there any indication that either a local or a systemic pyrexia would affect that once it is in the animal?

The stability of the matrix?

DR. COBB: We have no information on that. We do know that under laboratory conditions if that product is heated to 40 degrees it will agglomerate and clump because there is a change in the form of that glyceryl tristearate.

DR. RIDDELL: And if that were in the animal, how might that -- I know this is speculation. How might that impact the pharmacokinetics or the dispersal of that product? Or is it in an animal system, in a live system, not likely to occur?

DR. COBB: I really cannot speculate how likely those sorts of temperatures would be consistently reached within an animal. What I can tell you is that the release profile of moxidectin is very dependent on the spherical shape and the diameter of those microspheres. So if those microspheres become clumped, the expectation would be that there would be a slower-than-expected release of moxidectin because the surface area for release becomes smaller because of the agglomeration. That would be my speculation.

DR. RIDDELL: The logical conclusion would be that would not lead to toxicity but might lead to ineffectiveness. Thank you.

DR. CRAIGMILL: As chair I have one last question, and then I am going to ask Joanne --- if she will put up a slide because I would like to use it. We do have some sort of discrepancies in data. Dr. Hustead presented a slide which appeared on page five of our handout showing the total adverse events reported by year for three different products by year from 2001 to 2003, and I would like to just have some comments on these data because they show a dramatic increase in the number of reports for other heartworm meds. I would like to address this as a question related to under-reporting and whether or not the simple awareness that there had been some problems or things reported with relation to ProHeart has also caused an increase in adverse event reporting. I will particularly ask FDA personnel to plesae comment on this slide and what they think.

(Slide.)

Are these data correct that in fact ivermectin and pyrantel, the number of adverse reports has dramatically risen as well as for milbemycin?

DR. BROWN: I would like to go ahead and address some of those if I may. As I think you may remember from Dr. Post's slide, we do have a lot of reports sent in across the class of the macrocyclic lactones. Now you will

see that there is a big change in the number of reports for both milbemycin and the ivermectin pyrantel products.

One of the things that affected that was interpretation of the regulations by various sponsors as to which reports they should be sending in or not. When new interpretations were made clear to those other sponsors, they then sent in the reports that they had not so previously sent into us, and almost all of those -- I would say all of those were reports of ineffectiveness. Not just for heartworm disease, but also for roundworms and hookworms. So that is something. They sent a huge a number of those in all at once, and they went back to before the year 2000 and it took quite a while to process them all in of course.

That is a second part of that, which is that reports initially are triaged when they come in to the Center for Veterinary Medicine. We have drugs that have been on the market for years and years and years, and we feel that we have seen the types of adverse reactions, serious adverse events that occur with them and ideally have addressed those concerns already. For the newly-marketed drugs, we give those our priority. We evaluate those as quickly as possible when they are received, usually within a week, sometimes within a month.

But when we started to see back in 2003 that there were possibly situations that there could be concerns of ineffectiveness or other problems across this class of heartworm preventives, we went back and reviewed the reports that were waiting for their turn. And we pulled all the reports for all the heartworm preventives and reviewed all of them so that we could effectively make these comparisons, and that can show you these increases. Now Mary Bartholomew also has a comment to make.

DR. BARTHOLOMEW: I think it is perhaps fairer and more germane to the safety discussion going on right now to see the next slide, to take a look at the next one, then the effect of the increased reporting. Okay. That's the one. Then some of the effect of the increased reporting has been removed, and if you will take a look in the year 2003 then you get a sense of for two drugs that have approximately the same percent of market share what the adverse events are minus the ineffectiveness reports.

DR. BROWN: And I would like to add also to that that of course these are all the adverse events that come in, not necessarily the serious events that come in. So perhaps you might see a great deal of the regular kind of vomiting or diarrhea sort of reports coming in for those other products as opposed to the more serious events we have

been discussing for ProHeart 6.

DR. CRAIGMILL: So basically what you are saying is that these data are not really correct?

DR. BROWN: Well, I wouldn't say that they are not correct, but they are not correct when you think of the severity of reports that are coming in and considering the time period for which those reports are being submitted. In other words, you are seeing a jump in reports for these other heartworm products that have been on the market for years and years. Suddenly the are submitted within a certain year, and evaluated and entered into our system within a certain year. So from that standpoint they are correct, but looking from the point that they are going back for a number of years, just reported in one year, and that they are not necessarily serious events but more likely to be the more run-of-the-mill things like vomiting or diarrhea then I think that puts it in perspective.

DR. CRAIGMILL: Okay. So many of those reports of adverse effects for 2003 for ivermectin pyrantel, and milbemycin are actually from past years?

DR. BROWN: That's correct. That's correct. They may have not been submitted because of a difference in the reporting regulations, or they may have been submitted but have been waiting for their turn in evaluation. Whereas

the more recently marketed heartworm preventives are evaluated completely within a week or a month. The second set of the next most recently marketed would be getting the next priority, and under normal circumstances these would be getting the lowest priority. If you remember, we have seven people working part time to do these effects, and we get more than 25,000 reports a year. We have to usually let some of these reports wait their turn if we feel they have been out long enough and we have seen enough of them so that we know we are not getting any new information from them. But then in this circumstance when our concerns became evident across the class, we felt we should look at everything and get everything into the system.

DR. CRAIGMILL: Will you be looking to see in terms of adverse events, serious adverse events, what fraction of those that are of that influx that came in 2003 are actually from 2003 cases? In other words, are you going to separate out the past history from the current situation to see whether or not there has been an increase in reporting?

DR. BROWN: Yes. In our internal system, in our internal database we do that. We do that by the correspondence date, and we can also search then on the actual episode date. So we can look to see how many of

those occurred within a certain time period. And I think as you saw from our slides, we then looked at all of those classes and the adverse events for them during specific -- the past three marketing years, which were the first three years that ProHeart 6 has been out, and I think there you could see really quite clearly that we simply don't have the number of serious events for those drugs that we do for ProHeart 6.

DR. CRAIGMILL: And you feel those data are complete?

DR. BROWN: Yes. I do.

DR. CRAIGMILL: Okay. Could I ask for Fort Dodge?

DR. HUSTEAD: Sure. We believe the data is absolutely accurate. We obtained it from the CVM, so we assume the data is accurate as presented. We don't have any information as to when the events in 2003 for the other products actually occurred, because that is not part of the data set that we asked for. As to seriousness, there is no information in this data to know whether the events are serious or not. So that conclusion cannot be made from the data presented. They are just numbers of adverse events. These are the lack of efficacy events removed, so these are the events regarding safety.

DR. MEALEY: I have a comment on potentially what else may contribute to maybe an increase in reporting for all of these macrocyclic lactones. The discovery of a genetic mutation for ivermectin and macrocyclic lactone activity occurred and was published in 2001 and then picked up by, you know, AKC Gazette, and Dog World and Dog Fancy and then distributed by email all around, you know, the world about some of this stuff. I get emails and I was really getting a lot of emails during those times as well about any kind of -- any macrocyclic lactone in any breed and any potential toxicity. I was getting those at this time. So I think that that discovery generated interest to some extent in these compounds again, and so perhaps -- and I have no data, but I am just saying perhaps -- I am speculating -- that may have contributed as well to maybe an increase in the number of adverse event reports.

DR. CRAIGMILL: Any further questions from any member of the committee?

DR. TREPANIER: I have another question for Dr. Glickman then, because I really think the Banfield study is -- I think that data is so important, but I think that is also important to look at it from as many different ways as possible, and I think -- I know you have done multivariant analysis, but I think it would be important to look at all

the animals that got moxidectin and do actually a case control -- a matched case control comparison, same age, same health status, a very important one, perhaps same breed. Because the patients that got monthly heartworm may well be sicker, older, have other reasons to have anaphylaxis or vomiting or diarrhea, and it really clouds the issue. It seems like it is such a huge database. You can rely on the healthy dog studies that were done pre-approval because they are such a small number and it is clearly a relatively uncommon set of reactions. So is there a way to look at that data? It seems like that would be very important.

DR. GLICKMAN: There are many ways to look at the data, and there are lot of things that are attempting to do and should be done. In a sense doing subpopulations at risk, is there a unique group of animals either by their age, their medical history, or whatever, that would be more likely to react to one of the monthly heartworm medications than to ProHeart and vice versa. I agree with you. You know, you get a database this size, this rich in information, there are so many things you can do, and you have indicated another approach to doing what we tried to do by adjustment. I don't know that one way is better than the other. Certainly the two methods should give consistent findings. But the tendency is when you have a database this

large and have it over so many years, rather than doing the retrospective approach like you are talking, and matching and going back in time, it is to do this forward analysis. The big advantage of doing it the way we did is we can come up with an absolute risk, and incidence rate which gives you an absolute risk. What is the likelihood that if an animal got something they will have such-and-such reaction. Where if we do it the way that you suggest we lose that, but we can compare relative differences.

DR. TREPANIER: But can we say from that data that the groups that got moxidectin were same as the groups that didn't as far as -- you said you looked at that demographically, but it is not supposed to be used in debilitated animals, yet plenty of clinically ill animals get monthly heartworm preventative.

DR. GLICKMAN: I think the better way to answer that question is not for me as evaluating the data, but from Dr. Campbell in terms of what the protocols are for selecting dogs to receive, you know, oral versus injectable heartworm. You may want to comment on that. In other words, why would one animal get one product? Is it really up to the owner for the most part?

DR. CAMPBELL: Well, you know, it is up to the owner, but it is also up to the doctor. We believe that

it is the doctor's ethical responsibility to make a recommendation. Our doctors really believe that the best efficacy of all of the heartworm medications is ProHeart because we know that they got it, and so, you know, I don't want to, you know, embarrass anybody the room by asking who has oral heartworm medications in their drawer, but I will admit that I do, are overdue for my own dogs. So the reality is our doctors primarily when it was available prescribed ProHeart, not the orals, because it is a lot better product, and it is really, really safe. You know, so does that answer your question? Not really. Okay. So what was the rest of the question?

DR. GLICKMAN: But as far as I know from what I know that Banfield practices and what I saw in the database, there are no deliberate inspection criteria that a sick animal would get one product versus a well animal would get another. The preferential treatment is for ProHeart.

DR. CAMPBELL: Oh, absolutely not. If there was a sick patient we wouldn't prescribe either one, you know, and what we look at are what we believe are the barriers to care. You know, the things that stop people from coming in and getting care. So, you know, over 60 percent of our patients don't have to pay for office calls to come in because we want them to come in if they are ill.

So, you know, the doctor at that time will see on the computer what has been prescribed for that patient, and if they are on an oral medication they are going to say don't. You know, don't give that until Buffy gets well. So, you know, I don't think we are prescribing either of them, you know, if they are ill. Now the thing is if you give ProHeart and the pet gets ill four month later, you know, they have already in essence had it, you know, and so I suppose there is more of a chance that an ill dog is going to get -- has already got ProHeart than it is they would get an oral medication I think. Isn't that right, Larry?

DR. GLICKMAN: I think so. So I think the bias would be the other way.

Deliberation on Question One

DR. CRAIGMILL: If there are no further questions from the committee, we will go to deliberations and do a tally in response to these questions that were presented to the Advisory Committee by FDA. What I will do is I will basically do a tally and go around and ask individuals. We will do one question at a time. We will start with the first question, which is "Based on the presentations and information provided is ProHeart 6 safe for use in dogs?" We have been asked to provide a yes or a no answer. Personally as a toxicologist I don't like the

word "safe". I say this every meeting. I want to say acceptable risk, so that is the way I am going to answer it. You can go ahead and -- go ahead with a yes or no, but then please fill in afterwards qualifications, you know, whatever. So what I will do is I will go to the members and then go down the list, and Dr. Aref, Susanne.

DR. AREF: I have a hard time saying yes or no because I don't think we have seen enough good numbers. I think CVM or FDA has provided the sort of most -- have included a lot of numbers that might be sort of on the edge. I think that FDAH has excluded some numbers that they shouldn't have. I had a hard time especially with the last table we looked at where it looks like you have exactly the same adverse event for the two top products in the table. So I would say at this point I would say no, but maybe with further testing. I just don't think I can give an answer based on the knowledge we have.

DR. CRAIGMILL: Thank you. Corrie, Dr. Brown.

DR. C. BROWN: Very difficult to answer that question. I thought the Banfield data was excellent, and based on that it appears that ProHeart 6 is safe for dogs. The CVM reporting would indicate otherwise, but I had some problems with that data in that much of it seems

inadequately documented with respect to cause of death, and the manner of reporting seemed to me somewhat haphazard and a little subjective. So I would like to see that data put into a more rigorous format before deciding.

DR. CRAIGMILL: I'm supposed to press you for an answer.

DR. C. BROWN: I would be inclined to fall on the side of, yes, it's safe.

DR. CRAIGMILL: Thank you. Gregory Jaffe.

MR. JAFFE: I also have the difficulty in using the word safe because I think safety is not absolutely and I think in the end. But I guess I would answer the question if this sort of -- if the question is asking should this drug be back on the market tomorrow or not I would have to say no. I think at this point we still need some additional data to insure that it is safe for drug use. I think the data that FDA presented does put that into question, and so it seems to me should err on the side of getting more data before the drug goes back into use. I had difficulty understanding the different data sets because I think they didn't try to be comparative but tried to actually confuse. It would have been nice if FDA had been able to put some rates down there for rates. It would have been nice to better understand --- reports. Both groups

were using different numbers of describing them differently so that made it difficult. But it seemed to me there were enough adverse incident reports that FDA identified to question the use of this, and I think the voluntary recall should continue for the time being.

DR. CRAIGMILL: Thank you. Dr. Mealey.

DR. MEALEY: I don't envy the FDA for making this kind of a difficult decision, and like I said before I think it is difficult to determine if was the drug moxidectin that was actually the cause of some of these things or if it was the carrier or vehicle. I think the data for the liver, for some of the immune-mediated diseases, for the neurologic diseases, it is very difficult to say one way or the other because they were conflicting. They had data from the Fort Dodge that is very different from the data from the FDA. But the anaphylaxis in both the FDA and the materials provided by Banfield shows that anaphylaxis is greater with ProHeart than it is with any of the other heartworm preventives, and because, one, there are other --- there are alternative agents out there. Yes, ProHeart is comparable to vaccines, but I don't -- I think that is comparing apples and oranges. So I would compare ProHeart with the other heartworm preventives out there and at this point say that compared to those -- well, obviously

none of them are 100 percent safe, but I would like to maybe see a little bit more information there. And the fact that ProHeart is going to be administered more often than vaccines makes me err on the side of saying no, that it is not safe.

DR. CRAIGMILL: Thank you. Let's see. Dr. John McGlone.

DR. McGLONE: Well, thank you, everybody, for your presentations. I know it took a lot of time to prepare. I was trying to figure out what the facts are in this situation, and that is a difficult set to identify, and I came up with three facts.

One is that mostly from the written material that the product, as with probably almost every product, is toxic at very high levels. Not at the levels that are sold commercially of course. So that's one fact.

Secondly, there seems to be multiple factors that interact with adverse drug reactions with ProHeart 6. Most notably the age of the animal and whether it has been vaccinated or not, and these interactions might help explain some of the variability that is observed maybe.

The third fact, which is the fuzziest fact of all -- they get fuzzier as you go down the list. The third fact is that finding in the field are highly variable, and

that is not much of a fact is it, because it doesn't say one way or the other what happened. But there are some -- well, my characterization is that most of the reports from the field are largely positive on its effects, but there are some significant negative findings that cannot be ignored. It suggests a need for research to understand what those interacting variables are and how they can be managed through label change or training.

And the fourth fact -- I said there was only three -- is that the levels of adverse reactions are low. They are low in the general population and they are low in the subject animals here. So the risk it seems to me doing -- for some other purposes we use a qualitative risk assessment, and that is what I am still thinking about from our last meeting. It seems that the risk moves from very, very small to very small when you use this product, particularly when you use it in combination with certain other products and under certain circumstances. So moving a risk from a very low number to a low number doesn't clarify whether it is safe or not, because some people would not accept -- would accept zero risks for their pets for example, and they wouldn't like to move the risk from very, very small to very small. Other people might be willing to take that risk in favor of some benefits.

I don't think that there is enough information to do a proper risk benefit analysis for this product at this moment. I think there is too much variation in reports from the field. That has to be understood so that you can manage the risk a little better. So it depends on where you draw the line on safe, whether you draw it at, you know, whether the risk is moderate, or small, or very small, or very, very small. That is why the committee is having a problem. So I would say in the interest of the people who are highly motivated to not have their animals suffer that moving from very, very small to very small is still a risk, in which case I would have to say it is not safe at that level. Under other circumstances it might be an acceptable risk, but not in the current situation. Thank you.

DR. CRAIGMILL: Are you a lawyer, John?

(Laughter.)

DR. CRAIGMILL: Should I mark that as sort of a no at this point? I did. Thank you. Dr. Nelson. Oh, excuse me. I haven't finished with the committee. I haven't even figured -- Dr. Nolan, Lisa.

DR. NOLAN: I thought it was a very valuable session. I appreciated everybody's input. I was very touched by the folks who had lost their pets or family

members as they referred to them. They reminded us how high the stakes are I think in this drug. For me, I found the evaluation of the Banfield data to be quit compelling in support of the use of ProHeart, but like Dr. McGlone and others before him, I am impressed. I feel like it is relatively safe, but I would qualify that.

DR. CRAIGMILL: Thank you. Dr. Papich. That was a yes, yes? I got a yes out of that, a qualified yes. All of these answers are qualified. We are not going to have any straight ones.

DR. PAPICH: Well, we know that all drugs can produce some adverse effects, but when I look at adverse effects produced by drugs I differentiate between drugs that are used to treat a disease and drugs that are used as a prevention in healthy animals. Drugs that are used to treat a disease I think we do accept certain risks and we have a higher threshold for those risks because we realize the stakes that are present. But when a drug is used to prevent a disease and it is given to an otherwise healthy animal, I think the bar is raised a bit and I think we do have to have a higher standard. I also consider the nature of those adverse effects. If it was something minor like loss of hair at an injection site or something that is -- that an animal can recover from, that perhaps is acceptable. When

it is the death of an animal it is not, and I was compelled as was Dr. Nolan here by the visitors that we had today and some of their testimony.

I think that not only do we need a higher standard in considering and evaluating some of these products, but as a veterinarian I am a little bit ashamed of the veterinary profession in the way they have reacted as was cited today here. I think veterinarians could have handled this a lot better. But considering all of the data available, I am inclined to say no to this question at this time, but I leave the door open that we still have a lot to learn. The Banfield data, although very good, I am concerned whether or not we are relying too heavily on the Banfield data in comparison with other potential sources of data. We don't know at this point, at least I'm not sure, whether these reactions that are possibly caused by the drug, caused by the vehicle, caused by some other characteristic of the formulations. So there is a lot I think that we have left to learn about this, and it is not a dead issue perhaps. But maybe as we gather more data and learn more about this we will be able to understand the nature of this, of these reactions.

DR. CRAIGMILL: Okay. We move now to consultants. Dr. Bennett.

DR. BENNETT: Okay. I think it is really a tough call as well, and my question is for the second question. If we answer the first question and say is it safe, does that mean we're not going to address the second question?

DR. CRAIGMILL: No. In my opinion we are going to address it no matter what.

DR. BENNETT: Okay. Because I am sort of qualifying as everybody else, and I'm a qualified yes. I think clearly the cases, the reports are dramatic and worrisome, and my biggest issue again, because I live off of MedWatch databases and I look at these adverse events spontaneous reporting system, and I put those at the level of -- I go level one through five. I put those at level five in evidence because of the quality of the adverse event reports that come into the stars of MedWatch database, and I know you have a difficulty with that, too. The Banfield database had a little bit -- had some value to me because of the numerator/denominator issue, which is what I worry about mostly, and I wish we had four more Banfield-like databases so I could feel more comfortable that that was replicable around the country. I am concerned that there is no other Banfield-like database out there. Maybe there is or isn't. I'm not sure about that. If there were I would love to see

it, and otherwise I would say if I could see three more like that I would feel much more comfortable with my qualified yes. But yes is the way I put it.

DR. CRAIGMILL: Thank you. Dr. Luster.

DR. LUSTER: I thought the cases today by all the presenters including the Fort Dodge people and the public and the FDA were very strong. I just wish the data sets that they had or the way they could collect the data was a little bit stronger and could make our answer a little bit easier to come to grips with. But I think that from what I could tell is that some of the endpoints that they are looking at, some of the clinical manifestations, appear to look like there was an increase with ProHeart 6. So I have to vote no at this point, although -- and this was especially related to the anaphylaxis and --- type responses, although the incidents were really small, but they seemed to be prevalent there. Particularly in the sense that there are other drug alternatives other than ProHeart 6. Saying that, and probably what everybody else is thinking as well, but there is really a need here to conduct some sort of risk benefit analysis, particularly considering that there is an apparent high level of noncompliance with the tablets. But that data wasn't presented. It was just a general percent. I have no idea

what the noncompliance would be with ProHeart 6. I mean, I know if you go in and tell your vet will give it to you, but not everybody is going to go in and get a shot all the time. So anyways, I am saying at this point it is a no.

DR. CRAIGMILL: Okay. Dr. Groseclose.

DR. GROSECLOSE: Well, I appreciated both the testimony and the presentations by the various presenters and would agree that the quality of the data is really lacking to make any sort of decision. My vote is a qualified no mainly because I think there are data available. I think the clinical trial data that was presented suggests that there is really an adequate sample size to really answer most of the questions that are presented, and the Banfield piece is really a -- it appears to be sort of a retrospective look at a large population but is suggestive of low risk, but is not -- it doesn't have the quality of evidence that a clinical trial would have. I think the post-marketing surveillance by both groups, both the FDA and Fort Dodge, really are inadequate to address the question as well. I mean, they are basically numerated data and it is hard to say what the source of some reports were. We just didn't have that information. So a qualified no at this point.

DR. CRAIGMILL: Dr. Nelson.

DR. NELSON: I, too, want to make a comment that with the pet owners that were here we all sympathize with them. We went into this business because our pets are important to us, too, and when it is your pet it doesn't matter what the statistics are. If it is your pet, it is 100 percent.

Also the American Heartworm Society has not taken a position on this, but being a member of the society I am privy to lots of information from around the country, have veterinarians call us about the -- or email us about this particular product. And over a year ago when questions were coming up, or two years ago, you know, I spent a fair amount of time answering questions and also reviewing databases like on VIN and see what the comments are, calling colleagues, calling professors, universities, and trying to in my own mind find what kind of incidence is out there. And the more we looked, the more I looked, especially when the veterinary professionals are saying it was nine to one no problems, and there was --- a problem.

There was mention about this being a preventative drug, and we need to hold it to a higher standard, and I will agree to that point partially. When you look at the number of heartworm cases that we see every year, when you look at the statistics on compliance and

those people who purchase monthly preventatives and the 60 to 75 percent of the doses being given and the rest sitting in the draw. The number of cases that are going around out there, you also have to look at the number of animals that are getting heartworms and suffering and dying because of lack of proper preventative administration.

One of the things this product did was to address that issue. It also helped us address it other ways. My own particular practice, you know, when we started giving the injection we started sending reminders of the injection. We also started sending reminders for all the preventatives. But still we would find just the compliance rate was not there with the monthly pill.

Then also, you know, talking about making the decision based on the information provided today and provided in the reports, and when I review the clinical cases that are supposedly representative of the situation, I just see too many other possibilities for causes. While there is no 100 percent safe drug and no 100 percent effective drug, I would have to say a qualified yes.

DR. CRAIGMILL: Dr. Peterson.

DR. PETERSON: I have the advantage of having heard most of the other folks give their opinions so I can better formulate mine I guess. I think it is important to

keep in mind that the system that CVM has in place is a passive surveillance system, and I think it did its job from the standpoint that a passive surveillance system really does no more than raise the index of suspicion, which I think it did in this case. I think the data that speaks most appropriately to whether or not we have a safe situation, and I would also comment I don't like the word safe, but I have a little bit different perspective on that. I think the wrong question is being asked. I think people are making decisions based on at some level, an unknown level of what is safe and what isn't safe. I think a more appropriate question quite frankly is "Relative to the other products out here how does this product compare?" I think that is a little bit different question, but I think it is the more appropriate question. I know it is not being asked, so I will answer the one being asked. But I just want to make that for the record, that comment.

There were comments made relative to the increase in anaphylaxis as being a contributor to some people's decision. I think there is given the real world data and given how this preventive is administered, I think strongly biases any difference you would see and any increase in terms of anaphylactic reaction. As practicing veterinarians I think we all know the potential to see a

more immediate anaphylactic reaction I think was well described, and you tend to see that when you administer a product that is administered by injection as opposed to something that is given orally and you don't even know in fact when it is given, whether or not there was an association with their oral medication. It is more easy to determine a point in time association with an injectable. I think that tends to bias people's perspective on what is cause and relation here.

My feeling is that the Banfield data is really real world data, and I know as an epidemiologist I really don't know any other way to find out whether anything is at increased risk for causing problems, particularly relative to other medications that are designed to do the same thing other than a real world situation. I will grant you the data is not perfect, but I would also point out that that data, at least in the field of veterinary medicine, is very rare to have available to us. I think everyone here is familiar around the table with the veterinary literature, both in research and the clinical literature in terms of, you know, case reports of literally 60 to 100 cases, and that is generally pretty good. What we are dealing with here is hundreds of thousands of real world cases. My feeling is that that data very strongly demonstrated that

there is a lack of safety, however you want to define it, across all three drugs that were tested. I think it also demonstrated that there really wasn't much difference among those three drugs, particularly when you take into affect what may be contributing to the use of an injectable versus -- in terms of the reporting system, particular with reference to anaphylaxis relative to the oral medication.

So I really don't have any problems in making the decision that the answer to this question is yes, because I think the bigger question that needs to be answered is what is the relative safety of all of these types of medications. And I would tell you I have had some experience on the human side sitting on the Advisory Committee for Immunization Practices. I have seen the pictures of the babies who have died because they were attributed to deaths attributed to immunization for human vaccines, and while these are possible, I think what you have to do is you have to do some type of a risk benefit. Make a decision. I would propose to you also that I don't think that we are every going to have in the next one, two, even three years, definitive answers that will satisfy everyone to the question of whether or not something was safe. So my answer, and I don't really have any reservations based on the data I have seen, my answer to the

question is yes.

DR. CRAIGMILL: Thank you. Dr. Riddell, Gatz.

DR. RIDDELL: Well, I would like to thank all the parties involved for the material they presented to us, the presentations they made today, and for the people who came and gave the personal stories. My congratulations for having the strength to do that. When I try to evaluate decisions that I have been involved with that deal with topics like this, in the end it comes back to doing everything you can in a science-based mode. And granted science is not perfect and that is always going to be a difficult thing with something that is very subjective like this. I understand some of the comments about holding preventatives to a higher power, but yet we still have to remember that every pharmaceutical agent that we put in an animal has potential to have very powerful effects, whether it is very new and cutting edge or whether it is old. So those are concerns I think we -- there is not going to be -- obviously there is not a perfect adverse event reporting system. Otherwise we wouldn't be sitting here talking about this. But I think there's several strides to be made in that direction.

Looking at the same thing for the risk

benefit analysis, but the risk to a patient whose owners do not do better than the average for compliance in heartworm-infested areas is pretty severe. So when I look at that, look at all the possibilities, and look at what seems to be -- not being an epidemiologist, but judged by other people's evaluations to be the best data and the best science that is out there, that being the Banfield data set, I would have to say a qualified yes.

DR. CRAIGMILL: Thank you. Dr. Trepanier, Lauren.

DR. TREPANIER: Well, I also think the Banfield data is important. I think one piece that is missing from that data is a 30-day phone call to these clients to confirm that there were no adverse events in that time period, and we don't have that. We have a three-day phone call and then really relying on the owners to come back to them if there is a problem. And I do believe there is a lot of power in that data set. It does appear that these reactions are rare. It does seem from what the FDA presented that there does seem to be a higher signal in the patients that got ProHeart, and it may be because of the way it is administered and the way it is monitored. But these reactions when they occur can be catastrophic, and I also agree that there is a higher bar for a drug that is used in

a healthy, young animal where there's no other problems and then death is a potential side effect.

So I would have to say no since the burden of proof is on the company to prove that it is safe to a reasonable level, and I think when you look at relative risk you really need to put this drug in the context of how much extra protection is it going to give versus oral medications, which do appear to be safer at least based on the FDA data, and I think that is something that needs to be looked at. If this drug really truly does save more lives from heartworm then there may be a risk that can be accepted. So I do think that a more rigorous risk benefit analysis is really important.

DR. CRAIGMILL: Thank you very much. Am I supposed to vote, Steve? Not vote; give my assessment to this answer.

DR. SUNDLOF: (Nodding head.)

DR. CRAIGMILL: First of all, Last night about 8:30 Aleta came with a -- yes, Dr. Sams is not voting at this time. Last night about 8:30 Aleta handed out a package, double-sided copy of public comments. For the person who wrote in here that he thought that his comments would not be read, they were but at least one member. I went through all of these, and I am sure many of the others

did, and there are some very touching personal accounts of having lost pets. Having lost pets of my own I can relate to them very dramatically.

The drug in question here has basically been tested thoroughly according to all the FDA requirements, and the FDA accepted it on the basis of all those requirements on the studies that are normally done by any new animal drug to satisfy safety, effectiveness -- that's the most important things. That said, the number of case reports, there is no question that there have been a large number of adverse reaction reports on this particular product that have come in. Why do we have such a discrepancy between the FDA opinion of this and what is going on with the company's opinion of this? I don't know how to resolve that issue. I find it difficult to juggle those, and I am not sure whether even if we locked them in a room for a couple of days they would come to the same conclusion with the same data -- although it is an interesting idea.

(Laughter.)

DR. CRAIGMILL: When I review these data and again as a toxicologist I look at things in terms of acceptable risks, safety being an acceptable risk. For some people it is unacceptable. A risk is basically a probability of an adverse reaction occurring or an adverse

event. For the people whose dogs were affected that risk was one, and they have suffered the consequences and it has been awful. For thousands of other people who have used the compound, have had it, that risk was zero. It is acceptably safe to use this drug? I would give a qualified yes to that in my opinion, but I also will have some further comments when I get down to the section on safety concerns. Basically everybody here has said we need more data. How are we going to get more data if we don't have the drug being used? We are not. If this a drug where we can state there are acceptable risks and possibilities for gathering more information to further define those risks more effectively, that is why I am going to give it a qualified yes at this point. I love being last.

Deliberation on Question Two

At this point I would now like to -- again we will go through the ranks here and ask the following. "If there are remaining safety concerns with ProHeart 6, what additional avenues of research could be explored to mitigate and/or prevent the adverse events?" In other words, what do we need to do? And at this time Dr. Aref has been able to listen to us and formulate her answer. So one more round.

DR. AREF: I am not sure that -- I mean, I get worried about the multiple logistic model sometimes when

-- I don't know that all of the aggressors would be completely not correlated. I mean was the modeling investigated for that? So, I'm sorry, this should have been a question before. I mean, possibly somehow all these different data gatherings ought to be somehow put together to make for -- well, I don't know. The data is so confusing and not adding up somehow. Further research with further clinical trials maybe. I don't know. But that seems to be the only option if the drug is going to be accepted at some point, or since we are only doing qualified yeses and nos.

DR. CRAIGMILL: Thank you. Dr. Brown.

DR. C. BROWN: Well, I would like to suggest some things that can be done with the existing data, and that would be to take a closer look at the cases that have occurred and to really dissect out the other confounding factors. In particular administration of other vaccines at the time. What brand of vaccines were they, what was the -- how many times had the ProHeart 6 prior to that. So that would be from an epidemiologic sense.

But then I would also like to see a better follow-up with the animals that die and a correlation of the necropsy and histopathologic findings with the clinical disease and also the time frame post-administration. Does it all fit together with a toxicologic pattern, or are some

of these deaths due to something else and they are being report as adverse drug events, but really they are spurious incidents?

Then the third thing would involve some proactive work on the part of Fort Dodge Animal Health, and that would be the moxidectin administration, the ProHeart 6 administration at the same time as creating a febrile illness in a dog to see what those levels are. You mentioned that with a clumping at 40 degrees there would likely be a decrease in blood levels, but do we really know that? Thank you.

DR. CRAIGMILL: Thank you. Gregory Jaffe.

MR. JAFFE: Being I guess the one non-veterinarian medicine doctor here on the panel, it is hard for me to talk about the avenues of research that might be explored. But I think I would say that one of the things that might be done here is the Banfield data has been reviewed by Dr. Glickman, but it hasn't been reviewed by FDA I don't think and they haven't had a consultant analyze it. Since there is a lot of data there, it might have somebody else do it, a different analysis of that data. Especially taking in some of the comments that other panel members have said today, might be able to come up with confirming that information or providing additional data about the drug. So

I think that would be a useful thing to do. I think if you were to continuing using it there might be additional conditions that might be put on it if the agency decided to do that. Maybe it shouldn't be given with a vaccine at the time to get rid of some of these possibilities of something else happening. Maybe there should be a follow-up for the veterinarians to fill out with the patients afterwards to bring in data to the agency in a certain percentage of the number of vaccine -- the number of shots that are given so that we have some affirmative follow-up. So I think there are ways that if one is to continue giving the drug that they could get additional data at the same time and also get rid of some of the variables that seem to skew what we have in terms of the data now. But I think also having some of the parties look at each other's data some more might help get some additional information.

DR. CRAIGMILL: Thank you. Dr. Mealey.

DR. MEALEY: Not being an immunologist I am not sure that I can help anymore here except for maybe some more experimental investigation into the potential causes for anaphylaxis. Not specifically with moxidectin, but maybe with the vehicle. I would love to see another independent data, group of data. I have some concerns that there may be a bit of a conflict of interest with the

Banfield data. Maybe collective information from veterinary institutions, from the colleges of veterinary medicine collectively might give similar quantity of data as the Banfield data. And I would like to see more data on the efficacy and compliance of ProHeart versus some of the monthly. That has been one of the criticisms, that there is not good compliance with the monthly heartworm preventives, and I guess I would like to see data that it is easier for people to come in to a veterinary hospital twice and get an injection than administer doses of heartworm medication at home.

DR. CRAIGMILL: Thank you. Dr. McGlone.

DR. McGLONE: Well, as I might have said, I don't think there is really enough data to do a risk benefit analysis. But it seems to me that Fort Dodge Animal Health is highly motivated to collect such information, and the nature of that is really you need three kinds of studies. You need some basic studies on mechanisms. You need a large-scale clinical field trial, because I don't believe the 280 dog study was large enough to show even a small incidence of some of the problems that have been seen in the field. Maybe you won't see any even if you have 2,000 dogs, but a larger study would have a greater chance in such a thing. Then I think you need a prospective epidemiology

study. You need to start from scratch and agree on what you are going to collect and collect relevant information for a long enough period that you have confidence in the data. Perhaps from more than one Banfield-type organization.

I do think that there is an inherent problem in veterinary medicine. I can say that because I am not a veterinarian I guess. In that a lot of veterinarians including my veterinarian that takes care of my dogs sell the drugs. And when I go to the physician, he doesn't sell the drugs. In fact, he gives them to me for free, and then I go to the drugstore and buy what I need. So the physician doesn't have the kind of conflict of interest that veterinarians have. So that is kind of problem, because the members of this committee are asked to declare and live up to these positions, but the people in the field don't have to hold to the same standard. So basically we have a general problem with getting quality information in just a retrospective sort of way. So if you start from the beginning and set it up where that is not an issue, then you will get a larger quantity of data that is of higher quality.

Then when you have that, I think a change of label if appropriate -- it might not be appropriate -- and training of people in how the product is used and delivered

would be appropriate. I think that when you have the label change and the training organized, then you can do the risk benefit analysis and you will probably see that it's a wonderful product from the point of view of the company. Thanks.

DR. CRAIGMILL: Thank you. Dr. Nolan.

DR. NOLAN: Well, it seems to me this drug addresses a real concern in heartworm prevention and with other -- prevention of other disease, and that is compliance. If it is used it can really lead it looks to me to a decrease in a terrible disease. It would seem to me that risk benefits analysis would be dead on and very helpful in evaluating this drug. Unfortunately I am not a statistician, so I can't say what that involves. I would also wonder if it is possible to do some kind of follow-up study, a 30-day callback in the future to see if we can do some long-term stuff on it.

DR. CRAIGMILL: Thank you very much. Dr. Papich.

DR. PAPICH: We have raised a lot more questions than we have answered, and I think there is lots of room for some other investigations. I agree with the comment that somebody brought up earlier that if this drug is not available anymore there is not an ability to collect

more data. However, there is data for which we have records. If it is possible, it would be very helpful to try to mine data that -- other than the Banfield data that would perhaps be of some consistency that we could use to compare, and I think that would be helpful. Whether that is available or not, I'm not sure.

In the presentation one of the things that I found one of the most interesting was the relationship between the onset of some of the adverse effects that have been reported and what seemed to coincide with what would be a peak drug concentration after administration. That is one of the reasons I had asked some of the earlier questions about the kinetics and the release of the drug. That seems to me to be a relationship that we shouldn't ignore and could be explored further, perhaps looking at a larger group of dogs and looking at variability and release of the drug after an injection and looking at other conditions that may affect the release in a group of dogs. Pharmacokinetically it might be helpful.

Of the reactions that have been seen, I think there are some of them that appeared in the record such as malignancies that are I think perhaps red herrings. I don't think that this drug probably leads to malignancies, and it is possible that some of the elevations in liver enzymes

didn't have much to do with the drug. But the reactions that appeared immunologic in nature, those are -- and those were the largest group it appeared. Those are ones that I would hope that someone with better immunologic background than I do could think of some ways to explore that.

Also in dogs that have had reactions, if it would be possible it would be fascinating to explore potential genetic relationships among the dogs that have had similar reactions. We have experts on our panel who are better experts in pharmaco-genomics than I certainly am, but I think they would agree that pharmaco-genomics is in its infancy in veterinary medicine. But we do recognize that there are genetic relationships among the dogs that have certain types of reactions, and if that could be explored among the dogs that have had reactions to this drug, that would certainly be worthwhile.

DR. CRAIGMILL: Thank you, Mark. Dr. Bennett.

DR. BENNETT: I'm thinking back on the experience I had with the immunologic side effect with --- products which we just reported, and it was very rare, but it was immunologic and it lead to some responses from the FDA that I think were very insightful. The kinds of things that the FDA did then was -- one is they elevated the

warning to a black box warning, which I know you don't have here, but a black box warning does raise a level of awareness and reporting also in the public sector to build a higher level. Second thing they mandated in the other countries besides the US where the --- was a formal prospective pharmaco-vigilant study, a large-scale one, and it was formal and it was prospective. I thought that was also a useful thing. The third thing that they mandated as well and is important is I think the vehicle is an important issue, and I think that became an issue with the other product. It raises concern about the vehicle, and I think the vehicle is something that we got some insights from you that there is some question about the vehicle. And it leads me to think for instance if the study we heard from, those people are more rigorous with the vehicle, with the product, than the other people in the community, that may be a differential reporting rate. That maybe --- reporting for the study that you commissioned, and high lights because they did say you have a formal educational effort out there. You have got a web-based educational effort out there, and the same thing with the other product is what happened. The FDA and the other countries, the other countries, the regulatory authorities, did mandate formalized and a more rigorous approach. I thought that one speaker from the

outside requested that they think about a single use file had an interesting point. It would be interesting to know if a single use file would actually get us to the point of being a little bit --- with the vehicle.

DR. CRAIGMILL: Thank you. Dr. Luster.

DR. LUSTER: I am actually an immunologist by training, and since I'm an immunologist I tend to think that most --- drug reactions are really systemic allergy in disguise. Which is very hard to, as the drug companies can tell you -- pharmaceutical companies can tell you that is hard to identify and test for, and also is a major problem for many, many pharmaceuticals. But one of the tests that are currently being used which I think is worth exploring is the simple test which I think most FDA centers use as a guideline. The test now is a --- assay of the various materials. I would think that the drug itself is technically not to be extremely allergenic, but you would think that the materials, the microspheres, have been shown some of them to act as almost like an antigen depot. So that they are really serving as a continuing expulsion of the antigen, almost like an adjuvant. So that is --- to cause more of an immune-type response if that is what is occurring. But there are ways to test for that, and one is the --- assay. One can do immuno-pathology to look for

immune deposits on tissues and things like that. So it can be done, and if that if that is the case, I mean, there is also some of the pharmaceutical companies have developed --- to remove that antigenicity, and they can do masking for example. A lot of the materials used for imaging for example in humans can tend really to be antigenic, and they put what they call masks on it so the immune system no longer recognizes it as antigenic and they can be used. So there's some potential opportunities there. That's all.

DR. CRAIGMILL: Thank you. Dr. Groseclose.

DR. GROSECLOSE: Thanks. I think there are some things that you can do with no new data. One, I would follow up on the recommendations to do a risk benefit analysis and try to model that based on what we know. I mean, I do think the issue of compliance is a real one and it would give us some better idea of the value in terms of the risks. Also I would second the recommendation for a case control study using Banfield data. I do think that would be a good use of that data set and to review -- have FDA sort of review the study design to insure that it can answer a few more questions. I also think there is a need to try to resolve the disparate data that we have. Essentially there were three case definitions for these adverse events. There is the Banfield definition, the FDA,

and then the Fort Dodge, and those data are now out and available and are generating a lot of heat. I would think it is probably worth some effort to try to resolve those.

In other words, perhaps get reviewers and more than one reviewer per case to try to use at least a common case definition and try to see what we can come up with there. Ideally you could combine data from various clinical studies that have been done and some sort of a meta analysis, but I don't think that is possible just based on what I have heard about the types of studies. I don't think that those data can likely be combined. But it might be something to think about in the future, that one design study so that you could combine those data. I think, that may take us certainly closer to perhaps me closer to a qualified yes. But the prospective issue, you know, this is apparently the only microsphere technology out there, and I think that should be evaluated through prospective studies if at all possible with the same size that is adequate to try to address that issue.

DR. CRAIGMILL: Thank you. Dr. Nelson.

DR. NELSON: Allow me to comment about the veterinarian selling the product. It doesn't have anything to do with the research, and we discussed all the other areas. We can take the data we have. But whether the

veterinarian is selling ProHeart or selling Heartguard or Interceptor, it is really not a -- you are selling one or the other. So the economic benefit is there. There has been speculation about veterinarians -- and I had to say this -- that have been going more for ProHeart because trying to eliminate the internet pharmacies. You know, I can't speak for every practice, but our particular practice in general, you know, we have always been willing to match prices. In fact, when it came up as an issue, we reviewed these major internet pharmacies, and actually it was a pretty good eye-opener for me. It allowed me to raise my prices, because I was cheaper than most of them.

(Laughter.)

DR. NELSON: And I could do it in good conscious and still be cheaper. But as the data I would like to see, we know that these class of compounds do have very potent activity against both microfilaria and immature heartworms. I would like to have a little bit better idea of actually what effect the drug has on the L4, the L5, how quick it dies. Could this be correlating to the reaction? We know when these microfilaria are acting -- microfilaria, excuse me. When these larvae, L3s, L4s, L5s, die they can produce immunological responses as we are seeing with most of these cases. So that was some data I would really,

really like to see.

DR. CRAIGMILL: Thank you very much. Dr. Peterson.

DR. PETERSON: I have to be forgiven for thinking like an epidemiologist again I guess, but typically what happens with epidemiological population-based studies is you go from something like a passive surveillance systems which identifies the potential for an excess of disease or an excess of risk or whatever, to something like a cross-sectional study which was done with the Banfield data. Based on that, typically the next step is really not necessarily a case control study, but something that is done prospectively. The problem with prospective studies, particularly in this case, is it doesn't appear there is going to be any more data in the future to collect. Secondarily the other problem with prospective studies, and it is probably even worse in veterinary medicine than it is in human medicine where this is the typical way things are done, is there aren't going to be enough -- there isn't going to be enough money to do an appropriate prospective study. There will not be enough cases collected, and Dr. Glickman pointed out that for some of these rare occurrences you would literally have to have well over half-a-million cases to identify anything that is excess risk if you are

making comparisons between groups. So at least from an epidemiological perspective I don't think there really is going to be any more data that is going to add to the ability to make a decision relative to safety.

I think one other thing, and since some of my other colleagues have kind of touched on this also, I think we need to keep in mind I think -- and this is true of human medicine as well as veterinary medicine. I think as practitioners of veterinary or human medicine I think many times we don't do a very good job for a variety of reasons of communicating risk. I think we tend to some degree to either have clients who let us make the decision, or we try to influence them for a variety of reasons, some which were given round the table. I think we are going to be faced with these same kinds of problems in the future relative to whether it is this particular drug or whether it is other drugs. Whether it is drugs you use to treat, whether it is prophylactic medications, I think it is the same issue. I think we have to be very, very careful about putting things in perspective. Otherwise we are going to be faced with these same kind of issues in the future. The same is true with human vaccines, the same is the true with veterinary vaccines, it is true with all types of prophylactic medications. There is nothing that is 100 percent, and I

think what happens a lot time is I think people have expectations that because a veterinarian or a physician is prescribing or recommending something there is a certain degree of safety that goes along with that. I think that is true, but I think it needs to be communicated so that actually the client is making the decision for their pet in terms of whether or not they feel the risk is worth is. I don't think you can make guarantees, so I think yes. Since I gave a yes to the first question, I am having a hard time coming up with any recommendations. At least from the perspective of an epidemiologist that is gong to add additional information in terms of answering the question.

DR. CRAIGMILL: Thank you. Dr. Riddell.

DR. RIDDELL: I guess at the risk of sounding like an ogre, when you deal with a set of reactions that might by the World Health Organization be classified as rare or very rare, to get any kind of statistical power you are going to have to have large populations exposed to that, and so that suggests that I might be advocating using a population --- experiment. That is not the case. However, we have a product that may be potentially valuable and the compliance they shoot for, a very real disease in the canine population. We also need to know if it is safe, and several other good questions about its efficacy and the impact of

the microspheres on the immune system. They are all really important, but I think at some point in time to get the numbers that we are going to need to be able to truly evaluate this, it is going to have to go back into general maybe educated use, and it might be that we might have to be required sponsor-initiated educational program for those users that would not be unlike what a current sponsor has to do for the human potential ill effects from ---. While that is a bias that is taking a group that biased towards using it, making them responsible, and I think they are responsible for making sure that appropriate data for cases of adverse events reported and followed up on I think is probably only one of the true ways we have going to have to evaluate this. I don't think that the data sets like Banfield other than Banfield are going to be out there.

DR. CRAIGMILL: Thank you. Dr. Trepanier.

DR. TREPANIER: I also believe that a prospective study is ideal, although because I think the pet owning population is very sensitized to this drug, you may not be able to find a lot of people willing to allow their dogs to receive it. Also it would be very expensive. So I was trying to think of ways to work with the data that is available to try to get more information about perhaps mechanisms and is there a safe way to label this drug and

make it -- a safer way to label this drug. Certainly I think doing a meta analysis is one thing to consider. There are certainly other large computerized veterinary networks like VCA. The Animal Medical Center is also a very large practice. There might be ways to mine that data in a manner that is similar to Banfield that you have other data sets that could confirm or conflict with what was reported from Banfield. Also if you are trying to get at mechanisms, certainly the anaphylactic reactions may be very different from the convulsions. They probably are. But if there are serum --- from these patients that have had convulsions, do they have very high moxidectin concentrations? Or if there are CSF or brains from these patients. So are some of these patients having abnormally high release from this drug. I know that C-max concentrations were very narrow in initial studies, but that was with a very small group of dogs. We are talking about outliers here. We are expecting to have outlier responses.

Then the other issue of microfilaria being present and possibly triggering anaphylaxis, is there a way to go back and look at heartworm endemic versus heartworm non-endemic areas and see if instances of anaphylaxis is different in those two groups. Because that may be away, a less expensive way to try to get at that information.

DR. CRAIGMILL: Thank you. For my own comments, basically everything has been covered pretty much by all the other panel members. I think that if possible a retrospective case control while it might not add a whole lot to the data might be reassuring. That a prospective study with a very large clinical trial would be probably the only way to put this issue to bed, and that such a study would need to be -- the protocol would need to be agreed upon in advance by FDA and also Fort Dodge. In other words, work together to figure out what you need to answer this question if you are going to do that. In that, that would require the use of the drug in a large number of animals, and to do that I think a very good public education and informed consent program for the owners would be necessary. Because even at low rates, one out of 10,000, if that one is yours it is still a rate of one, and people need to know that is a risk. If you are completely risk adverse you need to warn people away from using this compound, or probably just about anything in that regard.

The other last -- first of all I should say that I am academician, which means I don't have to have practical ideas.

(Laughter.)

DR. CRAIGMILL: It would seem to me that this

issue is looking on the horizon for all heartworm products now that the awareness has been raised, and that this might be something that a consortium of the manufacturers of these drugs ought to get together and work on them together, even though they are competing on the sales. Why don't you get the data together to show that these products really are safe, or let's say acceptably risky to use.

I don't have any other comments at this point. Aleta, is there anything else we need to do? So we will turn it over to Dr. Sundlof for the benediction.

DR. SUNDLOF: Thank you, Mr. Chairman. I just want to thank you and the committee and all the folks who have participated in this today. As you see, these are very weighty decisions that we have before us. In my imagination I was hoping we would get a clear signal.

(Laughter.)

DR. SUNDLOF: But realistically I was prepared that we would not get that, and that appears to be where we are. So we will take the comments back to CVM. We will certainly have a thorough discussion based on what we heard today from this group, and we will come to some conclusion. Hopefully we can take into account especially the answers to the second question that I think laid out some very attractive possibilities for further investigation

in this. So again thank you all. I know it was a lot of information that you had to go through in a very short period of time, and with the weather and everything it was wonderful that you could all make it. A few people didn't. So thanks again, and I wish you a safe trip home.

(Whereupon, the meeting was adjourned at 5:14 p.m.)

Audio Associates
(301) 577-5882

ATTACHMENT 5

Mail

Close

Previous Next

From: "Hampshire, Victoria" <VHampshi@CVM.FDA.GOV>
To: Lynn O Post; Ann Hokinson
CC: Linda R Tollefson
Date: 9/7/2004 9:42 AM
Subject: RE: Requests from FDAH

Ann; that last sentence should say; either in the context of 1932A; or by hotline. Sorry for the incomplete sentence.

Victoria Hampshire, VMD
Adverse Drug Events Coordinator
Office Surveillance/Compliance
Center for Veterinary Medicine
Room 2624
7500 Standish Place
Rockville, MD 20855
301-827-7822

-----Original Message-----
From: Hampshire, Victoria
Sent: Tuesday, September 07, 2004 10:36 AM
To: Ann Hokinson; Post, Lynn O
Cc: Tollefson, Linda R
Subject: Requests from FDAH
Importance: High

Hello Ann;

I am acknowledging three requests from you on behalf of Fort Dodge Animal Health by voice mail:

1. A request for the product defect assessments FDA made reference to. That was previously forwarded to Steve Connell 9/3/04 at approximately 6PM.
2. A request for a copy of my slide presentation delivered September 3. I think it best to leave this request up to my leadership I would want you to appreciated that I will no longer share such slides unless it is in a meeting where I deliver the context verbally. I'm sure you can appreciate that slide shows represent bullet points of larger context items and are delivered with verbal explanation of the slide. I would not want them to be misinterpreted.
3. You have requested I reveal the academicians who I have consulted with. Please understand that these consultations have occurred either ithe context of 1932As and must remain confidential.

If you have any other requests related to the recent regulatory activities, unless it relates to a specific ADE case, please funnel them appropriately through Dr.Post.

Ann; that last sentence should say; either in the context of 1932A; or by hotline. Sorry for the incomplete sentence.

Victoria Hampshire, VMD
Adverse Drug Events Coordinator
Office Surveillance/Compliance
Center for Veterinary Medicine
Room 2624
7500 Standish Place
Rockville, MD 20855
301-827-7822

-----Original Message-----
From: Hampshire, Victoria
Sent: Tuesday, September 07, 2004 10:36 AM
To: Ann Hokinson; Post, Lynn O
Cc: Tollefson, Linda R
Subject: Requests from FDAH
Importance: High

Hello Ann;

I am acknowledging three requests from you on behalf of Fort Dodge Animal Health by voice mail:

1. A request for the product defect assessments FDA made reference to. That was previously forwarded to Steve Connell 9/3/04 at approximately 6PM.
2. A request for a copy of my slide presentation delivered September 3. I think it best to leave this request up to my leadership I would want you to appreciated that I will no longer share such slides unless it is in a meeting where I deliver the context verbally. I'm sure you can appreciate that slide shows represent bullet points of larger context items and are delivered with verbal explanation of the slide. I would not want them to be misinterpreted.
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If you have any other requests related to the recent regulatory activities, unless it relates to a specific ADE case, please funnel them appropriately through Dr.Post.

ATTACHMENT 6

From: Tom Corcoran
To: Rami Cobb
Date: 9/20/2004 1:41:08 PM
Subject: Advisory Panel

I spoke to Sundlof today. He told me they are working to hold the panel as quickly as possible before year end. I pushed him on the need to get this settled as quickly as possible. He agreed and said they had an internal working group to get this going.

Regarding the format he indicated that it would be a one or two day meeting. Format is FDA present or FDAH presents(he said the order could be determined later). Then public comments are made. After the public has had a chance to make their comments the panel questions the presenters. Panel deliberates and makes a recommendation.

Publication in the Federal Register asks for those who intend to make comments to reply in order to give the FDA some idea as to the possible length of the meeting.

We will be permitted to provide information to the Panel supportive of our position in advance. Obviously the FDA will do the same. The question posed to the panel will be FDA and FDAH have a differing view as to the safety of ProHeart 6. In the panels opinion is the product safe to be marketed?

I asked him for the status of the presentation Dr. Hampshire made. He responded that since we were asking it meant it had not been sent. I affirmed. He said he would find the hold. Regarding the academics, he stated Dr. hampshire was trying to obtain the permission of the people with whom she consulted.(C.T.,please check and see if they can withhold these names). I am under the impression that consultants have to identified. Is there any regulation that governs that I can go back to him and push him on?

Please disseminate to your working group this e-mail to the working group. I will direct all e-mails on this subject to your attention. Thanks,

Tom

CC: C.T. Newsum

ATTACHMENT 7

Fort Dodge Animal Health
Division of Wyeth
9225 Indian Creek Pkwy., Suite 400
Overland Park, KS 66210

E. Thomas Corcoran
President
913-664-7088 tel
913-664-7120 fax
tcorcora@fdah.com

FORT DODGE

September 23, 2004

Dr. Steve Sundlof, Center Director
Room 181
Center for Veterinary Medicine
7519 Standish Place
Rockville, MD 20855

Dear Dr. Sundlof:

Per your request the following are our suggestions for the Advisory Panel:

- Dr. Ian Tizard, BVMS, PhD
  Office 101 BVMS
  Texas A&M University
  College Station, TX 77843
  Telephone: 979-845-4276
  E-Mail: itizard@cvm.tamu.edu
  Position: Professor of Immunology

- Dr. Michael R. Peterson, DVM, MPH, DrPH
  10801 Steven Lee Court
  Fairfax, VA 22032
  Telephone: 703-681-3636
  Position: Deputy Director, Health Program Analysis and Evaluation, TriCare Management Activity, Office of the Assistant Secretary of Defense (Health Affairs)

You previously mentioned Dr. Tom Nelson, President of the American Heartworm Society, as a member of the panel. He would seem like an acceptable and logical choice.

None of these individuals have any financial or consulting arrangement with Fort Dodge Animal Health or Wyeth either past or present. You indicated you would begin the clearing process of these individuals. If you need anything further, please do not hesitate to call.

As of today, we have not received Dr. Hampshire's presentation from the September 1, 2004 meeting. Some delay I can understand; however, I think you would agree Fort Dodge Animal Health is entitled to see this in its entirety. At the September 1 meeting, material was presented very quickly with numerous slides being skipped over. Since this presentation obviously had strong influence on the decision reached by CVM, we need to see the presentation. I understand a written narrative will accompany the presentation. If there is a problem in providing, please let me know.

The other request I have posed to you is the list of academics Dr. Hampshire consulted with in evaluating ProHeart 6. The presentation made by Dr. Hampshire indicated individuals from the academic community were concerned about or opposed to ProHeart 6. Since the agency used these individuals' expertise to help arrive at the decision ProHeart 6 should be removed from the market, Fort Dodge Animal Health clearly has a right to learn the names of the individuals and their concerns and opinions and the type of advice provided to CVM.

I do not want either of these items to become major issues, but it is important we have access to all the information the Center used in order to take action against ProHeart 6.

I will wait to hear from you. If you have any questions, please do not hesitate to call. Thank you for your attention to these matters.

Sincerely,

Tom Corcoran

E. Thomas Corcoran
President

bcc: C.T. Newsum
Rami Cobb

ATTACHMENT 7A

Mail

Close

Previous Next

From: "Sundlof, Stephen F" <SSUNDLOF@CVM.FDA.GOV>
To: Tom Corcoran
CC:
Date: 9/24/2004 2:42 PM
Subject: FDA Slides from September 1 meeting
Attachments: ADE presentation to FDAH edited September 1 2004.ppt (30,153,216 bytes)

Dear Tom,

Attached please find the PowerPoint presentation which you requested from the September 1, 2004 meeting. In considering your request for the names of the experts outside the Agency which Dr. Hampshire referred to during her presentation, CVM has determined that the information is pre-decisional and therefore considered confidential, thus we are declining to provide their names. We have made significant progress in securing a date and venue for the advisory committee meeting, although we cannot finalize until we have determined the availability of the committee members. I will let you know the specifics as soon we can firm up the arrangements.

Sincerely,

Stephen F. Sundlof, D.V.M., Ph.D.
Director, FDA Center for Veterinary Medicine

ATTACHMENT 8

ProHeart® 6

Apparent Conflict of Interest

November 19, 2004

Confidential

Apparent Conflict of Interest

Wyeth has learned of information that presents the appearance of a conflict of interest with respect to the following CVM employee:

Victoria A. Hampshire, VMD
Adverse Drug Event Coordinator
CVM's Office of Surveillance and Compliance

Dr. Hampshire's Involvement

Dr. Hampshire prepared two presentations analyzing ProHeart® 6 adverse event reporting.

The first analysis entitled "ProHeart® 6 Adverse Event Reporting to the FDA" was presented to Fort Dodge on August 11, 2004.

The second analysis was presented to Fort Dodge on September 1, 2004 in an attempt to further explain the conclusions reached in the August 11, 2004 presentation.

These two reports formed the basis for FDA's decision to request withdrawal of ProHeart® 6 from the market.

Apparent Conflict of Interest

In September 2004, while conducting a web search of anti-ProHeart® 6 internet activists, we became aware of an apparent affiliation between Dr. Hampshire and an internet veterinary pharmacy, Advanced Veterinary Applications, marketing one or more products that compete with ProHeart® 6.

Apparent Conflict of Interest

Public records revealed the following:

- Advanced Veterinary Applications (AVA) is an active Internet veterinary pharmacy located at http://www.advancedvet.com.
- AVA markets heartworm medications that directly compete with ProHeart® 6, including Heartgard®.
- As of August, 2004, Maryland Secretary of State records identify Dr. Hampshire as the registered owner of an unincorporated entity trading as Advanced Veterinary Applications.
- Internet listings and state records identified AVA's business address and the residence of Victoria A. Hampshire as both being [redacted]

Advanced Veterinary Applications

LOGIN

STORE

WELCOME

ENCYCLOPEDIA

HOME

CHECK A PRIOR ORDER'S STATUS | # OF ITEMS IN CART: 0 | PURCHASE TOTAL: $0.00 | check out >

All Categories | GO!

search the catalog

Help

- **accessories**
  Leashes and Collars, Training Products
- **dental**
  Brushes/Toothpaste, Enzymatic Dental Chews, Oral Rinses
- **household cleaning**
  Carpet and Fabric Cleaners, Insecticide, Odor Neutralizers
- **medication / healthcare**
  Anthelmintics, Behavioral, Laxative/Hairball, Miscellaneous
- **skin/coat care**
  Allergy Control, Anti-itch, Anti-sebhorreic Shampoo, Antibacterial

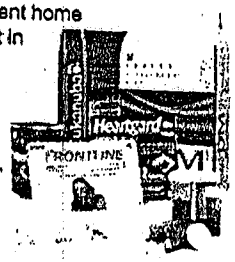
Veterinary Product Catalog

Welcome to Advanced Veterinary Applications's veterinary product catalog, your online source for high quality Animal Healthcare.

Prescription Medications, Diets and More!

We can provide convenient home delivery of every product in our pharmacy!

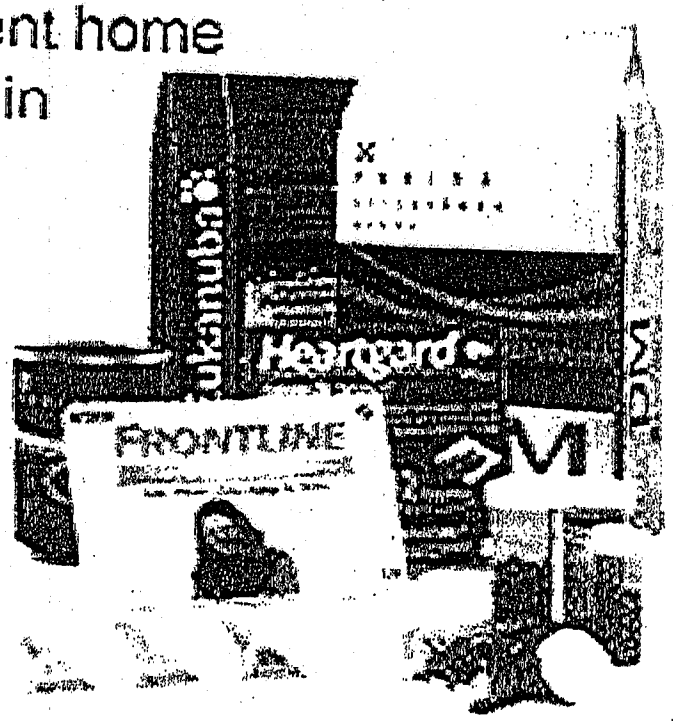
Ask us about our complete offering of prescription medications, heartworm, flea and tick preventives, therapeutic diets and much more.



Prescription Medications, Diets and More!

We can provide convenient home delivery of every product in our pharmacy!

Ask us about our complete offering of prescription medications, heartworm, flea and tick preventives, therapeutic diets and much more.



Apparent Conflict of Interest

- To confirm AVA was an active business, we placed two orders for product through the AVA website
- Orders are sent to VetCentric (fulfillment house) for processing
- VetCentric ships product and invoices to customers
- AVA receives the difference between the amount billed the customer and VetCentric's product cost

Order Number: 471922 Order Date: Oct 10 2004 5:3 IPM

Ship To:
Thomas OHare
40 East Gate
Copiague, NY 11726

Patient Information:

Purchased From:
Advanced Veterinary Applications

Problems with your order? Please contact our customer support staff at: orders@vetcentric.com.

Number	Product Name	Quantity	Price	Instructions
	Bitter Apple F/Pets Spray, 8 oz Bottle	1 EA	$6.08	

Subtotal:	$6.08
Tax:	$0.00
Shipping &Handling:	$3.95
Total Order:	$10.03

Mode of Transport: Standard
For refills, please visit www.advancedvet.com or call 1.866.VET.CENTRIC (838.2368).

HEARTGARD Brand Products help you provide the best protection for your pet against internal worms that may pose a serious threat to its health. Many of these worms can affect both pets and people. Fortunately, prevention is easy with HEARTGARD. By giving your dog or cat HEARTGARD once a month, you can prevent heartworm disease year round. With HEARTGARD Plus, you can also protect your dog against roundworms and hookworms. Call us if you have questions regarding HEARTGARD brand products or if you are interested in convenient home delivery, through VetCentric, our home delivery pharmacy. HEARTGARD is a registered trademark of Merial Ltd.

When it comes to fleas and ticks, there's no room for compromise. FRONTLINE@ is the world's best selling flea and tick protection for dogs and cats. FRONTLINE kills 100% of fleas on your pet within 18 hours and keeps working an entire month or more to keep your pet flea-free, according to Merial's research studies. Plus, additional Merial studies show that FRONTLINE kills 100% of ticks on your pet within 48 hours, including those which may transmit dangerous diseases that may affect pets and people. Call us if you have questions regarding FRONTLINE brand products or if you are interested in convenient home delivery, through VetCentric, our home delivery pharmacy. FRONTLINE@ is a registered trademark of Merial Ltd.

Potential Bias

In October 2002 Dr. Hampshire was in contact with Jean Brudd, an anti-ProHeart® 6 Internet activist.

(Jean Brudd has retained an attorney and is demanding compensation from Fort Dodge for the loss of her two dogs.)

i-dog™ a dog.com forum

Last Day | Last Week | Topics | Search | Register

Jean Brudd (jean_brudd)
New Member
Username: jean_brudd

Post Number: 19
Registered: 9-2003

Posted on Tuesday, July 13, 2004 - 1:11 am:

Janis and Erin,
I too am so sorry to hear about your babies. I've been "there" (twice), so I have a feeling I know just how absolutely devastated you are, and you have my deepest sympathy.

Janis, my first dog died from IMHA. I had never heard of it either. Dr. Victoria Hampshire of the FDA told me personally in October of 2002 that IMHA is a "common side effect" found with ProHeart 6. Not that that makes you feel better, but I just wanted to let you know that you are not a part of a small group whose dogs died with this disease after receiving the ProHeart 6 shot. My Tasha only had ProHeart 6 in her system, not anything else. Her death absolutely devastated me. And then less than two months later, I lost Niki to a type of cancer rarely found in his breed. My dog Casey survived, but his immune system was affected also. He's under medication still, but he looks to be just fine now. Who knows, though, if his life span will be shortened. God, I hope not.

Erin, did you ever get a diagnosis of what they thought was wrong with your dog? It sounds like an anaphylactic reaction, which is up at the top of the list of the reported FDA adverse reactions to moxidectin (ProHeart 6). I hope to heck your vet is not saying "Oh, it could not have been the shot." I'd be curious if he plans on ever giving that shot again.

Ladies, please, PLEASE make sure you fill out a form 1932a adverse effects report with the FDA if your vet will not do so for you. It doesn't take long to fill out, and the form comes with its own "stamp." You can find further instructions on how to find this form at our Web site at www.thepetguardian.com under

Potential Bias

On September 3, 2004, less than one hour after the FDA released an announcement regarding the recall of ProHeart® 6, Dr. Hampshire had a telephone conversation with Meri Christensen, an anti-ProHeart® 6 activist, to inform her of the FDA's actions and to encourage continued submission of adverse event reports directly to Dr. Hampshire.

Potential Bias

Fri Sep 3, 2004 6:05 pm posting from Meri Christensen:

I just got off the phone with dr hampshire
she said although fd has agreed to pull the crap
the fda cannot regulate what individual vet practices do
the fight isnt quite over but we are really winning
she said this has been in the works and that is why she postponed
her call to me, she had to wait until the press release came out.
she is still encouraging people who have not yet sent information to
her should do so and those ppl who have not had an adverse reactions
report filed should make sure it is done

she asked that relevant files and reports be sent directly to her with the
proheart 6 case number in side and proheart 6 + the case number be put on the
outside.
its through these efforts and the hard work of some in particular and all of us in
general that this has happened, to me it sounded like she was the only one
working on this, and that it was her that had to convince a panel that it was
worthwhile pursueing. she has been working on this for a long time.

Potential Bias

E-mail from Dr. Larry Glickman, Professor of Epidemiology at Purdue University and consultant to Fort Dodge:

Good speaking with you. After we spoke my wife who was also at the fda-fdah meeting because she has been doing the data analysis, reminded me of another comment made by Victoria Hampshire. When Victoria was asked "Don't you have a concern that the vast majority of Proheart 6 reactions were reported to you by pet owners and very few by veterinarians? she responded and I quote as best I can from memory "We do not trust veterinarians to report Proheart 6 associated reactions to fda. Veterinarians know that owners cannot buy Proheart 6 over the Internet and thus they want to protect their income by not reporting any adverse events."

>>>"Larry Glickman"<ltg@purdue.edu 9/9/2004 5:06:43 PM >>>

Confidential

Recent Changes in Internet Information

From an anti-ProHeart® 6 Internet newsletter, "Paws for Progress:"

9/3/04	Paws for Progress Newsletter(C)	Special

"Knowledge is Power"
~unknown~

Special Edition!

Some of you have already heard, some of you may not have yet heard yet. It is a busy week end with the Labor Day Holiday and also the hurricane season in Florida.

It was announced by the FDA on Friday afternoon QUOTE:

Fort Dodge to Comply with FDA's Request to Recall ProHeart 6 Injectable Heartworm Product from the

Happy Labor Day! And our labor has paid off!

Please help us!
ADE Survey

STILL very Important!!

HOT!
Immune Problems???
Liver Problems ??
plus moxidectin/six month injection?

FDA's concern is based on voluntary self-reporting to FDA by veterinarians and owners whose dogs have suffered adverse drug experiences (ADEs) to ProHeart®6 (which contains the drug moxidectin) as well as the mandatory reporting of adverse events by Fort Dodge Animal Health.

Fort Dodge Animal Health has agreed to recall any product that has already been distributed to veterinarians.

As of August 4, 2004, FDA's Center for Veterinary Medicine (CVM) had received 5,552 adverse event reports for ProHeart®6. The actual number of adverse events is likely even higher because studies show that only a fraction of actual ADEs are reported.

The Agency has observed an increase in the number of cases associated with liver and bleeding abnormalities followed in some cases by death.

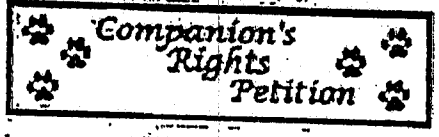
#####

UNQUOTE

Still in Disbelief?

MSNBC - Associated Press - Reuthers - Yahoo Fiance - CNN

This news has been greeted with many tears..... Tears of happiness, to know that our dogs did not die or were not harmed in vain.

CLICK 

CLICK

Our work is not over! We MUST get the vet boards to down on us today.

From Myra Kirkland: I am extremely elated that the FDA has pulled the ProHeart 6 shot from the market. It has taken Many individuals Many hours to achieve this goal. Thanks to ALL who had a hand in this! We must continue however to be sure that the individual veterinarians stop giving this drug and that dog owners still report reactions to the FDA on the ProHeart 6 shot. A special thanks to Victoria Hampshire, VMD with the FDA who has been a vital part in the adverse drug surveillance on ProHeart 6. Jean, Janice and I now know our dogs DID NOT DIE IN VAIN. We will continue to spread the word on this dangerous shot. Thanks to all, Myra

From Dr. Bob: Dr. Bob called Janice and told her HOW PROUD HE WAS OF ALL OF US

From Janice Storey: Celebrate! that we finally after two long years (for me) .....have WON. Phase I is over. Phase II is just beginning. TODAY IS THE BEST DAY OF MY LIFE. I loved my poor Trouble so very much and now he will know how much I truly loved him. SCORE ONE FOR THE BELOVED DOGS AND THEIR PET GUARDIANS!!!!

From Dr. Jean Dodds: "Great News !!!! "

From Laurryn: Congratulations! I don't know of a single person who will give credit to only one person or even a couple. Special Thanks to EVERYONE who has taken the time to tell their story, to tell others, sending emails, making copies, to be interviewed. It took all of us coming together to reach this point!

Our work is not over! I know for a fact that at the American Heartworm Society Seminar July 24, 2004 that they discussed the 12 month injection.

Things to do YET! Notify your media - Notify your State Vet Boards and Notify your Vets! We don't know how long it will take for offical recall from manufacturer to go out.

ProHeart®6 is an approved injectable sustained-release heartworm prevention product for dogs. Heartworm disease is a serious and potentially fatal condition of dogs, cats, and other species of mammals. The parasite that causes heartworm disease is transmitted through the bite of a mosquito.

FDA is also advising veterinarians to avoid administering this product to dogs until further notice. Pet owners should consult their veterinarians regarding their pet's health care needs.

Since the product was approved in June 2001, Fort Dodge Animal Health has cooperated with FDA to investigate numerous adverse event reports. As a result, Fort Dodge has voluntarily changed the label to include post approval safety information including rare reports of death and a caution to practitioners that dogs should have a negative test for heartworm before administration.

Despite these label changes, FDA is still receiving unexplained adverse event reports, some of them severe. FDA's concern is based on voluntary self-reporting to FDA by veterinarians and owners whose dogs have suffered adverse drug experiences (ADEs) to ProHeart®6 (which contains the drug moxidectin) as well as the mandatory reporting of adverse events by Fort Dodge Animal Health.

Fort Dodge Animal Health has agreed to recall any product that has already been distributed to veterinarians.

As of August 4, 2004, FDA's Center for Veterinary Medicine (CVM) had received 5,552 adverse event reports for ProHeart®6. The actual number of adverse events is likely even higher because studies show that only a fraction of

If you do not file a complaint with the FDA.....
you're giving the manufacturer ammunition to use against you.
They can then claim there are so few cases of adverse reactions.... nothing needs to be done.

When you don't file, you stack the statistics in the manufacturers favor.
Don't depend on your vet's office.
(Thanks for the F.A.C.T idea Laurie!).

It is not over yet! FDA is still asking for all reports of adverse reactions, to be sure that all of your companions records were submitted for evaluation.

From Jean Brudd: Thanks to everyone who has worked so hard and for so long. I know our work is not finished making sure this drug will stay off the market. This is an example of how determination pays off. Regardless of vets and lawyers and whomever else thinking we're crazy, we finally proved them wrong. Our dogs at the Rainbow Bridge are smiling down on us today.

From Myra Kirkland: I am extremely elated that the FDA has pulled the ProHeart 6 shot from the market. It has taken Many individuals Many hours to achieve this goal. Thanks to ALL who had a hand in this! We must continue however to be sure that the individual veterinarians stop giving this drug and that dog owners still report reactions to the FDA on the ProHeart 6 shot. A special thanks to FDA who has been a vital part in the adverse drug surveillance on ProHeart 6. Jean, Janice and I now know our dogs DID NOT DIE IN VAIN. We will continue to spread the word on this dangerous shot. Thanks to all, Myra

Interpretation of Data

Dr. Hampshire does not appear to have treated the ADE data or reports in an unbiased and objective manner, resulting in misleading interpretations of both.

Interpretation of Data

In Dr. Hampshire's presentation on ProHeart® 6 adverse events, she included a slide relating to the reporting rate for PH6 initial reports. The slide showed the frequency of initial reports for PH6 trending upward for June, July and August 2004.

Neoplasia (FDA Slide)

Neoplasia

"We observe the emergence in the database of neoplasia complaints with similar sorts of patterns and in youngish dogs."

- This discussion is accompanied by a photograph of an elderly, 10 ½ years old dog with lymphoma in one eye, and glaucoma in the other.
- Eight months after injection of PH6, the dog was diagnosed with lymphoma in the right eye. The ophthalmologist noted that he has seen this same problem in a number of dogs which had not been treated with PH6.
- Two veterinarians told the owner that the lymphoma most likely spread to other parts of the dog's body.
- Lymphoma is a common cancer of dogs, with a reported incidence of 11.4/10,000 dogs/year.[1]

[1] Morris & Dobson ISBN 0-632-05282-1

Neoplasia (continued)

Despite the evaluations of these attending veterinarians, FDA has assigned the following signs in this dog as being "probably related to the drug."

Anorexia	Depression/Lethargy	Neoplasm
Weight Loss	WBC High/Blood Problem	Ataxia
Circling	Blindness	Hyphaema
Eye/Eyelid Lesion		

Interpretation of Data

After Dr. Hampshire insisted on multiple additional tests, she ignored a distemper diagnosis by a university neurologist and the same diagnosis on necropsy by a university pathologist for a dog that had received ProHeart® 6.

Interpretation of Data

A 2 year old apparently healthy dog was treated with PH6 several days after vaccination. Two days later the dog had a seizure, and became seriously ill.

The dog was diagnosed with distemper by an expert neurologist at Oklahoma State University.

The diagnosis was not accepted by FDA, and further testing was required including echocardiogram and bile acids.

At necropsy, histopathology conducted by a university pathologist confirmed the diagnosis.

The FDA requested additional confirmation by special staining sections. The diagnosis was confirmed as distemper.

Despite not being related to PH6, this dog's report contributes to the FDA analysis. The range of signs includes seizures, liver, cardiac, blindness and intestinal problems.

Interpretation of Data

Dr. Hampshire claimed there was an increasing frequency of ineffect complaints. When adjusted for units sold, the rate has not increased and is extremely low.

"We observe the increasing frequency of ineffect complaints."

	No. of Reports	Months	Doses Sold+	Rate
6/01-10/01*	2	4	4.3 million	NA
11/01-4/02*	7	6	2.1 million	0.0003%
5/02-4/03*	157	12	4.1 million	0.004%
5/03-4/04	248	12	7.7 million	0.003%

+assumes a 21 kg dog

*from time of infection to time of earliest possible diagnosis ≥6 months

- The efficacy of PH6 is 99.997%.

ProHeart 6 Review by Boards of Health In Other Major Markets

- **Canada** – The Veterinary Drugs Directorate reviewed safety and post-marketing experience in September, following the US recall.

  ProHeart 6 is not recalled and remains on the market.

- **EU** – The EU Pharmacovigilance Group reviewed the EU post-marketing experience in early September, and follow-up information was sent to the reference Member State, Italy.

  GUARDIAN SR is not recalled, and remains market leader in Italy.

- **Australia** – The APVMA reviewed pharmacovigilance data for ProHeart 12 (3X ProHeart 6) following the US recall

  ProHeart 12 is not recalled, and remains market leader.

- **Japan** – Our commercial distributor notifed JMAFF of a voluntary stop sale in September following the US recall. JMAFF approved re-commencement of sales in October.

Summary

Dr. Hampshire's involvement in an internet pharmacy marketing FDA-regulated animal health products, at least one of which competes with ProHeart® 6, raises the appearance of a conflict of interest.

Dr. Hampshire's public statements and communications with anti-ProHeart 6® activists appear to reflect a bias against the product.

Dr. Hampshire presented data in a biased fashion, reflecting an apparent lack of scientific objectivity and impartiality.

ProHeart 6® Apparent Conflict of Interest

Backup Materials

Confidential

Affiliation of Dr. Hampshire With Advanced Veterinary Applications

Entity Detail

Maryland Department of Assessments and Taxation 4

Taxpayer Services Division
301 West Preston Street ■ Baltimore, Maryland 21201

Main Menu | Security Interest Filings (UCC) | **Business Entity Informati**
(Charter/Personal Property) New Search | Get Forms | Certificate of Sta
SDAT Home

Taxpayer Services Division

Entity Name: HAMPSHIRE, VICTORIA
Dept. ID #: L05436670

Personal Property

Mailing Address

HAMPSHIRE, VICTORIA
ADVANCED VETERINANY APPLICAHIONS

Personal Property Filings

Asmt. Year	Filing Date	Extension	Penalty Amount	Penalty Paid Date
2004		No		
2003		No		
2002		No		
2001		No		
2000	02/14/2000	No		

Personal Property Assessments Summary

Asmt. Year	Date Assessed	County Base	Town Base	Date Certified
2004				
2003				
2002				
2001				

34264757475

CORPORATE RECORDS & BUSINESS REGISTRATIONS

This Record Last Updated:	08/01/2004
Database Last Updated:	10-29-2004
Update Frequency:	MONTHLY
Current Date:	11/01/2004
Source:	AS REPORTED BY THE SECRETARY OF STATE OR OTHER OFFICIAL SOURCE

COMPANY INFORMATION

Name:	HAMPSHIRE, VICTORIA

FILING INFORMATION

Filing Date:	08/10/1999
Status:	ACTIVE
Status Attained Date:	08/10/1999
Business Type:	UNINCORPORATED ENTITY
Registration ID #:	L05436670

Where Filed:	SECRETARY OF STATE/DEPARTMENT OF ASSESSMENTS AND TAXATION/CORPORATE CHARTER DIVISION
	301 W PRESTON ST
	BALTIMORE, MD 21201

PRINCIPAL INFORMATION

Name:	HAMPSHIRE, VICTORIA
Title:	UN-INCORPORATED ACCOUNT OWNER

ADDITIONAL DETAIL INFORMATION

Additional Details:	TRADING AS: ADVANCED VETERINANY APPLICAHIONS

Maryland Department of Assessments and Taxation
MONTGOMERY COUNTY
Real Property Data Search

Go Back
View Map
New Search
Ground Rent

Account Identifier: District - 07 Account Number - 00612618

Owner Information

Owner Name: BALABAN, ROBERT S &
VICTORIA A HAMPSHIRE

Use: RESIDENTIAL

Principal Residence: YES

Mailing Address:

Deed Reference: 1) /11429/ 53
2)

Location & Structure Information

Premises Address

Legal Description
BANNOCKBURN

Map	Grid	Parcel	Sub District	Subdivision	Section	Block	Lot	Group	Plat No:
GN42				72		5	17	81	Plat Ref:

Special Tax Areas

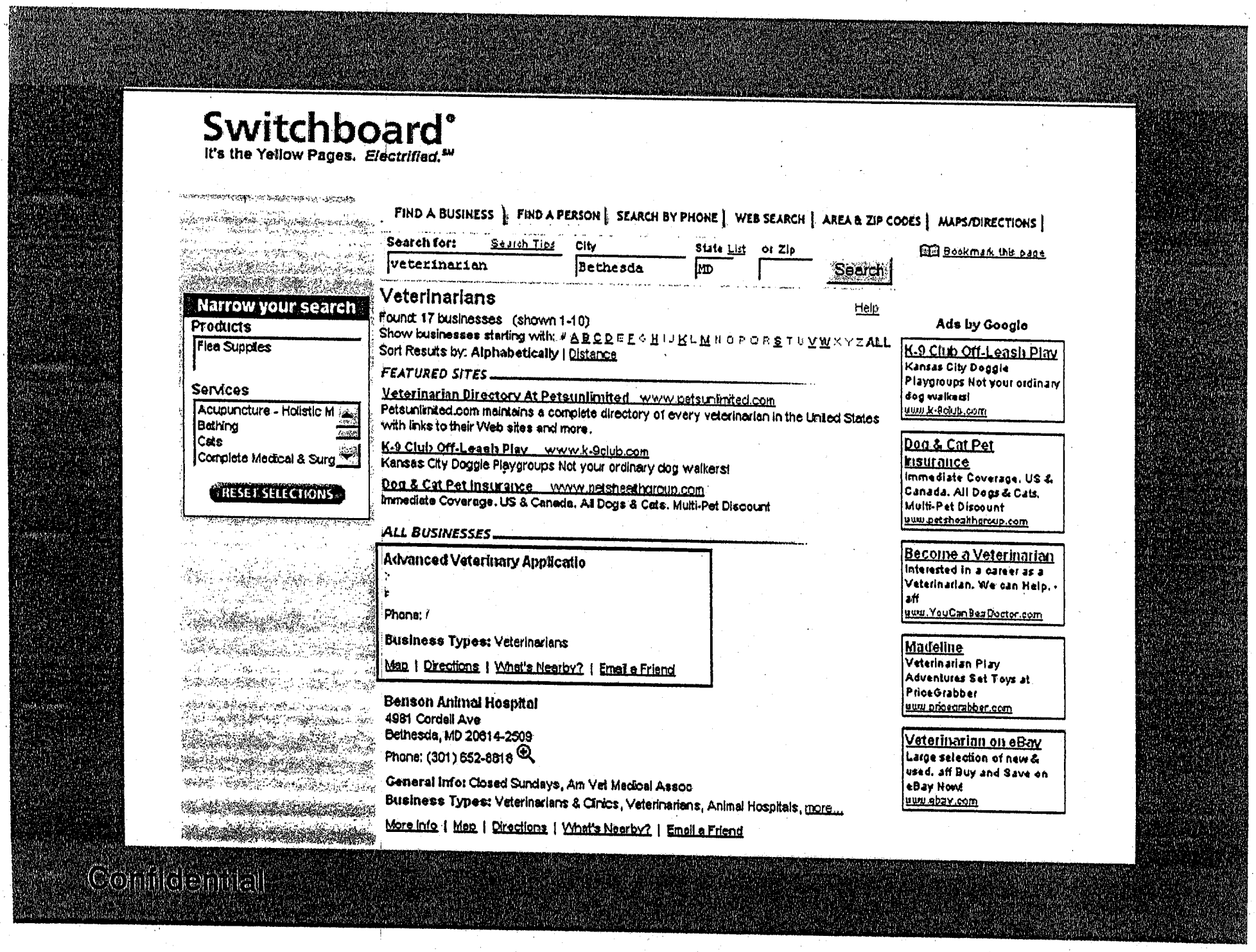
Town
Ad Valorem
Tax Class 38

Primary Structure Built	Enclosed Area	Property Land Area	County Use
1957	1,554 SF	69,629.00 SF	111

Stories	Basement	Type	Exterior
1	YES	STANDARD UNIT	BRICK

Value Information

	Base Value	Value As Of 01/01/2002	Phase-in Assessments As Of 07/01/2004	As Of 07/01/2005
Land:	294,810	294,810		
Improvements:	208,280	208,280		
Total:	503,090	503,090	503,090	NOT AVAIL
Preferential Land:	0	0	0	NOT AVAIL



Appendix D

Meeting Participants

Lynn C. Anderson, DVM, Senior Director, Comparative Medicine/LAR, Merck Research Laboratories, Rahway, N.J.

Kathryn Bayne, MS, PhD, DVM, Associate Director, American Association for the Accreditation, of Laboratory Animal Care International, Rockville, Md.

B. Taylor Bennett, DVM, PhD, Biological Resources Laboratory, University of Illinois, Chicago, Ill.

Marcelo Couto, DVM, PhD, Scientific Advisory Committee, American Association for Laboratory Animal Science, Memphis, Tenn.

W. Ron DeHaven, DVM, Deputy Administrator, U.S. Department of Agriculture, Animal and Plant Health Inspection Service, Animal Care, Riverdale, Md.

Nelson Garnett, DVM, Office of Laboratory Animal Welfare, National Institutes of Health, Bethesda, Md.

G. F. Gebhart, PhD, Professor and Head, Department of Pharmacology, College of Medicine, University of Iowa, Iowa City, Iowa

Victoria Hampshire, VMD, Advanced Veterinary Applications, Bethesda, Md.

John E. Harkness, DVM, Laboratory Animal Veterinarian, College of Veterinary Medicine, Mississippi State University, Mississippi State, Miss.

ILAR Journal

ILAR Journal Home

ILAR Journal V44(3) 2003
Behavioral Research Outside the Laboratory

View/Download article (PDF):
Regulatory Issues

Regulatory Issues Surrounding the Use of Companion Animals in Clinical Investigations, Trials, and Studies<

Victoria A. Hampshire

Victoria A. Hampshire, V.M.D., is Director of Advanced Veterinary Applications, Bethesda, Maryland.

Abstract

Laboratory animal veterinarians sometimes encounter animals with rare conditions and may subsequently become involved in the performance of related animal research outside the laboratory, in homes, in veterinary clinics, or in universities to which owners have donated their animals for study. Similarly, veterinarians may monitor animal companion vaccination studies, performed to optimize preventive health care or minimize physiological variability and research confounders associated with a preventive medicine program for dogs and cats utilized for research procedures. These nontraditional uses of dogs, cats, and other companion animals in research have spurred the establishment of regulations to ensure that the animals benefit from clinical veterinary products and techniques. Included and described are the 2002 Public Health Service Policy, the Animal Welfare Act (AWA), the Federal Food, Drug, and Cosmetic Act, and the regulations of the US Department of Agriculture in response to the AWA. The complexities of clinical research with companion animals outside standard biomedical research facilities are discussed.

Original Screen Shot of Meri Christensen Web Posting

APPENDIX – post #2052 of *Yahoo!* group Canine Drug Dangers

caninedrugdangers · Canine Drug Dangers

Group Member | Edit My Membership |

Messages

Messages Help

Reply | Forward | View Source | Unwrap Lines

Search Archive

Message 2052 of 2376 | Previous | Next | [illegible] | Message Index

Msg # [illegible] Go

Home
Messages
Post
Chat
Files
Photos
Links
Database
Polls
Members
Calendar

Promote

☆ = Owner
☆ = Moderator
☆ = Online

From: "russeqirl" <[illegible]>
Date: Fri Sep 3, 2004 6:05 pm
Subject: another reminder

i just got off the phone with dr hampshire
she said although fd has agreed to pull the prop
the fda cannot regulate what individual vet practices do
the fight isnt quite over but we are really winning
she said this has been in the works and that is why she postponed her call to
me. she had to wait until the press release came out.

she is still encouraging people who have not yet sent information to her should
do so and those of who have not had an adverse reactions report filed should
make sure it is done

she asked that relevant files and reports be sent directly to her with the
proheart 6 case number in side and proheart 6 + the case number be put on the
outside.

its through these efforts and the hard work of some in particular and all of us in general that this has happened. to me it sounded like she was the only one working on this, and that it was her that had to convince a panel that it was worthwhile pursueing. she has been working on this for a long time.

here is her mailing information
please cross post this to relevant lists
thanks tfor everyones hard work

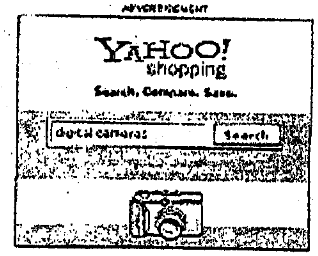
Victoria Hampshire, VMD
Adverse Drug Events Coordinator
Office Surveillance/Compliance
Center for Veterinary Medicine
Room 243[illegible]
7500 Standish Place
Rockville, MD 20855
301-827-7022

Keri
Mini [illegible]
Luke CGC,AKC/ASCA CD,FI,PDX,FDCH
Angie CGC,FD,PDX,FDCH,FM,FMX,TDCH
We miss you Angie, forever in our hearts
If tears could build a stairway, and memories a lane, I'd walk right up to heaven and bring you home again
LOVE [illegible]? - BEWARE OF PROHEART 6 (injectable heartworm preventative) - GET THE FACTS
http://www.thepetguardian.com/
[illegible]
----- Original Message -----
From: Jean
To: [illegible]
Sent: Friday, September 03, 2004 3:24 PM
Subject: RE: this is why [illegible] incredible

And, Keri, WE know you helped. It's everyone's effort, and even though this has been difficult so many times and people's tempers have flared, I'm proud to know all of you.

I wonder how long it's going to take me to not be in shock over this. I always wanted this day so bad and knew in my gut it would happen, but I just cannot believe it is here. God loves the dogs, that's for sure!

ADVERTISEMENT



ATTACHMENT 9

Mail

Close

Previous Next

From: Rami Cobb
To: Anna Beckingham
CC:
Date: 9/27/2004 7:51 AM
Subject: Fwd: FDA Slides from September 1 meeting
Attachments: ADE presentation to FDAH edited September 1 2004.ppt (30,153,216 bytes)

Anna,
Would you please print the attachment for me.
Thanks,
Rami

>>> Tom Corcoran 9/24/04 4:17:35 PM >>>

Predecisional–I think we have touched on a problem they may have.

Tom
>>> "Sundlof, Stephen F" <SSUNDLOF@CVM.FDA.GOV> 9/24/2004 2:42:00 PM >>>
Dear Tom,

Attached please find the PowerPoint presentation which you requested from the September 1, 2004 meeting. In considering your request for the names of the experts outside the Agency which Dr. Hampshire referred to during her presentation, CVM has determined that the information is pre-decisional and therefore considered confidential, thus we are declining to provide their names. We have made significant progress in securing a date and venue for the advisory committee meeting, although we cannot finalize until we have determined the availability of the committee members. I will let you know the specifics as soon we can firm up the arrangements.

Sincerely,

Stephen F. Sundlof, D.V.M., Ph.D.

Director, FDA Center for Veterinary Medicine

ATTACHMENT 10

Mail

Close

Previous Next

From: Tom Corcoran
To: ssundlof@cvm.fda.gov
CC: C.T. Newsum; Rami Cobb
Date: 10/4/2004 4:53 PM
Subject: Advisory Panel

Steve, I will call you tomorrow to discuss the status of the panel. As you can imagine we are all getting anxious to see the scheduled date. I need to pass this along ASAP. There are a couple of other items I am curious about:

In your e-mail of 9/24/04 you indicated the Power Point presentation was being passed along . In going through the presenttion slides were omitted. Would you look into this and let me know if the missing slides were omitted for a specific reason?

In your e-mail of the same day you stated CVM had determined the information regarding the academics referenced in Dr. Hampshire's presentation was pre-decisional and therefore considered to be confidential. Predecisional to what? At our meeting on September 1, you announced to us you had reached a decision ProHeart 6 should be removed from the market. I need to understand the context of the "predecisional" statement that guides you to withhold the information from whom in the academic world you received advice on ProHeart 6. Obviously the nature of the advice is also key. This is very important to us as we prepare for the Advisory Panel.

Also, as you probably know personnel from CVM and FDAH participated in a teleconference last week at the request of FDAH. The objective of the call was to try and determine why CVM has different numbers for adverse events than FDAH. The feedback I am getting is CVM is telling us we are not going to receive reconciliation of the numbers or explanations. If this is the position of CVM please confirm to me. We are trying to be cooperative and make the panel a presentation based on scientific facts. The confrontational tone exhibited by some of the CVM personnel at the September 1, meeting seems to be continuing. Why? We are trying to come to the best answer and it would seem if CVM has information that would be helpful to FDAH in understanding the ProHeart 6 issue from CVM's side you would want to share the information. I also believe you have an obligation to share the information-- considering the serious nature of a product recall and stop sale. Sorry to go on so long, I will call you tomorrow morning. Thanks,

Tom

ATTACHMENT 11

Telephone Call with Dr. Steve Sundlof on October 5, 2004

I received a call back from Dr. Sundlof. The panel is tentatively slated for January 14. However, Sundlof stated a couple of the panel members were not available for the 14th and if it turned out others became unavailable, the panel would meet the first week of February.

On the issue of the "missing" slides from Dr. Hampshire's September 1 presentation, Dr. Sundlof stated he was told we were given all slides with data. Slides with commentary and conclusions were omitted. I told him this was totally unacceptable. If CVM presented this information as factual and it was the basis of their decision to demand we voluntarily recall ProHeart 6, we had an absolute right to see the complete presentation and they had an obligation to provide. I further told him that unless we received the entire presentation, I was going to make a big issue of initially withholding the presentation and then submitting only a portion of the presentation. I assured him this would be carried to the highest levels, and I wasn't speaking of FDA. He stated, "Message received."

He is holding to the position of not providing the names of the academics with whom CVM consulted on ProHeart 6. I told him we had a right to the information because if CVM had used consultants to evaluate ProHeart 6, we were entitled to know the nature of the advice and the individuals involved. He stated on the advice of their attorneys they were not going to provide the names in case this went to a hearing. I asked what he meant by hearing. He replied they needed to decide if they were going to have a hearing on this issue. He was using "hearing" as a distinct term from the Advisory Panel. He stated Fort Dodge Animal Health was under a voluntary recall and stop sale and should the product be put back on the market, they (FDA) would need to decide whether or not to proceed with a hearing, which is a step in the process of removing a product from the marketplace. He stated if a hearing is held, they would identify the academics who would testify as expert witnesses for FDA.

He told me he had spoken to Dan McChesney, who is in charge of surveillance and compliance, about proper business decorum on the part of Drs. Post and Hampshire. He asked that I provide him feedback if the situation persists.

Sundlof agreed to call me back on the status of the missing slides.

cc: Rami Cobb
Steve Chu
Brent Standridge
Steve Connell
C.T. Newsum

ATTACHMENT 12

From: Tom Corcoran
To: Brent Standridge; C.T. Newsum; Rami Cobb; Steve Connell
Date: 10/7/2004 9:28:56 AM
Subject: Fwd: September 1 Slide Presentation

From Dr. Sundlof.
Tom

>>> "Sundlof, Stephen F" <SSUNDLOF@CVM.FDA.GOV> 10/7/2004 8:57:24 AM >>>
Dear Tom,

Attached is the complete slide set from the September 1 meeting. The set I sent previously mostly omitted the conclusion slides because I thought, and still do think, that it is more important for FDAH to draw their own conclusion from the data in the reports FDAH sent to CVM rather than focusing on what FDAH considers problems with CVM's conclusions.

With regard to how we count cases, our folks went over this with Steve Connell and others from FDAH in July. The short version is that the nearly 6000 reports we now have are on individual animals but these animals have one or more clinical signs associated with box 19 of the 1932. The clinical signs are reviewed and where possible assigned to a specific organ system or condition (e.g. anaphylaxis). In our system a single dog with an event that started as anaphylaxis, and then developed liver complications would be placed in the count of dogs reported with anaphylaxis and with the count of dogs reported with liver complications. We do it this way because it is the only way to capture all the systems or conditions associated with the adverse event. If the dog above was reported with anaphylaxis and 2 indicators of liver complications, the dog would be reported once under anaphylaxis and once, not twice, under liver complications.

I do not fully understand your method of analysis, scoring and classification of adverse events report to FDAH, but if FDAH focuses on what it considers to be the primary cause of the reaction and considers that the only system involved or condition, even though there are other clinical signs that would suggest other system involvement, then I could understand that we would have different numbers based on system involvement or condition. We plan to describe to the Veterinary Medical Advisory Committee how we analyze the adverse event reported so that the members can understand our difference in numbers.

Sincerely,

Stephen F. Sundlof, D.V.M., Ph.D.

Director, FDA Center for Veterinary Medicine

ATTACHMENT 13

Mail

Close

Previous Next

From: Rocky Bigbie
To: M. Gatz Riddell
CC:
Date: 9/10/2004 11:25 AM
Subject: Re: Fwd: RE: Proheart 6

A vendetta certainly would explain some of the bewildering behavior. Careful analysis of the data can't explain it. A scientific approach can't explain it. Unbiased regulatory intervention can't explain it; but, by golly a vendetta certainly would. I've not heard that but it makes sense. I'll check on that.

>>> "M. Gatz Riddell" <riddemg@vetmed.auburn.edu> 9/10/2004 11:12:07 AM >>>
Rocky,

The same could be said for catching me thinking. I have a slight concern about Dr. Glickman's lack of bias since he does work periodically ofr FDAH. Keep that to yourself but I have look for unbiased input. He has spoken with Elizabeth and she is good with him and I trust her intuition. I have also heard
that Tori Hampshire might have been on a mission with some type of ax to grind or a vendetta to carry out. Any thoughts on that? I don't think the prevailing attitude at FDA-CVM is as negative at was esposed at the meeting towards veterinarians inputs or motives. I will leave Elizabeth to contact Larry if we need to further. I, hopefully, will get back in Auburn tomorrow with the FDA and FDAH presentations waiting for me. Thanks, look forward to any rumors you have heard about personal vendettas by the FDA representative.

Gatz

M. Gatz Riddell, Jr.
147 McAdory Hall
Auburn University, AL 36849
TEL: 334-844-6705
FAX: 334-844-6715
riddemg@vetmed.auburn.edu

ATTACHMENT 14

From: Tom Corcoran
To: Wallace, Craig
Date: Fri, Sep 10, 2004 9:00 AM
Subject: Fwd: Re: today's phone converstation

Craig, Brent, is there anyway we can get wide dissemination of this from Larry? Assuming he would agree.

Tom

>>> Craig Wallace 9/9/2004 10:00:47 PM >>>
FYI

>>> "Larry Glickman" <ltg@purdue.edu> 9/9/2004 5:06:43 PM >>>
Elizabeth,

Good speaking with you. After we spoke my wife who was also at the fda-fdah meeting because she has been doing the data analyis, reminded me of another comment made by Victoria Hamphire. When Victoria was asked "Don't you have a concern that the vast majority of Proheart 6 reactions were reported to you by pet owners and very few by veterinarians? she responded and I quote as best I can from memory "We do not trust veterinarians to report Proheart 6 associated reactions to fda. Veterinarians know that owners cannot buy Proheart 6 over the internet and thus they want to protect their income by not reporting any adverse events".

Another thing to give you a flavor for the meeting. However, this one is particularly important because it reflects a deliberate attempt by Victoria to exclude veterinarians in the decision making process.

Larry

---- Original Message ----
From: "Dr. Elizabeth Curry-Galvin" <EGalvin@avma.org>
To: "Larry Glickman (E-mail)" <ltg@vet.purdue.edu>
Sent: Thursday, September 09, 2004 1:48 PM
Subject: got a busy signal in the 1:30 to nearly 2pm zone

> Hope to call between 3-4
>
> Elizabeth Curry-Galvin, DVM
> Assistant Director, Scientific Activities
> American Veterinary Medical Association
> 1931 N. Meacham Road, Suite 100
> Schaumburg, IL 60173-4360
> Phone 847-925-8070, extension 6633
> Fax 847-925-9329
> E-mail Egalvin@avma.org
>
>
> AVMA Convention 2005...held concurrently with the World Veterinary Congress!

> Minneapolis, MN
> July 16-20
> www.avma.org
>
>
>

ATTACHMENT 15

Pamela B. Stuart
ATTORNEY AND COUNSELLOR AT LAW
The J. Raymond Stuart Building
1750 N Street, N.W.
Washington, D.C. 20036
Telephone: (202) 835-2200

TELECOPIER
202-835-2202
E-MAIL: pamstuart@aol.com
http://www.pamstuartlaw.com

MEMBER DC, FL, MD, NY, AND VA BARS

May 16, 2006

Senator Charles Grassley
Committee on Finance
United States Senate
219 Dirksen Senate Office Building
Washington D.C. 20510

Re: Request for Production to Lea-Ann Germinder and Germinder and Associates dated April 17, 2006

Dear Senator Grassley:

On behalf of Lea Ann Germinder, APR, and Germinder & Associates, Inc., Susan McGreevy and I are pleased to forward to you their response to your request for cooperation with the Committee's ongoing review of the relationship of the pharmaceutical industry with the Food and Drug Administration and specific allegations regarding Wyeth Pharmaceuticals and events surrounding the recall of the heartworm medication, ProHeart6. In response to the request, Mrs. Germinder has made available to me for review all of the records related to ProHeart6 presently in her care, custody and control at her offices in New York and Kansas City and her home in New Jersey. She has advised me that no documents related to ProHeart6 have been destroyed other than in connection with the departure of employees as is the normal practice of Germinder & Associates, Inc. It is the normal practice of the firm when an employee is terminated or departs for another job for that employee's emails to be deleted from the firm's computer system and for the employee's files to be purged of duplicate copies of documents already located elsewhere in the firm's files.

In accordance with the instructions provided in the April 17th letter, I have prepared the following narrative responses on behalf of Mrs. Germinder and Germinder & Associates, Inc. and have submitted documents responsive to your requests from the files of Germinder & Associates, Inc. in searchable pdf format on an accompanying CD-ROM. I have also provided an Excel spreadsheet which lists each of the documents by its document number so that the Committee staff may prepare an index to the documents we are providing in response to your request. Also, where appropriate, I have described what I have observed concerning the records

Pamela B. Stuart
ATTORNEY AND COUNSELLOR AT LAW

of Germinder & Associates, Inc. that may be helpful in deciding whether additional records may be needed by the Committee.

In addition, as we discussed, Mrs. Germinder is willing to make herself available for an interview with the Committee staff at a mutually agreeable time and date and would appreciate if the Government would absorb the cost of her travel to Washington in order to accomplish the business of the Committee

(1) State whether or not there has been any communication between Wyeth,or any Wyeth agent, and GAI regarding the Committee's review of allegations related to Wyeth, ProHeart 6, and/or Dr. Victoria Hampshire. If so, describe in detail the nature and subject matter of all communication(s) between Wyeth and GAI, including but not limited to the date, time, and person(s) involved in all communication(s). In particular, between November 17, 2005, and the date of this letter, state whether or not GAI played any role whatsoever in providing Wyeth with information and/or documents related to the Committee's review. If so, identify, describe in detail, and provide a copy of all such information and/or documents, including but not limited to business and personal email communication(s).

In discussions with the Committee staff on May 8, 2006, I promised that Mrs. Germinder would provide all documents available to her responsive to this request and a detailed summary of her recollection of any such communications.

On November 17, 2005, Mrs. Germinder was at an out of town business meeting and received an email from Meg Hutchinson, one of her employees, stating that Brett (sic) Standridge, Senior Vice President of Fort Dodge Animal Health ("FDAH"), a subsidiary of Wyeth Pharmaceuticals ("Wyeth") had called and needed to talk to her as soon as possible. Mrs. Germinder knew that Craig Wallace, Director of Marketing, her usual point of contact at FDAH, was on vacation and that Brent Standridge, his boss, was probably calling in place of Mr. Wallace. Mrs. Germinder returned the call to Mr. Standridge, who inquired, "Who is Tom O'Hare?" Mrs. Germinder replied that Mr. O'Hare was her brother. Mr. Standridge asked if Mr. O'Hare was a private investigator. Mrs. Germinder said, "No." The call ended and Mrs. Germinder emailed Ms. Hutchinson to reassure her that everything was fine and advise her that Mrs. Germinder had returned the call to Mr. Standridge.

Mr. Standridge subsequently called Mrs. Germinder back and stated that Senator Grassley had launched an investigation into accusations that Wyeth had hired a private investigator to investigate Victoria Hampshire for the purpose of having her removed from her

post. He told her that Mr. O'Hare was named on the Senate floor as a private investigator and that Mrs. Germinder could read Senator Grassley's letter on the internet. Mrs. Germinder told Mr. Standridge that even though Mr. O'Hare was not a private investigator that a researcher, one of the subcontractors to Germinder & Associates who worked on the ProHeart6 project, did have New York state credentials as a private investigator. Mrs. Germinder reminded Mr. Standridge that this aspect of the staffing of the project had been discussed with and approved by Fort Dodge before the research was done.

Shortly thereafter, Mrs. Germinder called Craig Wallace to advise him of the call. It appeared to her that he was unaware of the specifics of the Grassley inquiry from the Senate as he was on vacation. Mrs. Germinder had not seen the Grassley letter to Wyeth either. Mr. Wallace told Mrs. Germinder that Kelly Goss, an FDAH Communications employee, would be handling the FDAH media response to the Grassley letter.

On November 20, 2005, Mrs. Germinder, Lou Latorra of Latorra, Paul & McCann (a large advertising and public relations agency that is a competitor to Mrs. Germinder's firm and the public relations agency of record for ProHeart6), and Tom Nelson, president of the American Heartworm Society, received a copy of an internal FDAH memo via email from Craig Wallace. As an agency, Germinder & Associates, Inc. is bound by a confidentiality agreement with FDAH and would routinely receive such correspondence but was concerned about it going to Mr. Nelson. Mrs. Germinder expressed concern via email as to whether Mr. Nelson had a confidentiality agreement with FDAH.

Mrs. Germinder spoke to Mr. Wallace and other FDAH representatives about other FDAH business during the period following Wyeth's receipt of the Grassley letter. She was advised that Wyeth was cooperating with the inquiry. On December 22, 2005, Mrs. Germinder was informed by Brent Standridge that Wyeth had submitted a response to the letter from Senator Grassley and that Germinder & Associates, Inc. had been named in the response. She requested a copy of the response but was not given one.

In early 2006, Kelly Goss requested copies of signed estimates on the ProHeart6 matter. She said she was unsure who it was for but thought it was for the law firm representing Wyeth in Washington, D.C. Mrs. Germinder explained that she would require a written request and that she would prepare an estimate for her time and that of her accountant needed to comply with such a request. No further discussion took place and Mrs. Germinder did not supply signed estimates on the ProHeart6 matter to Ms. Goss.

There presently are no written policies regarding document retention at Germinder & Associates, Inc. Because of the volume of material processed, the agency's policy is to retain

known essential work product and delete nonessential work product, electronic records such as email communications of past employees and nonessential prior year documents. At year-end, non essential documents are deleted and/or archived as appropriate which makes immediate access to such documents difficult. For example, four employees who were employed at Germinder & Associates, Inc. at the time of the research related to Victoria Hampshire are no longer associated with the agency.

Emails responsive to Request no. 1 being submitted (GA-1-00001 through GA-1-00007) are:

11/17/05 Meg Hutchinson email to Lea-Ann Germinder advising Brett Standridge called and needs to talk to you ASAP

11/17/05 Lea-Ann Germinder email to Meg Hutchinson advising did talk with Brent Standridge; everything is fine.

11/17/05 Lea-Ann Germinder email to Meg Hutchinson identifying Brent Standridge.

11/18/05 Paula Norton email to Craig Wallace forwarding Grassley Response from K. Goss

11/20/05 Craig Wallace email to Tom Nelson, Lea-Ann Germinder, Latorra attaching Grassley response from K. Goss

11/21/05 Lea-Ann Germinder email to Craig Wallace asking whether he has confidentiality agreement with Tom Nelson.

(2) Describe in detail the business relationship between Wyeth and G&A, including but not limited to the percentage of G&A's revenue that is directly or indirectly attributable to Wyeth. Describe in detail the nature and substance of all business contracts and/or agreements between G&A and Wyeth between January 1, 2003 and the date of this letter.

In discussion with the Committee staff on May 8th, I agreed that we would initially provide information and documents concerning the projects or assignments given to Germinder & Associates, Inc. by Wyeth Pharmaceuticals or its subsidiary, Fort Dodge Animal Health, that involved ProHeart6 and/or the work of the Food and Drug Administration such as producing materials that later appeared on the FDA's website. Because of competitive and proprietary concerns, we agreed that the response would be general in nature but would affirm that

Germinder & Associates, Inc. derives a significant portion of its overall revenue from Wyeth and its subsidiaries.

Germinder & Associates, Inc. is a five person public relations agency owned by Lea-Ann Germinder, APR with sales in excess [redacted] annually. The firm provides a full range of services including strategic counsel, national product launches, corporate and crisis counsel, partnership programs, Internet communications and monitoring, media training, media relations and events. Mrs. Germinder was accredited in public relations by the Public Relations Society of America in 1992. She holds a Bachelor of Communications Arts from the University of Dayton. She is a past president of the Greater Kansas City Public Relations Society of America.

Mrs. Germinder began doing business with Fort Dodge Animal Health while working for Harmon Smith Advertising, Inc. Germinder & Associates, Inc. was established in 1998. The firm launched the website goodnewsforpets.com, a web-based PR services web site for the pet specialty and general media, at a Western Veterinary Conference with a virtual newsroom in 2000. The firm specializes in animal health and in business and not-for-profit partnerships. Its other affiliated web site is www.dvmvac.org. Both web sites accept sponsorships and post information from multiple sources.

The relationships in the niche industry of animal health are extremely complex and not well known to the general public. Fort Dodge Animal Health has utilized the services of Germinder & Associates, Inc. in a wide variety of projects since approximately 1998. Wyeth Animal Health has contracted for some projects with Germinder & Associates, Inc. since 2004. Germinder & Associates, Inc. has never had a general written contract with either of Wyeth's animal health divisions governing the relationship. Rather, Germinder & Associates, Inc. serves as an independent contractor and executes projects with Fort Dodge Animal Health according to signed estimates which set forth a scope of work as directed by the Vice President of Marketing, Craig Wallace. Within the constraints operating on a small agency, Germinder & Associates, Inc. observes standard agency practices and adheres to the Public Relations Society of America's Code of Ethics in its business dealings. Because Germinder & Associates, Inc. does not have any ongoing retainer agreement with Wyeth, it operates on assigned projects. For each project, Germinder & Associates, Inc. is told what the scope of work is to be and is asked to prepare an estimate of fees and expenses. Germinder & Associates, Inc. then submits those estimates to FDAH and Wyeth Animal Health ("WAH") and each company must have an appropriate representative sign off on the estimate before Germinder & Associates, Inc. may do the work and submit invoices for payment.

Due to the highly specialized nature of Germinder & Associates, Inc.'s business, its *pro bono* work, and its position as a leading public relations firm in the niche field of animal health,

there are a number of individuals and organizations influential in the field with whom both FDAH and Germinder & Associates, Inc. may have affiliations and communications at any given time both jointly and individually. However, for many projects, FDAH and/or WAH has relied upon Germinder & Associates, Inc.'s established contacts among veterinarians, state veterinary organizations, reporters, television outlets, associations influential in the animal health field and others to advance positions helpful to the companies.

A significant portion of the billings of Germinder & Associates, Inc. on an annual basis is attributable to Fort Dodge Animal Health and Wyeth Animal Health. I have reviewed an income statement prepared by Mrs. Germinder at the request of her attorneys for this project showing an income by customer for the period from January 1, 2003 through April 17, 2006. The total billings of the firm attributable to ProHeart6 over that period are [redacted] and virtually all of that income came during the period from mid-2004 through 2005. It is impossible to break out the cost of the assignment relating to Dr. Hampshire separately but it appears to me to have been less than [redacted].

I have divided the documentary response to this Request into two parts. The documents contained in this production responsive to Request no. 2 are those documents from the files of Germinder & Associates, Inc. that appeared to relate directly to the work of the Food and Drug Administration such as documents that showed actions by Germinder & Associates, Inc.'s monitoring or influencing activities of veterinarians, state veterinary societies, pet owners and others in response to the voluntary recall of ProHeart6 in September 2004 or the hearing held by an advisory panel on January 31, 2005. GA-2-00001 (at page 8 of 1545) to GA-2-00451 (at page 459 of 1545). The documents also include examples of Germinder & Associates, Inc.'s ongoing monitoring of internet sites known to be opposed to ProHeart6 that mention the FDA for purposes of advising FDAH on an appropriate response. Documents responsive to this request that show the type of assignments Germinder & Associates, Inc. carried out that involved ProHeart6 but do not specifically involve the work of the FDA were included in the response to Request no. 3.

(3) Identify all business contracts and/or agreements between GAI and Wyeth related to ProHeart 6, including but not limited to Wyeth's concerns about adverse events reporting and media coverage, and describe in detail the scope, terms and conditions of all GAI work. In complying with this request please include all invoices that GAI submitted to Wyeth for services performed from January 1, 2003-Present.

In discussion with your staff on May 8, 2006, we agreed that initially our response should be limited to all communications that set forth the scope of work on assignments from Wyeth

related to ProHeart 6, including but not limited to Wyeth's concerns about adverse events reporting and media coverage and will include logs, emails and invoices as well as a description of the scope of work if the actual communications with Wyeth are too cryptic to be understood. In a later refinement of this agreement, we agreed to provide all estimates relating to ProHeart 6 work, even if the estimates did not turn into actual assignments. This latter agreement may require us to supplement this document production at a later date.

As noted above in response to Request no. 2, Germinder & Associates, Inc. works with Wyeth on a project by project basis under signed estimates and scope of work defined by those estimates as directed by the Vice President of Marketing. There is no standard contract with terms and conditions defined by the parties. Germinder & Associates, Inc. also operates based on 26 years of agency experience under the guidelines of acceptable agency practices and the Public Relations Society of America Code of Ethics. Germinder & Associates, Inc. operates two websites that FDAH posts information on – www.goodnewsforpets.com and www.dvmvac.org. The websites operate under standard sponsorship agreements under which FDAH pays Germinder & Associates, Inc. a fee for the privilege of posting information on those websites. For the period from January 1, 2003 to April 17, 2006, Germinder & Associates, Inc. derived [redacted] related to ProHeart6 accounts from FDAH that specifically was allocated to goodnewsforpets.com but approximately [redacted] over that period in its Fort Dodge Animal Health Vaccine accounts was allocated for projects involved with the www.goodnewsforpets.com website, including [redacted] for sponsorship. Mrs.Germinder gave permission for the FDA newsletter editor to post information on ProHeart6 from goodnewsforpets.com.

Germinder & Associates, Inc. has been working with FDAH on ProHeart6 since 2003. The assignments have been extremely varied. For example, one project has involved FDAH's support of the American Heartworm Society which Germinder & Associates, Inc. helped establish. The Society derives its support from a variety of industry sponsors including competitors to Fort Dodge Animal Health. The marketing and communications sponsorship that FDAH has provided to the society via Germinder & Associates, Inc. since 2003 has been worth about [redacted] per year to Germinder & Associates, Inc. As the American Heartworm Society also is currently a separate client of Germinder & Associates, Inc., the files concerning this assignment are at Mrs. Germinder's home in New Jersey. Because I was unaware of their connection to ProHeart6, these files have not been reviewed. Should there be a second round of production and the Committee wishes to review these files, they will be provided.

Mrs. Germinder has been working with FDAH on a variety of different projects relating to ProHeart6 in addition to the American Heartworm Society. Beginning in 2004, Mrs. Germinder was asked to:

monitor on-line reports and discussions concerning ProHeart6 (Project 065 and 075)
assist in preparing and sending out mailings to influential people in the veterinary community (Project 066)
perform outreach to veterinarians on the subject (Projects 067 and 074)
conduct outreach efforts to pet owners concerning the recall of ProHeart6 (Project 068 and 072)
perform internet research concerning the recall of ProHeart6 (Project 069)
conduct a blog initiative (Project 073)

The Project numbers correspond to numbers contained on the estimates prepared by Germinder & Associates, Inc. for each assignment for FDAH. Thus, to trace the cost of a particular project, it is useful to look at the series of estimates and invoices for a particular project number. They may not give an accurate picture, however, because the client may have declined to proceed with a particular proposed project or estimate or may have changed the scope of work from time to time.

Much of the planning work by Germinder & Associates, Inc. with respect to ProHeart6 was started prior to the recall of ProHeart6 which occurred over the Labor Day weekend in September 2004. The first assignment with respect to the recall came immediately after the announcement of the voluntary recall of the product by FDAH on September 4, 2004. During the period from September 6, 2004 to October 5, 2004, Germinder & Associates, Inc. was asked to assist FDAH in outreach to the veterinary profession, limited outreach to media and pet owners, and continuing to monitor and provide online coverage of the reaction to the recall of ProHeart6 by FDAH. Information was exchanged daily between individuals at FDAH and Lea-Ann Germinder and her staff and at this time it is impossible to reconstruct each conversation and email for several reasons. First, the volume of back and forth conversation was too great to recall. Second, most of Mrs. Germinder's staff at the time is no longer employed by Germinder & Associates, Inc. and so their emails have been deleted from the firm's computer system as is the normal practice of the firm when an employee departs. Third, Mrs. Germinder left her laptop computer on an airplane in November 2004. She reported the loss to the airline and to airport security but the laptop was never recovered. It had a security lock on it, but all of her emails from that time were on that laptop and any back up copies of them that existed at that time were deleted when agency personnel departed and during an end of the year clean-up. As a result, she does not have complete records at this time of all contacts she had during that time period and she is relying on her best recollection to reconstruct exactly what contacts she had during that time period. The primary contacts at FDAH for Germinder & Associates, Inc. that time were Craig Wallace, Sean Pettit and Kelly Goss. During that time period, Germinder & Associates, Inc. assisted FDAH as directed in executing the outreach plan related to the recall of ProHeart6 which involved placing hundreds of calls to veterinarians, veterinary medical associations, key

contacts in the industry, and ongoing monitoring of websites maintained by activists who opposed ProHeart6 to ascertain their background so that FDAH could respond to them more effectively. During that period, Mrs. Germinder spoke with many, many individuals.

The documents I have assembled in response to Request no. 3 include a summary of all invoices on the ProHeart6 account, the estimates and invoices on the ProHeart6 account that were available in New Jersey and Kansas City and illustrations of the assignments that Germinder & Associates, Inc. performed for FDAH on the ProHeart6 account. It extends from GA-3-00001 at page 461 of 1545 to GA-3-00805 which appears on page 1265 of the total of 1545 pages produced. These were assembled by Mrs. Germinder and not reviewed by me due to time constraints. They include invoices for matters relating to the American Heartworm Society which is sponsored in part by FDAH. They also include summary documents showing invoice amounts.

(4) Identify all business contracts and/or agreements between GAI and Wyeth related in any way to Dr. Victoria Hampshire, including but not limited to researching, investigating, or purchasing information related to Dr. Hampshire, and describe in detail the scope, terms and conditions of all such work. In complying with this request, provide the Committee with the following information and documents:

a. Describe in detail the course of events that led to any such contract and /or agreement, including but not limited to identifying all communications between Wyeth and GAI, the persons involved, and the dates and times of all communications.

b. Describe in detail the actions taken by GAI, including but not limited to whether or not GAI subsidized, either directly or indirectly, an investigation of and/or research related to Dr. Hampshire.

c. Provide a copy of all communications, documents, and records related to Dr. Hampshire, including, but not limited to: (i) all Wyeth and GAI contracts and/or agreements; (ii) all communications between Wyeth and GAI, including but not limited to emails and contemporaneous notes from conversations; (iii) all internal GAI communications; (iv) all invoices and checks; and (v) all communications between GAI, all GAI agents, and/or any third party.

In my meeting with staff on May 8th, we agreed that the initial response would be limited to assignments from Wyeth or its subsidiaries, including Fort Dodge Animal Health, to Germinder and Associates, Inc. that involved the investigation of Dr. Victoria Hampshire's business outside the FDA, any assignments involving drugs that Dr. Hampshire was the medical reviewer for, and any assignments to Germinder and Associates, Inc. from Wyeth or its subsidiaries that mentioned Dr. Hampshire in the scope of work of the assignment.

At some point in 2004, Mrs. Germinder heard from FDAH that it was receiving reports of adverse drug reactions to ProHeart6 and was working closely with the FDA but that its scientists could not find a uniform cause for these reactions. Different people at FDAH told Mrs. Germinder that they felt that FDAH staff had researched every case brought to its attention and felt that many of the reports of adverse reactions were not attributable to ProHeart6 such as when the dog already had been injured before receiving the injection. However, others in the animal health community were informing Mrs. Germinder that information was appearing on the internet about ProHeart6 and she was looking for ways to address the issue by informing breeders and pet owners about the science of the product. After a discussion with Craig Wallace, Vice President for Marketing at FDAH, Mrs. Germinder was requested to look at methodologies to reach out to influential people in the non-veterinarian sectors of the community. FDAH felt that most of the negative information about ProHeart6 was coming from those who were not veterinarians who were not educated about the science behind the ProHeart6 product. The assignment given to Germinder & Associates, Inc. was to monitor the internet and organizations, meetings and publications to determine who was active in the ProHeart6 debate so that FDAH could implement a plan for reaching them and engaging them in a positive discussion about the product. The internet monitoring project was initiated in mid 2004.

Dr. Victoria Hampshire of the Food and Drug Administration was one of the speakers at a symposium sponsored by the American Heartworm Society in July 2004 attended by many influential individuals in the animal health industry. She presented a talk. Fort Dodge Animal Health was one of the sponsors of the symposium.

In August while Mrs. Germinder was traveling, her firm was asked to stop work on the project and provide the list of contacts that had been developed. She declined to do so as the list was proprietary and had not been completed. Shortly thereafter, over Labor Day weekend, she learned that the Food and Drug Administration had issued a press release announcing that FDAH had recalled ProHeart6 voluntarily. Mrs. Germinder had not been notified in advance by FDAH of the planned recall press release. She was on the highway enroute to moving her household to New Jersey when she learned about the recall from her employee, Catherine Couch, who had been assigned to monitor the PR Newswire. FDAH later confirmed to her that it had been working with other PR firms to advise it about the recall. She believes they were Porter Novelli

and Latorra, Paul & McCann.

During this period, Mrs. Germinder had a conversation with Craig Wallace at FDAH about Dr. Victoria Hampshire's statement about not trusting veterinarians to report adverse events as ProHeart6 was not available through internet pharmacies but only through veterinarians who injected it. Professor Larry Glickman had heard the statement and he repeated it to Mrs. Germinder because Craig Wallace wanted her to hear it directly from someone who had heard it from Dr. Hampshire.

Mrs. Germinder and Craig Wallace of FDAH spoke on the Sunday of Labor Day weekend 2004 about a communications outreach plan to respond to the recall. She was directed by Mr. Wallace to put the plan down on paper and she did so. She was co-directed by Mr. Wallace and Sean Pettit on activities that were part of the plan she had developed that included research and outreach. FDAH was also coordinating internally with other PR firms including Latorra, Paul & McCann but Mrs. Germinder does not know the specifics of what that firm was doing. Catherine Couch, Kimberly Gier, Kate Piotrowski and Lindsey Scott were the Germinder & Associates, Inc. employees who worked on the assignment. Kelly Goss, at FDAH, was handling the media relations with the Latorra firm (with some assistance from Germinder & Associates, Inc.).

Between September 6, 2004 and October 12, 2004, Germinder & Associates, Inc. engaged in an outreach campaign to veterinarians, veterinary medical associations and key contacts in the animal health community and members of Congress and others believed to have influence at FDA and to continue to monitor and provide online coverage of the recall. Information was exchanged daily by Germinder & Associates, Inc. with individuals at FDAH.

During that period of time (sometime between September 6, 2004 and October 12, 2004), Craig Wallace asked Mrs. Germinder to "google" Victoria Hampshire. She did that while she was on the phone with him and found a listing of a website called www.advancedvet.com from that google search. Mr. Wallace directed her to look at that listing which was for Advanced Veterinary Applications. She saw that it was promoting Heartguard, a competitor to ProHeart6. Mr. Wallace told Mrs. Germinder that they thought that the phone number listed on the website was Dr. Hampshire's home phone number but they were not sure. Mrs. Germinder turned the research assignment over to Catherine Couch of her staff and once they understood the site was live, attempted to "mystery shop" the site to understand how it worked by ordering product via three different pet owners. Dan O'Hare, one of the ProHeart6 subcontractors and her nephew, was asked to place an initial order for Bitter Apple, a spray that repels pets from furniture. Dr. Steve Levy, a veterinarian in Connecticut, was contacted to see if he could order Heartguard, from Advanced Veterinary Applications via the internet. Dan O'Hare placed an order over the

internet using the business name of XC Direct and used his father, Tom O'Hare's, credit card to do so. He was unable to order Heartguard but was able to order over $1000 worth of other products. Dr. Levy also was not successful in ordering Heartguard from Advanced Veterinary Applications. Another pet owner from Maine was enlisted to try to order product from the website and also was unsuccessful in ordering Heartguard from Advanced Veterinary Applications.

There was no separate estimate or scope of work for the request that this particular website believed to be associated with Dr. Hampshire be researched. It was handled as part of the ongoing internet monitoring assignment that Germinder & Associates, Inc. was handling for FDAH. FDAH did not request that any other FDA employee be researched in this way by Germinder & Associates, Inc.

Toward the end of the research project, Catherine Couch suggested that additional resources were needed. Mrs. Germinder became concerned that given the nature of the Internet that someone experienced in research should verify information available publicly over the internet. She wanted to make sure that this was done correctly and legally and contacted a researcher and longtime acquaintance, Donna Daiute, who also had credentials in New York State as a licensed private investigator. Ms. Daiute undertook the assignment as a researcher and was directed to use public records to validate the ownership of the web site. Germinder & Associates, Inc had a written contract with Donna Daiute which appears at pages 1289-90 (GA-4-00023).

The research project developed information that apparently Advanced Veterinary Applications purchased products from or had some relationship with an internet-based pharmacy called Vetcentric which had outlets in various cities including Annapolis, Maryland for resale through its website as persons who clicked on Advanced Veterinary Applications would also be directed to Vetcentric. The documentation obtained appeared to show that Dr. Hampshire did business from her residence address and possibly also another location in Bethesda, Maryland located near the National Institutes of Health which was advertised for rent in the Washington Blade.

Catherine Couch and Donna Daiute briefed Lea-Ann Germinder on the results of the research.. Mrs. Germinder in turn briefed Craig Wallace. She told Craig Wallace that the attempts to order Heartguard from Dr. Hampshire's website were unsuccessful but that the site was live and other products were ordered.. Mrs. Germinder and Mr. Wallace were in daily contact with respect to this and many other unrelated matters while the research was being conducted.

Pamela B. Stuart
ATTORNEY AND COUNSELLOR AT LAW

The documents gathered as a result of Germinder & Associates, Inc.'s research into Dr. Hampshire's internet site were provided to FDAH as part of a report to Fort Dodge Animal Health on October 12, 2006. The report covered the topics of the FDA response, Victoria Hampshire, Advanced Veterinary Applications (the website associated with her residence address), Vetcentric (a large internet pharmacy that sold veterinary prescription medicines and products over the internet), dogs adverse reactions, including websites, organizations, opponent veterinarians, pet owners, affiliate organizations, owners of websites promoting opposition to ProHeart6, and CAPS, a website (www.caps-web.org), including a release concerning a ProHeart6 lawsuit. All documentation in the report related directly or indirectly to Dr. Hampshire has been provided in response to this request. It is important to note, however, that the documentation relating to Dr. Hampshire was mostly her scholarly journal articles and constituted only about 25% of the volume of the outreach report. If Dr. Hampshire's scholarly articles had been omitted, the material concerning Dr. Hampshire would have been a very small fraction of the volume of the report. All of the information gathered about Dr. Hampshire came from publicly available sources.

The Germinder & Associates, Inc.' report drew no conclusions and made no recommendations concerning actions that FDAH might take concerning Dr. Hampshire. It merely turned the information it had gathered about Dr. Hampshire over to FDAH as had been requested by Mr. Wallace.

The documents that have been provided to the Committee in response to its request in connection with Request 4 include all documents that have any relation to the inquiry or research concerning Dr. Victoria Hampshire or anything in the files of Germinder & Associates, Inc. that mentions Dr. Hampshire. I have included at the end of the compilation of documents responsive to Request no. 4 a series of handwritten notes. Only one of them mentions "Tori Hampshire." I made the decision to include all of them in response to this request because Mrs. Germinder has no present recollection of any of these notes. The notes are in different handwriting. Some of them appear to relate to the campaign concerning the FDA but since one note mentions Dr. Hampshire, out of an abundance of caution I decided to include all of them as responsive to Request no. 4.

I have also included as responsive to Request no. 4 all checks written to Donna Daiute during this period even though her duties included monitoring the internet and not just the research involving Dr. Hampshire. She has continued to work as an independent contractor for Germinder & Associates, Inc. I have also included documents related to XC Direct, Dan O'Hare and Tom O'Hare which are also responsive to Requests no. 9 and 10. We also have provided the Estimate that covered this work although there was no specific Estimate that covered only this assignment or that mentions Dr. Hampshire.

Pamela B. Stuart
ATTORNEY AND COUNSELLOR AT LAW

(5) Provide a summary and total of all GAI invoices and Wyeth payments for costs and /or expenditures for GAI work related to:

a. Wyeth's concerns about adverse events reporting and media coverage related to ProHeart6; and/or

b. Researching, investigating, and/or purchasing information related to Dr. Hampshire.

In conversations with staff on May 8, 2006, I agreed that all available documents would be provided. They have been included in response to Request no. 3.

(6) Identify all individual(s) and/or agent(s) (including full name, title, and contact information) employed by and/or associated with GAI, either directly or indirectly, who were involved in any way with research and/or the investigation of Dr. Hampshire. In the event that any individual(s) and/or agent(s) is/are no longer associated with GAI, identify that individual(s) and/or agent(s) as well.

Lea-Ann Germinder
Donna Daiute (independent contractor) [redacted]
Catherine Couch (no longer employed) [redacted]
Kimberly Gier (no longer employed) [redacted]
Kate Piotrowski (no longer employed) [redacted]
Lindsey Scott intern no current address or phone
Tom O'Hare (identified below)
Dan O'Hare (identified below)

(7) Identify several proposed dates and times that Mrs. Germinder could be available in Washington, DC for an interview with Committee staff during the month of May 2006.

We agreed to defer picking a date for Mrs. Germinder's interview until after staff has had a chance to review the documents produced.

(8) Identify all business contracts, and/or agreements between GAI and Mr. Thomas "Tom" O'Hare (Mr. T O'Hare) of Copaigue, New York. Provide complete contact information for Mr. T O'Hare, including, but not limited to, a telephone number. Identify the relationship between GAI and Mr. T. O'Hare, including but not limited to any financial relationship, and/or describe in detail any information

known to GAI about Mr. T. O'Hare. State whether or not GAI is able to make Mr. T. O'Hare available for an interview. If so, identify several proposed dates and times that Mr. T. O'Hare could be available in Washington, DC for an interview with Committee staff during the month of June 2006.

In meeting with staff on May 8, 2006, I indicated my understanding that Mr. O'Hare was a relative of Mrs. Germinder and that there was no written contract between Germinder & Associates, Inc. and Tom O'Hare and that he is an independent contractor. I have since confirmed that Mr. O'Hare is Lea-Ann Germinder's brother and provides computer consulting services to her on an ad hoc basis for a fixed fee of $1500 per month as a "moonlighting" assignment in addition to his regular job. He may be contacted at [redacted]. His email address is [redacted]. His sole role in the research related to Dr. Hampshire was to give his credit card to his son, Dan, for use in ordering the product from the website. Tom O'Hare and Germinder & Associates do not have a written contract for his consulting services.

Because Tom O'Hare is an independent contractor and not directly affiliated with Germinder & Associates, Inc., the Committee staff should make its own arrangements directly with Mr. O'Hare for an interview if it deems an interview to be appropriate.

(9) Identify all business contracts, and/or agreements between GAI and Mr. Dan O'Hare (Mr. D. O'Hare). Provide complete contact information for Mr. D. O'Hare, including but not limited to a telephone number. Identify the relationship between GAI and Mr. D. O'Hare, including but not limited to any financial relationship, and/or describe in detail any information known to GAI about Mr. D. O'Hare. State whether or not GAI is able to make Mr. D. O'Hare available for an interview. If so, identify several proposed dates and times that Mr. O'Hare could be available in Washington, D.C. for an interview with Committee staff during the month of June 2006.

In discussions with Committee staff on May 8, 2006, I indicated my understanding that there was no written contract with Dan O'Hare who is Tom O'Hare's son. It turns out that I was in error in that respect and a copy of the written contract is being provided as part of the response to Request no. 4 in connection with the request for all documents related to the investigation of Dr. Hampshire. Mr. Dan O'Hare is Mrs. Germinder's nephew and is the principal of XC Direct. He is an independent contractor. He may be reached at [redacted].

Because Daniel O'Hare is an independent contractor and not directly affiliated with Germinder & Associates, Inc., the Committee staff should make its own arrangements directly with Mr. O'Hare for an interview if it deems an interview to be appropriate.

Pamela B. Stuart
ATTORNEY AND COUNSELLOR AT LAW

(10) Identify all business contracts and/or agreements between GAI and XCDirect. Provide complete contact information for XC Direct, including but not limited to a telephone number. Identify the relationship between GAI and XCDirect, including but not limited to any financial relationship.

In conversation with staff on May 8, 2006, I indicated that I believed that XC Direct was a "doing business as" type of name for Dan O'Hare and this belief was correct. The telephone number for Mr. Dan O'Hare is [redacted]. The financial relationship was between Daniel O'Hare and Germinder & Associates, Inc. which is being provided in response to Request no. 4.

Please let me know if I may answer any questions or be of further assistance.

Sincerely,

Pamela B. Stuart

Pamela B. Stuart

Counsel to Lea-Ann Germinder, APR
and Germinder & Associates, Inc.

cc: Mrs. Germinder
Susan McGreevy, Esq.

ATTACHMENT 16

Mail

Close

Previous Next

From: Craig Wallace
To: Brent Standridge
CC: Steve Connell; Rami Cobb
Date: 9/16/2004 7:17 AM
Subject: Fwd: FW: Tori Hampshire

We are monitoring websites for activity by Dr. Hampshire. Listed is the current body of info on her activities.

>>> "Lea-Ann Germinder" <lgerminder@germinder.com> 9/15/2004 3:10:23 PM >>>
Here is what Kimberly found specifically in searching for Tori
Hampshire. She clearly has an agenda and I don't see why these links
can't be pointed out to others as fair game for verifying her comments.
We will add her name to the list to search.

LG

lgerminder@germinder.com
Lea-Ann Germinder, APR
President
Germinder & Associates, Inc.
Correspondence:
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Office & Shipments:
6201 Brookside Blvd.
Kansas City, MO 64113
(816) 822-0192 Ph.
(816) 213-8238 Cell
(816) 822-0610 Fax

----Original Message----
From: Kimberly Gier [mailto:kimberlyg@germinder.com]
Sent: Wednesday, September 15, 2004 5:23 PM
To: 'Lea-Ann Germinder'
Subject: Tori Hampshire

Lea-Ann,

Here are the links to the information I found on Tori Hampshire:

http://www.avma.org/onlnews/javma/jan04/040115f.asp - This is the JAVMA article, where she talks about the majority of reports coming from

consumers who have found the FDA link on the Internet.

http://www.health-and-medical.com/veterinarian/veterinary_medicine/veterinary_medicine_msg25595/veterinary_medicine_msg25595.shtml - Dr. Hampshire discusses Rimadyl adverse reactions in the alt.pets.dogs.labrador newsgroup

http://bbs.sitstay.com/showflat.php?Cat=1,2,3,4,9 <http://bbs.sitstay.com/showflat.php?Cat=1,2,3,4,9&Board=health&Number=129953&page=0&view=collapsed&sb=5&o=&fpart> &Board=health&Number=129953&page=0&view=collapsed&sb=5&o=&fpart= - Sandra Jane Slayton (goldenmom) talks about her dog's story, including her correspondence with Dr. Hampshire.

http://www.thepetguardian.com/html/body_proheart_6_info.html - Dr. Hampshire is quoted on giving ProHeart6 to heartworm-positive dogs.

http://www.srdogs.com/Pages/proheart6.html - Dr. Hampshire's quote about heartworm-positive dogs is repeated here.

http://www.dogsadversereactions.com/newsletterSpecial.html - Gives "special thanks" to Dr. Hampshire for being "a vital part in the adverse drug surveillance on ProHeart 6"

http://www.i-dog.com/board/messages/46/73027.html?1089394035 - Jean Brudd talks about her correspondence with Dr. Hampshire.

http://64.233.179.104/search?q=cache:UWNSGVjvJoMJ:www.goldendogs-online.com/forum/forum_posts.asp%3FTID%3D2162%26PN%3D1%26TPN%3D1+victoria-hampshire <http://64.233.179.104/search?q=cache:UWNSGVjvJoMJ:www.goldendogs-online.com/forum/forum_posts.asp%3FTID%3D2162%26PN%3D1%26TPN%3D1+victoria-hampshire&hl=en> &hl=en - Sandra Jane Slayton (3 goldens) tells the story of her dog, including her correspondence with Dr. Hampshire.

There is nothing here that is really damning by itself, but she does have a tendency to show up wherever there are anti-Fort Dodge activists. I will print these references and courier them to Sean in the morning.

Kimberly Gier

Germinder & Associates

kimberlyg@germinder.com

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Kansas City, MO 64113

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ATTACHMENT 17

Mail

Close

Previous Next

From: Rami Cobb
To: Brent Standridge; Craig Wallace
CC: Steve Connell
Date: 9/16/2004 7:22 AM
Subject: Re: Fwd: FW: Tori Hampshire

Very Interesting, it all helps to point towards there being a personal agenda on her part.
Rami

>>> Craig Wallace 9/16/04 8:17:16 AM >>>
We are monitoring websites for activity by Dr. Hampshire. Listed is the current body of info on her activities.

>>> "Lea-Ann Germinder" < lgerminder@germinder.com > 9/15/2004 3:10:23 PM >>>
Here is what Kimberly found specifically in searching for Tori
Hampshire. She clearly has an agenda and I don't see why these links
can't be pointed out to others as fair game for verifying her comments.
We will add her name to the list to search.

LG

lgerminder@germinder.com
Lea-Ann Germinder, APR
President
Germinder & Associates, Inc.
Correspondence:
P.O. Box 22529
Office & Shipments:
6201 Brookside Blvd.
Kansas City, MO 64113
(816) 822-0192 Ph.
(816) 213-8238 Cell
(816) 822-0610 Fax

-----Original Message-----
From: Kimberly Gier [mailto:kimberlyg@germinder.com]
Sent: Wednesday, September 15, 2004 5:23 PM
To: 'Lea-Ann Germinder'
Subject: Tori Hampshire

Lea-Ann,

Here are the links to the information I found on Tori Hampshire:

http://www.avma.org/onlnews/javma/jan04/040115f.asp - This is the JAVMA article, where she talks about the majority of reports coming from

consumers who have found the FDA link on the Internet.

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http://bbs.sitstay.com/showflat.php?Cat=1,2,3,4,9 < http://bbs.sitstay.com/showflat.php?Cat=1,2,3,4,9&Board=health&Number=129953&page=0&view=collapsed&sb=5&o=&fpart> &Board=health&Number=129953&page=0&view=collapsed&sb=5&o=&fpart= - Sandra Jane Slayton (goldenmom) talks about her dog's story, including her correspondence with Dr. Hampshire.

http://www.thepetguardian.com/html/body_proheart_6_info.html - Dr. Hampshire is quoted on giving ProHeart6 to heartworm-positive dogs.

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http://www.i-dog.com/board/messages/46/73027.html?1089394035 - Jean Brudd talks about her correspondence with Dr. Hampshire.

http://64.233.179.104/search?q=cache:UWNSGVjvJoMJ:www.goldendogs-online.com/forum/forum_posts.asp%3FTID%3D2162%26PN%3D1%26TPN%3D1+victoria-hampshire < http://64.233.179.104/search?q=cache:UWNSGVjvJoMJ:www.goldendogs-online.com/forum/forum_posts.asp%3FTID%3D2162%26PN%3D1%26TPN%3D1+victoria-hampshire&hl=en> &hl=en - Sandra Jane Slayton (3 goldens) tells the story of her dog, including her correspondence with Dr. Hampshire.

There is nothing here that is really damning by itself, but she does have a tendency to show up wherever there are anti-Fort Dodge activists. I will print these references and courier them to Sean in the morning.

Kimberly Gier

Germinder & Associates

kimberlyg@germinder.com

Correspondence:

PO Box 22529

Office and Shipments:

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Kansas City, MO 64113

Ph. 816.822.0192

Fax 816.822.0610

Very Interesting, it all helps to point towards there being a personal agenda on her part.
Rami

>>> Craig Wallace 9/16/04 8:17:16 AM >>>
We are monitoring websites for activity by Dr. Hampshire. Listed is the current body of info on her activities.

>>> "Lea-Ann Germinder" < lgerminder@germinder.com > 9/15/2004 3:10:23 PM >>>
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LG

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Ph. 816.822.0192

Fax 816.822.0610

ATTACHMENT 18

Mail

Close

Previous Next

From: Brent Standridge
To: Craig Wallace
CC: Steve Connell; Rami Cobb
Date: 9/16/2004 9:38 AM
Subject: Re: Fwd: FW: Tori Hampshire

I had already hired an investigator to do the same. We can compare.
Brent

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Kansas City, MO 64113

Ph. 816.822.0192

Fax 816.822.0610

ATTACHMENT 19

October 1, 2004

Dan O'Hare
40 East Gate
Copiagne, NY 11726

This is to confirm the terms of your engagement as an independent contractor/consultant/freelancer to Germinder & Associates, Inc. (the "Company").

1) This arrangement will be effective October 1, 2004 until it is renegotiated. It is further understood that we both will have the right to terminate this agreement at any time if you are unable to perform the duties contracted for this engagement.

2)A) Your principal responsibility will be to perform as an independent contractor/agent any additional projects you are assigned. You will perform your services diligently and competently, as is appropriate to fulfill the objectives of your assignment as specified above. You will furnish the necessary tools, materials and the like to fulfill your assignment under this Agreement, and you will be responsible for the costs associated with your work, if any, including benefits and business expenses except those as agreed to be covered by Germinder & Associates as part of the project.

B) You will have no authority to order services or materials for the Company or bind the Company to pay for them without specific prior written permission by an authorized Company employee. Any such costs or commitments so incurred without such permission will be your sole responsibility, whether or not they are used or beneficial to the Company or the task described in section 2)A) above.

3)A) It is understood and agreed that your fees during the Term will be provided in a written estimate and covered by purchase order. It is agreed that you will be available to work as your schedule permits and we will advise you of projected work as soon as possible.

If your services will exceed this estimate, any services above the estimate must be approved in advance by Lea-Ann Germinder, President.

B) You will invoice the Company on a project basis. Our terms are net 30 days. This invoice should be submitted to Lea-Ann Germinder for payment approval.

C) Any normal and reasonable business expenses incurred by you in the Company's behalf will be reimbursed, providing those expenses have been approved in advance by Lea-Ann Germinder and are itemized on your invoice.

4)A) It is further understood and agreed that your engagement as an independent contractor/consultant/freelancer will not constitute you, or your employees, as employees of the Company for any purpose whatsoever, and that you will not be

entitled to the benefit of any employee plans or programs, including insurance, of the Company.

B) You agree that you and your employees will not act in any manner to discriminate against or harass any employees of the Company because of the employee's race, color, age, sex, national origin, ancestry, religion or disability, and you agree to indemnify the Company for any costs or liabilities arising from your or your employees' discriminatory or harassing acts.

C) You acknowledge that, as an independent contractor/consultant/freelancer, you will be responsible for the withholding and payment of all Federal, State and Local income taxes and Social Security taxes associated with the fees you receive and that you will hold the Company harmless against liability incurred with the respect to such taxes.

5) As an independent contractor/consultant /freelancer, you also agree that you will not, at any time (whether during the Term or after termination of this agreement), disclose any confidential information or trade secret of the Company or any client of the Company, or utilize such confidential information or trade secret for your own benefit or for the benefit of third parties, and all memoranda, notes, records, or other documents compiled by you or made available to you during the Term concerning the business of the Company and/or its clients shall be the property of the Company and shall be delivered to the Company on the termination of your engagement or at any other time upon request.

6) In entering this agreement, you hereby grant to the client all right, titles and interest in and the right to copyright materials conceived or first produced for the Company or its clients by you upon its production, and you agree that such copyrightable materials are works made for hire exclusively for the Company or its clients under the copyright laws of the United States. In the event that any such work shall not be a work made for hire under said copyright laws, you hereby assign to the client upon production all rights, titles and interests in such work and to execute whatever assignment of copyright and ancillary and confirmatory documents as may be required or appropriate to transfer exclusive title in such work to the copyright therein to the Company.

7)A) You are free to perform services for other persons both during and after your engagement with the Company. However, you agree not to render services to any persons during the Restricted Period (as hereinafter defined) to extent such services result from your use of specific knowledge of the Company's trade secrets or engagement with Company, in order to compete directly or indirectly with the Company without first securing permission of the Company. "Restricted Period" shall mean the period during which this agreement remains in effect and for (6 months) thereafter.

B) As used in this paragraph, the term "Company" shall mean the Company and its subsidiaries on affiliates and the term "Client" shall include (1) anyone who is a client of the Company at the time of the alleged prohibited conduct; (2) anyone who was a client at any time during the one year period immediately proceeding the date of the alleged prohibited conduct; and (3) any prospective clients to whom the Company had made a presentation during the Term of this agreement.

This agreement shall, of course, be terminated immediately by the Company in the event you become unable to perform your duties or breach its undertakings hereunder.

If the foregoing is satisfactory and reflects your understanding of our oral arrangement, please so indicate by signing and returning the enclosed copy of this agreement.

C) You agree that the Company shall be able to seek not only legal, but equitable remedies, to enforce its rights and protect its business interests under this section. You agree that a reasonable monetary remedy for your breach of this section, if such were to happen, would be an amount equal to 70% of the total gross revenues earned by you from any engagement or services which are in violation of this section.

Sincerely,

Germinder & Associates, Inc.
By: _____
Lea-Ann Germinder, President

Agreed and Accepted:

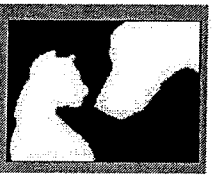
By: _____
Dan O'Hare

[redacted] SS#

ATTACHMENT 20

Durham Veterinary Hospital
Durham, Connecticut

The Friendly Practice for Your Pet



Home

Services

Veterinarians

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Publications

178 Parmelee Hill Road
Durham, Connecticut
06422

Hours by appointment:
Monday-Friday
8:00 AM-5:30 PM
Saturday
8:00 AM-Noon

Phone:
860-349-3485

Steven A. Levy, VMD - Professional Resume
Connecticut State Police Surgeon- K9 Unit EMD, Durham, CT

Durham Veterinary Hospital, PC
178 Parmelee Hill Road
Durham, CT 06422

Fax 860-349-8649
Phone: 860-349-3485

Work Experience

- **1979-present.** Durham Veterinary Hospital, Durham, CT
  Hospital Director, Clinical Veterinarian.
- **1990-present.** Fort Dodge Animal Health, Overland Park, KS
  Consultant- Canine Lyme disease.
- **2000-present.** IDEXX Laboratories, Westbrook, ME
  Consultant- Lyme disease diagnostics.

Education

- VMD 1977 University of Pennsylvania, School of Veterinary Medicine, Philadelphia, PA.
- Short Course in Medical Acarology 1990 The Ohio State University, Columbus, OH.

Professional Memberships

- 1977 to present. AVMA.
- 1977 to present. Connecticut VMA.
  - 1982-1991. Member CVMA Executive Board
  - 1991. President CVMA
- 1994-2001. President and founder American Veterinary Lyme Disease Society.
- 2004 to 2006. Connecticut VMA.
  - Member Board of Directors

Awards and Honors

- 1993 AVMA Practitioner Research Award.
- 1994 AAHA Region I Outstanding Practitioner Award.
- 1998 to present Connecticut State Police Surgeons Program: Canine Unit

Public and Emergency Service

- Fire fighter/EMT since 1972
  - Member Rhinecliff, NY FVD and Rescue Squad 1972 -1977
    - EMT 1972-1975
  - Member Guilford, CT Volunteer Fire Department 1977-1979
  - Member Durham Volunteer Fire Company 1980-present
    - Captain 1985-1989
    - Assistant Chief 1989-1992 and 1994
    - Chief of Department 1993 and 1995-2006
    - EMT 2002-present

Certifications (Partial List)

- EMT
- Fire Fighter I
- Incident Command System
- Hazardous Materials Operational
- Managing Company Tactical Operations I, II, and III.
- Various tactical, strategic and operation courses on building construction, vehicle fires and rescue, fire flow, safety, critical incident management and safety.
- 2006 Deputy Director of Emergency Management, Durham, CT
- 2006 to present- Director of Emergency Management and Chief of Operations, Durham, CT. (CT DEMHS Region #2).
- Connecticut State Police Surgeon- Canine Unit
  - Appointed to newly created position of CSP K-9 Unit Surgeon under the Administration of Henry Lee, PhD, Commissioner of Public Safety and Colonel John F. Bardelli, Commanding Officer of Connecticut State Police.

- Created a comprehensive health maintenance care program for up to 75 State Police Canine Teams in Patrol, Arson, Explosive and Narcotic Detection Units.

Publications (Selected listing) [1-17]

1. Elfassy, O.J., F.W. Goodman, S.A. Levy, et al., Efficacy of an amitraz-impregnated collar in preventing transmission of Borrelia burgdorferi by adult Ixodes scapularis to dogs. J Am Vet Med Assn, 2001. 219(2): p. 185-189.
2. Barthold, S.W. and L.K. Bockenstadt, Passive immunizing activity of sera from mice infected with Borrelia burgdorferi. Inf and Immun, 1993. 61(11): p. 4696-4702
3. Levy, S.A. and P.H. Duray, Complete heart block in a dog seropositive for Borrelia burgdorferi. Similarity to human Lyme carditis. J Vet Int Med, 1988. 2(3): p. 138-144.
4. Levy, S.A. and L.A. Magnarelli, Relationship between development of antibodies to Borrelia burgdorferi in dogs and the subsequent development of limb/joint borreliosis. J Am Vet Med Assn, 1992. 200(3): p. 344-347.
5. Levy, S.A. and D.W. Dreesen, Lyme borreliosis in dogs. Canine Practice, 1992. 17(2): p. 5-14.
6. Levy, S.A., S.W. Barthold, D.M. Domback, et al., Canine Lyme borreliosis. Comp Cont Ed, 1993. 15(6): p. 833-846.
7. Levy, S.A., B.A. Lissman, and C.M. Ficke, Performance of a Borrelia burgdorferi bacterin in borreliosis-endemic areas. J Am Vet Med Assn, 1993. 202(11): p. 1834-1838.
8. Levy, S.A., Why I vaccinate dogs against infection with Lyme disease. Comp Cont Ed, 1997: p. 1268-1275.
9. Levy, S.A., Borreliosis (Lyme Disease), in The Merck Veterinary Manual, S.E. Aiello, Editor. 1998, Merck & Co., Inc.: Whitehouse Station, NJ, USA.
10. Levy, S.A., Ticks and Tick Control, in The 5-Minute Veterinary Consultant, Canine and Feline, L.P. Tilley and J. Francis W. K. Smith, Editors. 2000, Lippincott Williams & Wilkins: Baltimore, MD 21201 USA.
11. Levy, S.A., Lyme Disease. Standards of Care, 2001. 3(9): p. 1-6.
12. Levy, S.A., T.P. O'Connor, J.L. Hanscom, et al., Utility of an In-office C ELISA Test Kit for the Determination of Infection Status of Dogs naturally Exposed to Borrelia burgdorferi. J Veter Thera, 2002. 3(No 3): p. 308-315.
13. Levy, S.A., Use of a C6 ELISA Test to Evaluate the Efficacy of a Whole-Cell bacterin for the Prevention of naturally Transmitted Canine Borrelia burgdorferi Infection. J Veter Thera, 2002. 3(4): p. 420-424.
14. Levy, S.A., Determination of infection status of dogs and cats naturally exposed to Ehrlichia equi in an area highly endemic for Borrelia burgdorferi. IX International Congress on Lyme Borreliosis. August 2002, New York, NY. Accepted for poster presentation., 2002.
15. Levy, S.A., T.P. O'Connor, J.L. Hanscom, et al., Evaluation of an in-office C6 test kit for Lyme disease in dogs as a tool for the determination of infection status of cats naturally exposed to Borrelia burgdorferi. Vet Therapeut, 2003.
16. Magnarelli, L.A., J.F. Anderson, H.R. Levine, et al., Tick parasitism and antibodies to Borrelia burgdorferi in cats. J Am Vet Med Assn, 1990. 197(1): p. 63-66.
17. Magnarelli, L.A., S.A. Levy, J.W. Ijdo, et al., Reactivity of dog sera to whole-cell or recombinant antigens of Borrelia burgdorferi by ELISA and immunoblot analysis. J Med Microbiol, 2001. 50: p. 889-895.
18. Levy, S. A., Clark, K. K., and Glickman, L. T. Infection rates in dogs vaccinated and not vaccinated with an OspA Borrelia burgdorferi vaccine a Lyme disease-endemic area of Connecticut. Intern J Appl Res Vet Med, 2005. 3(1): p. 1-5.

ATTACHMENT 21

Lea-Ann Germinder

From: Lea-Ann Germinder [lgerminder@germinder.com]
Sent: Monday, October 11, 2004 10:49 AM
Dan O'Hare (sales@xcdirect.com)
Subject: Save Shipping Info FW: Advanced Veterinary Applications order confirmation (#471922)
Importance: High

Dan,

To finish this job:

1. Please make sure you keep me apprised of the shipment and when it is received.
2. We may discover something from the shipping package, such as it is dropshipped. Email me who is it sent from as soon as you receive it.
3. Fedex to me the original box including all packing labels and materials.

Thanks, Lg

lgerminder@germinder.com
Lea-Ann Germinder, APR
President
Germinder & Associates, Inc.
Correspondence:
Box 22529
ce & Shipments:
6201 Brookside Blvd.
Kansas City, MO 64113
(816) 822-0192 Ph.
(816) 213-8238 Cell
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-----Original Message-----
From: Snake1Fire@aol.com [mailto:Snake1Fire@aol.com]
Sent: Sunday, October 10, 2004 6:00 PM
To: lgerminder@germinder.com
Subject: Fwd: Advanced Veterinary Applications order confirmation (#471922)

Here is the copy of the order I made through advancedvet.com

Thanks
Dan

-----Original Message-----
From: pharmacy@vetcentric.com [mailto:pharmacy@vetcentric.com]
Sent: Monday, October 11, 2004 8:56 PM
To: snake1fire@aol.com
Subject: Advanced Veterinary Applications Shipment Notification (#471922)

Dear Thomas OHare,

Your order from Advanced Veterinary Applications has been shipped via UPS Ground to:

Thomas OHare
40 East Gate
Copiague, NY 11726

For reference and tracking delivery of your purchase, please use the link(s) displayed below.

http://www.vetcentric.com/track.cfm?SM=1&tNo=1ZA975F10300476513

Please retain a copy of this email for your records. For prescription refill information and other questions regarding your purchase:

- Visit http://www.advancedvet.com
- Email our central pharmacy at pharmacy@vetcentric.com
- Call our central pharmacy toll-free at 1.866.VET.CENTRIC (838.2368)

The following item(s) are included in this shipment:

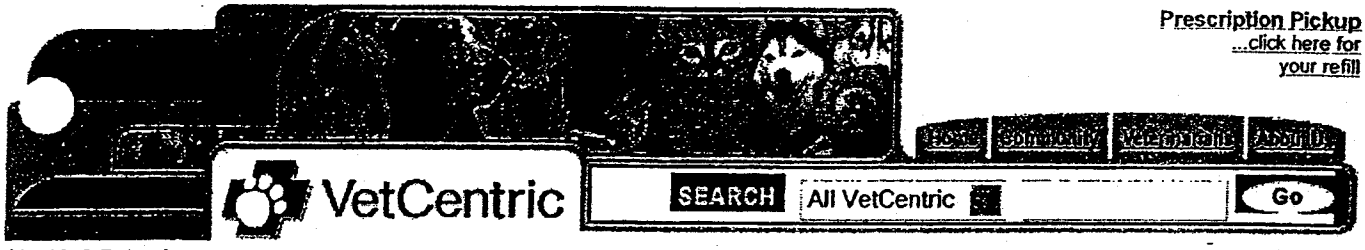
OTC	Bitter Apple F/Pets Spray, 8 oz Bottle	1	$6.08

Thank you for using the Prescription Management Services at Advanced Veterinary Applications provided by VetCentric.

Regards.

Dr. Unknown at Advanced Veterinary Applications

This is an auto-generated message that cannot accept incoming e-mail messages. Please do not reply to this message.



Prescription Pickup
...click here for your refill

Health & Behavior
Dogs
Cats
Horses
Birds
Fish
Ferrets
Rabbits
Pocket Pets
Reptiles, Etc.
On The Farm
Wildlife
About Our Pharmacy
...click here
Encyclopedia
Glossary
UserCentric
Register
Help
View This Month's Practice Profile
..click here

Looking For Your Prescription?

VetCentric has partnered with your veterinarian to provide you with convenient home delivery of prescription medications and therapeutic diets.

To refill your pet's prescription, please visit your veterinarian's web site or call us toll-free at: **1.866.VET.CENTRIC (838.2368)**

You can also enter your Rx number or telephone number below to be directed to your veterinarian's web site.

Rx Number:
or
Phone Number:

Find my Rx

How to find your Rx number
The Rx number can be found on the prescription label and on the packing slip.

This is Your Rx Number

FTDO 000048

Prescription Pickup
...click here for your refill

Health & Behavior
Dogs
Cats
Horses
Birds
Fish
Ferrets
Rabbits
Pocket Pets
Reptiles, Etc.
On The Farm
Wildlife
About Our Pharmacy
...click here
...es
Encyclopedia
Glossary
UserCentric
Register
Help
View This Month's Practice Profile
...click here

The VetCentric Veterinary PHARMACY

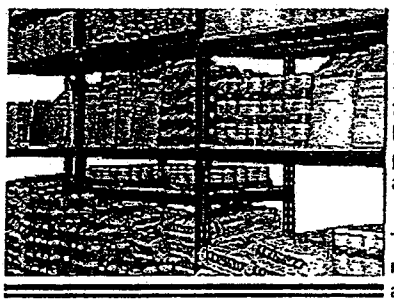
Did you know that VetCentric can deliver your pet's prescription medications, therapeutic diets, and even customized compounded medications directly to your door? Whether it's a monthly heartworm preventive like Merial's HEARTGARD® brand products or highly specialized medications like chemotherapy drugs, we're here to meet the needs of you, your pet, and your veterinarian.

And, because VetCentric supports and respects the client-patient-veterinarian relationship, our service is only available to you through your veterinarian.

Our headquarters in Annapolis, Md., are equipped with the most comprehensive veterinary pharmacy in America.

We've got state-of-the-art equipment to customize chemotherapy and ophthalmic drugs for the individual needs of your pet.

We've got the capabilities to produce medications in a transdermal form (perfect for those impossible-to-pill cats; the preparation comes in a gel that is rubbed directly into the skin.)

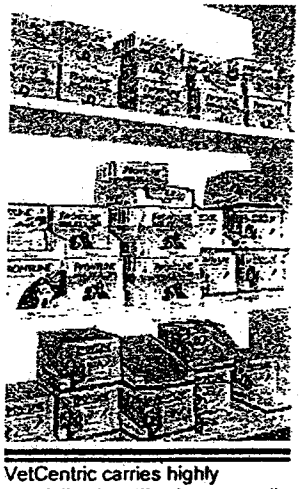


We can also compound drugs into more palatable liquid forms, available in all sorts of pet-preferred flavors, including chicken, bacon, and tuna. For exotic pets, we even offer apple and bubblegum.

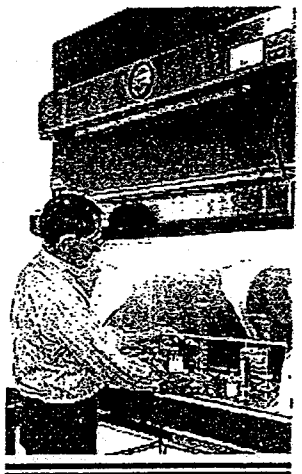
The VetCentric Pharmacy's mission is ensuring the accurate formulation and prompt delivery of your pet's prescriptions and veterinarian-recommended healthcare products.

If you have questions or concerns about your pet's prescriptions, our staff veterinarians and customer service team are available with the information you need.

We're proud to provide animals all across the United States with the benefits of modern veterinary medicine.



VetCentric carries highly specialized medications as well as the products you know best like HEARTGARD® brand products and FRONTLINE® flea and tick preventive from Merial.



State-of-the-art equipment like this Biological Safety Cabinet

ATTACHMENT 22

Order Number: 476780 **Order Date:** Oct 15 2004 5:13PM

Ship To:
Thomas OHare
40 E GATE
COPIAGUE, NY 11726-3214

Patient Information:

Purchased From:
Advanced Veterinary Applications
7307 Nevis road
Bethesda, MD 20817

Problems with your order? Please contact our customer support staff at: orders@vetcentric.com.

Rx Number	Product Name	Quantity	Price	Instructions
	3V Caps , 6 oz Pump Bottle	1 EA	$15.91	
	3V Caps M/L , 60 ct Bottle	1 EA	$11.70	
	Allerpet C F/Cats , 12 oz Bottle	1 EA	$9.05	
	Allerpet D F/Dogs , 12 oz Bottle	1 EA	$9.05	
	Alo Cetic Otic Soln, 12 oz Bottle	1 EA	$7.96	
	Cerumite , 15 ml	1 EA	$5.15	
	CET Chews Treat Lge , 16 oz	1 EA	$14.98	
	CET Chews Treat Med , 16 oz	1 EA	$14.98	
	CET Fingerbrush Kit Poultry , 44 gm	1 EA	$5.62	
	CET Forte Chews F/Cats Poultry , 24 Chews	1 EA	$11.54	
	CET Forte Petites F/Sm Dogs , 24 Chews	1 EA	$7.18	
	CET Toothpaste *Malt* Red , 70 gm	1 EA	$5.62	
	CET Toothpaste *Poultry* Grey , 70 gm	1 EA	$5.62	
	Chlorhexiderm 2 % Shampoo, 8 oz Bottle	1 EA	$8.42	
	Chlorhexiderm 2 % Shampoo, 12 oz Bottle	1 EA	$11.54	
	Comfort Geriatric , 100 Tab Bottle	1 EA	$17.78	
	Derm Caps 100 lb Dog , 60 ct Bottle	1 EA	$20.28	
	Derm Caps ES , 60 ct Bottle	1 EA	$15.13	
	Derm Caps Regular , 60 ct Bottle	1 EA	$10.92	
	Ear/Skin Cleanser , 4 oz Bottle	1 EA	$8.42	
	Ear/Skin Cleanser , 16 oz Bottle	1 EA	$20.44	
	Ear/Skin Cleanser , 16 oz Bottle	1 EA	$20.44	
	Epi Otic Otic Soln, 8 oz	1 EA	$11.54	
	Epi Soothe Oatmeal Cream Rinse, 8 oz	1 EA	$11.70	
	Epi Soothe Oatmeal Shampoo, 8 oz	1 EA	$7.64	
	Equalizer , 14 oz Spray	1 EA	$10.14	
	EtiDerm Shampoo, 16 oz	1 EA	$18.72	
	F O N Feline Spray, 8 oz	1 EA	$10.61	
	Feliway Natural Spray, 60 ml	1 EA	$25.12	
	Felovite II/Taurine Gel, 2.5 oz Tube	1 EA	$5.77	

Humilac , 8 oz	1 EA	$8.27
Hylyt Shampoo, 8 oz	1 EA	$7.49
Laxatone , 2.5 oz Tube	1 EA	$4.99
Laxatone Tuna , 2.5 oz Tube	1 EA	$4.99
Maxiguard *Cat*Dog* Oral Clean , 4 oz–Bottle	1 EA	$10.92
Maxiguard Oral Gel F/Pets , 4 oz–Bottle	1 EA	$12.48
Micro Vet Equine Traditional Powder, 6 lb Bucket	1 EA	$28.70
Nutri–Cal , 4.25 oz Tube	1 EA	$11.54
OFA Plus Ez–C W/Garlic 50–70Lb , 60 tbs	1 EA	$18.72
Oticalm Ear Clean Otic Soln, 4 oz Bottle	1 EA	$5.62
Otomite Plus , 0.5 oz Bottle	1 EA	$5.46
Pearlyt Shampoo, 12 oz Bottle	1 EA	$6.71
Pet Form Chew Tabs , 50 tbs Bottle	1 EA	$6.08
Pet Tabs Plus F/Dogs , 60 tbs Bottle	1 EA	$11.08
Preventic Collar	1 EA	$12.95
Protecta Pad Cream, 4 oz Jar	1 EA	$15.13
Prozyme Powder, 200 gm Tub	1 EA	$21.37
Relief Cream Rinse, 12 oz Bottle	1 EA	$19.66
Relief Shampoo, 8 oz Bottle	1 EA	$11.86
Select Antioxidant Dog/Cat , 60 tbs Bottle	1 EA	$26.36
Strongid C 2X Powder, 10 lb Pail	1 EA	$78.00
Strongid Paste, 20 ml Syringe	1 EA	$26.21
Synovi MSM Equine Granules, 720 gm Jar	1 EA	$54.60
Synovi MSM Granules, 720 gm Jar	1 EA	$54.60
Synovi MSM , 90 tbs Bottle	1 EA	$52.26
Synovicre , 720 gm Jar	1 EA	$59.59
Synovicre M/L , 90 tbs Bottle	1 EA	$57.10
T Lux Golden Formula Tar Shampoo, 8 oz Bottle	1 EA	$11.54
Virbac Knockout Fogger , 6 oz Bottle	1 EA	$6.40
Synovi MSM Tablets, 120 tbs Bottle	1 EA	$62.40
Nature's Miracle Stain/Odor Remover , 32 oz Bottle	1 EA	$12.17
Pet Tabs Tablets, Bottle of 500	1 EA	$56.50
Groom–Aid Spray, 7.3 oz Spray	1 EA	$10.14
EFA–Caps Capsules, 60 Cap Bottle	1 EA	$9.98
EFA–Caps HP Capsules, 60 Cap Bottle	1 EA	$13.10
OFA Plus Ez–C W/Gar 20lb , 60 tbs	1 EA	$18.72
Cat Lax , 2oz Tube	1 EA	$4.99

Subtotal: $1,197.65

Tax: $0.00

Shipping &Handling:	$0.00
Total Order:	$1,197.65

Mode of Transport: Free Next Day

For refills, please visit www.advancedvet.com or call 1.866.VET.CENTRIC (838.2368).

HEARTGARD® Brand Products help you provide the best protection for your pet against internal worms that may pose a serious threat to its health. Many of these worms can affect both pets and people. Fortunately, prevention is easy with HEARTGARD®. By giving your dog or cat HEARTGARD® once a month, you can prevent heartworm disease year round. With HEARTGARD® Plus, you can also protect your dog against roundworms and hookworms. Call us if you have questions regarding HEARTGARD brand products or if you are interested in convenient home delivery, through VetCentric, our home delivery pharmacy. HEARTGARD® is a registered trademark of Merial Ltd.

When it comes to fleas and ticks, there's no room for compromise. FRONTLINE® is the world's best selling flea and tick protection for dogs and cats. FRONTLINE® kills 100% of fleas on your pet within 18 hours and keeps working an entire month or more to keep your pet flea–free, according to Merial's research studies. Plus, additional Merial studies show that FRONTLINE® kills 100% of ticks on your pet within 48 hours, including those which may transmit dangerous diseases that may affect pets and people. Call us if you have questions regarding FRONTLINE® brand products or if you are interested in convenient home delivery, through VetCentric, our home delivery pharmacy. FRONTLINE® is a registered trademark of Merial Ltd.

ATTACHMENT 23

Dr. Steven A. Levy
Durham Veterinary Hospital, PC
178 Parmelee Hill Road
Durham, Connecticut 06422

LeaAnn –

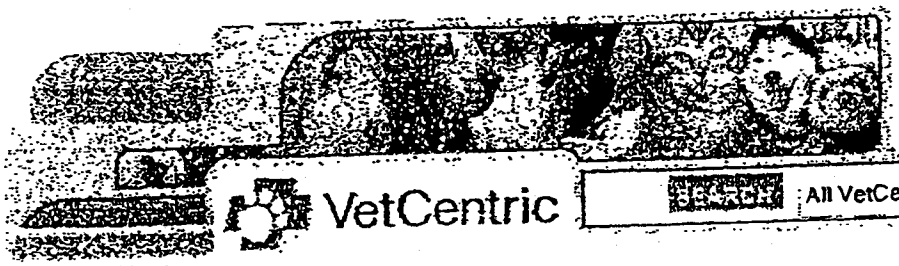
3 pages follow.

the starting point was your email.

Steve

1

Presc



Health & Behavior
Dogs
Cats
Horses
Birds
Fish
Ferrets
Rabbits
Pocket Pets
Reptiles, Etc.
On The Farm
Wildlife
About Our Pharmacy
...click here
Utilities
FAQs
Encyclopedia
Glossary
UserCentric
Register
Help
View This Month's Practice Profile
...click here

Looking For Your Prescription?

VetCentric has partnered with your veterinarian to provide you with convenient home delivery of prescription medications and therapeutic diets.

To refill your pet's prescription, please visit your veterinarian's web site or call us toll-free at: 1.866.VET.CENTRIC (838.2368)

You can also enter your Rx number or telephone number below to be directed to your veterinarian's web site.

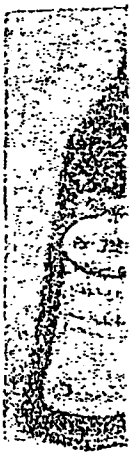
Rx Number: ___ ___ ___ ___

or

Phone Number: 860-669-9968

Find my Rx

How to find your Rx number
The Rx number is on the prescription packing slip.



This is Your

2

Presc

VetCentric

SEARCH All VetCentric

Home Community Veterinarian

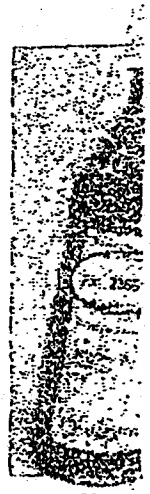
Health & Behavior
Dogs
Cats
Horses
Birds
Fish
Ferrets
Rabbits
Pocket Pets
Reptiles, Etc.
On The Farm
Wildlife
About Our Pharmacy
...click here
Utilities
FAQs
Encyclopedia
Glossary
UserCentric
Register
Help
View This Month's Practice Profile
...click here

Multiple practices are associated with phone number 860-669-9968.
You are listed as a client of more than one practice. Please select which hospital prescribed your prescription:

Advanced Veterinary Applications	Bethesda	MD	20817
The Durham Veterinary Hospital, PC	Durham	CT	06422

Back to Locate Rx

How to find yo
number
The Rx number
the prescription
packing slip.



This is Your

Advanced Veterinary Applications

LOGIN

STORE

WELCOME

ENCYCLOPEDIA

HOME

PRESCRIPTION HOME DELIVERY

Welcome to Advanced Veterinary Application's Prescription Management Service. We our clients home delivery of prescription medications and therapeutic diets.

If you are here to pick up a prescription, register your animals or view your medicine ca "**Login**". If you are interested in having home delivery of prescription medications and please contact us today.

If you are here to shop our online store, please click the "**Store**" link. In addition, we in through our reference encyclopedia of animal healthcare topics, ranging from behavior care to common and not-so-common diseases. Information about our practice and ser at **www.advancedveterinaryapplications.com**.

We're offering this Prescription Management Service because we are committed to pro with the latest and most effective care and services available. We welcome your comm suggestions, so let us know what you think during your next visit to our clinic!

-- The Staff at **Advanced Vete**

Phone: (301) 221-5086
Email: vetcare@msn.com

ATTACHMENT 24

10-18-04

Steve,

As I told you, I was unable to complete the purchase of Heartguard on-line, as there was some difficulty with account numbers. Specifically, when I attempted to log-in to Vetcentric with my Advanced Vet username and password, I received a message that this was invalid. When I attempted to register as a new user under this e-mail (or telephone number), I was told that the account already existed.

Vetcentric left a message on my answering machine noting that they had a prescription from you, and a request for a prescription through Advanced Vet, and asked for me to call to say how I would like to proceed.

I was able to return the call to Vetcentric (866-838-2368) today. They reiterated that I had a prescription from you and a request for a prescription through Advanced Vet. I told the sales representative that I wanted to go through Advanced Vet. She clarified, "You're saying that Advanced Vet is your veterinarian?" I said yes. She added, "And you want us to get a prescription from them?" Again, I said yes. She said that this would be accomplished and took a credit card number.

When I asked to confirm the price of the medication, she said that she did not have this, and offered to call me back once the prescription was obtained. I declined, noting that I felt I had wasted enough time on the Internet, already.

I hope all of this is helpful to you. They said that they would send the product in 5-7 days after they received the prescription which, she guessed, would be tomorrow or the next day. I'm not sure about identifying Advanced Vet as my vet, but this seemed the only way to proceed with the order.

Kelly

10-19-04

Steve –

The newest iteration. Vet Centric called tonight to say that they had your prescription. They had contacted Advanced Vet, they said, but had not received an answer. The representative (a new one, this time), advised me to go ahead and purchase based on your prescription, as they had no word from Advanced Vet. I asked them if they were affiliated with Advanced Vet. He said no, but characterized Advanced Vet as "registered" with them. I asked if the price was the same based on the prescription by you vs. Advanced Vet, and he said that the cost would be the same. It seemed odd not to place the order as requested, so I did so.

Kelly

ATTACHMENT 25

GERMINDER & ASSOCIATES INCORPORATED

October 12, 2004

Craig S. Wallace
Director, Companion Animal Business
Fort Dodge Animal Health
9225 Indian Creek Prkwy #400
Overland Park, KS 66210

Re: Negative Communications Campaign Against ProHeart6

Dear Craig:

Enclosed is the interim research status report as of 10/12/04 related to our public relations work for Fort Dodge Animal Health. This information is taken under advisement that we conducted this research in accordance with standard public relations research practices for background use only to determine the stakeholders who are conducting a negative communications campaign against ProHeart6.

We hope that understanding who these stakeholders are, what motivates them, the tactics they use, and the key messages they wish to convey will assist you in executing your business strategy regarding this matter.

The research began with reviewing FDA public outreach and a review of the spokesperson's outreach. We then looked at activists' outreach and news articles as the FDA had indicated Internet communications from the public combined with negative media coverage has been key to their decision-making process. Enclosed are the outreach reports primarily gained from online research. We will forward additional activity and phone research with a summary report as those are conducted.

Thank you for your consideration of these matters, and please feel free to contact me at any time to discuss. We all look forward to a positive outcome.

Best regards,

Lea-Ann Germinder, APR
President

Enclosure

P.O. Box 22529
Kansas City, MO 64113
Tel: 816.822.0192
Fax: 816.822.0610

102 Charlton Street
New York, NY 10014
Tel: 212.367.2170
Fax: 212.414.0538

ATTACHMENT 26

FORT DODGE®

Fort Dodge Animal Health ProHeart®6 Recall Interim Research Report

ProHeart®6
(moxidectin)

As of October 12, 2004
Presented to Fort Dodge Animal Health

"Victoria Hampshire" Homepage | Advanced Search

Search using: Google Ask Jeeves

WEB RESULTS (Showing Results 1 - 10 of 62)

1. **Hampshire** County Council
The exhibition uses copies of contemporary photographs, press reports, letters and posters to evoke the ways in which Queen Victoria's coronation and jubilees were celebrated in towns and villages around **Hampshire**.
www.hants.gov.uk/cxpuxn/c1546.html - June 25, 2004 - 5 KB

2. Unknown Restaurant
Find direct links to restaurant reviews all over the web, or write your own review of a restaurant. ... Canada/BC/**Victoria/Hampshire**_Grill_ Ltd1027422136 **Hampshire** Grill Ltd 2187 Oak Bay Ave # 118 **Victoria** BC V8R 1G1 Canada ...
chefmoz.org/cgi-bin/review.pl?ID=Canada%2FBC%2FVictoria%2FHampshire_Grill_L - August 26, 2004 - 3 KB

3. Shane Warne
Shane Warne. Test Debut: Australia v India at Sydney, 3rd Test, 1991/92. Major Teams: Australia, **Victoria, Hampshire**. Wisden Cricketer of the Year 1994. Selected as one of five Wisden Cricketers of...
mpce.com/warne.htm - September 30, 2003 - 4 KB

4. untitled
Register Now. (Form can be opened or downloaded.) Veterinarians and Technicians: Mark your calendars for July 23, 24 and 26, 2004! ... Claudio Genchi, University of Milan, Italy. Dr. **Victoria Hampshire**, Food and Drug Administration, USA ... Dr. **Victoria Hampshire** (Food and Drug Administration, CVM) ...
www.heartwormsociety.org/symposiuminfo.htm - July 15, 2004 - 21 KB

5. Deramaxx
... Event Reports as of mid-February 2003 according to **Victoria Hampshire** DVM, the coordinator of Adverse Event Reporting ...
www.cyberdobes.com/PDF/Deramaxx.pdf - April 12, 2004 - 38 KB

6. LUSC Adelaide Whites
Links to..Leeds UtdSquareballSingaporeVictoriaHampshire LUSC. Leeds United 0 v Stoke 0. 28/09/04. A frustrating game for us, as we threw everything at Stoke yet their defence held out to give them a...
www.geocities.com/leedsunitedadelaide/Adelwhites_homepage - September 28, 2004 - 17 KB

7. Furniture and Removals Specialists - Harrison & Rowley - Furniture >...
Harrison and Rowley, a furniture and removals company based in Bedfordshire .. ... available in six finishes. **Victoria, Hampshire,** Rosedale, Somerset, Riverdale and Lynmouth ... available in six finishes. **Victoria, Hampshire,** Rosedale, Somerset, Riverdale and Lynmouth ...
www.harrisonandrowley.co.uk/furniture/beds - August 1, 2004 - 17 KB

AGE1
OB

8. Untitled Document
... Very fast delivery. Perfect". - **Victoria, Hampshire**. "Excellent quality and fit ...
www.neddys.com/testimonial/testimonial.htm - January 28, 2004 - 4 KB

9. Press Releases
Hantsweb® is your comprehensive gateway to information on **Hampshire** - for residents and visit ... school site to be restored 2001/01/29 Queen **Victoria** & **Hampshire;**New exhibition at Records...
www.hants.gov.uk/cxpuxn/i5.html - September 22, 2004 - 163 KB

10. Shane Warne factbox
... Teams: Australia, **Victoria, Hampshire**. Test debut: v India, Sydney, 1991-92 ...

"Victoria Hampshire" Homepage | Advanced Search

Search using: HotBot Ask Jeeves

CUSTOM FEED FILTERS

WEB RESULTS by Google (Showing Results 1 - 10 of 114)

1. Alan David Mullally : England, Leicestershire, Western Australia ...
... Born, July 12, 1969. Major Teams, England, Leicestershire, Western Australia, **Victoria, Hampshire**. Known As, Alan Mullally. Batting Style, Right Hand Bat. ...
www.cricketzone.com/player/alan_david_mullally/ - 8 KB

2. Heavenly Bodies South East Escorts
... Watford escort Ms Jaguar Sittingbourne Dominatrix escort Chloe Northampton Escort service Sabrina Milton Keynes escort **Victoria Hampshire** Wiltshire Dorset ...
www.heavenlybodiesuk.com/southeastescorts.htm - 16 KB

3. Register Now
... 9:00-9:30 Evaluation of Efficacy of Heartworm Preventative Products at the FDA. Dr. **Victoria Hampshire** (Food and Drug Administration, CVM). ...
www.heartwormsociety.org/symposiuminfo.htm - 21 KB

4. Back to www
... **Victoria Hampshire**, VMD, the adverse drug events coordinator in CVM's Office of Surveillance and Compliance, recently wrote in an article for the Journal of ...
www.itsfortheanimals.com/CVM-FDA-HOW-IT-WORKS.HTM - 23 KB

5. Fleet NewsNet
... T: 01733 468340. E: lee.fisher@emap.com. **Victoria Hampshire** Account Manager. T: 01733 468554. E: **victoria.hampshire**@emap.com. Leanne Patterson Project Manager. ...
www.fleetnewsnet.co.uk/contact/index.asp - October 10, 2004 - 48 KB

6. Emerging issues regarding informed consent - January 15, 2004
... If you have comments or questions about this issue, contact Dr. **Victoria Hampshire** at (301) 827-0158, or VHampshi@CVM.FDA.GOV. —Dr ...
www.avma.org/onlnews/javma/jan04/040115f.asp - 18 KB

7. Understanding Deramaxx® Adverse Drug Events
... the drug. Below is an explanation of the data provided by **Victoria Hampshire**, VMD, the Adverse Event Coordinator of the CVM. In ...
home.insightbb.com/~e.murray/Stats/stats.html - 12 KB

8. Animals in Print - Action Alerts Number 07 - A Newsletter ...
... If you have comments or questions about this issue, contact Dr. **Victoria Hampshire** at (301) 827-0158, or VHampshi@CVM.FDA.GOV . ...
www.all-creatures.org/aip/alert-07.html - 12 KB

9. Emerging issues regarding informed consent
... sites. If you have comments or questions about this issue, contact Dr. **Victoria Hampshire** at (301) 827-0158, or VHampshi@CVM.FDA.GOV. ...
www.magdrl-nj.com/documents/InformedConsent.doc - 0 B

10. Nat'l Academies Press, Definition of Pain and Distress and ...
... of Iowa, Iowa City, Iowa. **Victoria Hampshire**, VMD, Advanced Veterinary Applications, Bethesda, Md. John E. Harkness, DVM, Laboratory ...
books.nap.edu/openbook/0309072913/html/113.html - 30 KB

"Victoria Hampshire"

Homepage | Advanced Search

Search using: HotBot Google

WEB RESULTS by (Showing Results 1 - 10 of 123)

1. Alan David Mullally : England, Leicestershire, Western Australia
Alan David Mullally : England, Leicestershire, Western Australia, **Victoria**, **Hampshire** : Cricket : CricketZone.Com...
www.cricketzone.com/player/alan_david_mullally/

2. ABC Sport - Cricket World Cup - An eventful career
Shane Keith Warne Shane Keith Warne Born 13 September 1969 Melbourne Teams Australia **Victoria Hampshire** Test debut v India Sydney 1991-92 107 matches...
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Investigator must follow proposal submission procedures indicated below. *Each individual listed below must initial and date indicating review.*

1. _____ Reviewed and approved by your ACUC Lab/Branch representative. You can obtain your ACUC Lab/Branch representative's name and phone number by contacting the ACUC Executive Secretary (see chart below.)

2. _____ Reviewed and approved by Occupational Safety and Health Consultant or Health Physicist if required. *Required for Recombinant DNA, Infectious Agents, Toxins and Radiation Safety.*

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4. _____ All sections are completed, signatures in Section O and forms under Section K are attached, and proposal is ready for submission to ACUC.

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List home telephone number only if investigators wish to be called there; if not, they agree to accept the judgment of the attending veterinarian in dealing with emergencies outside working hours.

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Not current, recording - Crystal Thomas

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Conditional deletion of the *Bcl-x* gene from erythroid cells results in hemolytic anemia and profound splenomegaly

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SUMMARY

Bcl-x is a member of the Bcl2 family and has been suggested to be important for the survival and maturation of various cell types including the erythroid lineage. To define the consequences of Bcl-x loss in erythroid cells and other adult tissues, we have generated mice conditionally deficient in the *Bcl-x* gene using the Cre-loxP recombination system. The temporal and spatial excision of the floxed *Bcl-x* locus was achieved by expressing the Cre recombinase gene under control of the MMTV-LTR. By the age of five weeks, Bcl-x conditional mutant mice exhibited hyperproliferation of megakaryocytes and a decline in the number of circulating platelets. Three-month-old animals suffered from severe hemolytic anemia, hyperplasia of immature erythroid cells and profound enlargement of the spleen. We demonstrate that Bcl-x is only required for the survival of erythroid cells at the end of maturation, which includes enucleated reticulocytes in circulation. The extensive proliferation of immature erythroid cells in the spleen and bone marrow might be the result of a fast turnover of late red blood cell precursors and accelerated erythropoiesis in response to tissue hypoxia. The increase in cell death of late erythroid cells is independent from the proapoptotic factor Bax, as demonstrated in conditional double mutant mice for Bcl-x and Bax. Mice conditionally deficient in Bcl-x permitted us for the first time to study the effects of Bcl-x deficiency on cell proliferation, maturation and survival under physiological conditions in an adult animal.

Key words: Bcl-x, Bax, Bcl2 family, Erythropoiesis, Hyperplasia, MMTV-LTR, Cre recombinase

INTRODUCTION

The production of mature erythroid cells from pluripotent hematopoietic stem cells requires the coordinated action of different cytokine signaling pathways to assure controlled cell proliferation, survival, differentiation and death. The homeostasis of erythroid cells is sustained by factors within these signaling cascades that affect the survival of progenitor cells and the turnover of mature red blood cells. Erythropoiesis occurs in distinct stages that are characterized by the site of erythroid cell origination, the expression of embryonic and adult globins, and the cytokines that trigger the developmental program. Primitive erythropoiesis begins around embryonic day 7 (E7) when nucleated red blood cells originate in the blood islands of the yolk sac. These cells express embryonic globins and are not dependent upon erythropoietin (EPO; Wu et al., 1995; Lin et al., 1996). EPO is the major cytokine for definitive and adult erythropoiesis. Definitive erythropoiesis starts at approximately day E10 when the site of red blood cell production shifts to the fetal liver and the erythrocytes express predominantly adult globins. At birth, erythroblastic islands in the bone marrow and the red pulp of the spleen become dominant sites of erythrocyte production.

Several genes have been shown to promote proliferation, differentiation and survival of erythroid cells. The GATA family of transcription factors and their transcriptional co-activators have emerged as key players for erythropoiesis (Pevny et al., 1991; Orkin, 1998). GATA1 is required for very early stages of red blood cell development (Weiss et al., 1994; Fujiwara et al., 1996), and GATA consensus motif target sites are found in the regulatory elements of genes expressed in erythroid cells including the EPO receptor. In contrast to GATA1, the ligand EPO, the EPO receptor (Wu et al., 1995; Lin et al., 1996) and its associated kinase JAK2

The On-Line Newsletter

Action Alerts

Join the compassion parade to help stop cruelty to our fellow beings. Your letters and calls do help!

Emerging Issues Regarding Informed Consent

Consumers calling hotline with concerns. The staff at the Food and Drug Administration's Center for Veterinary Medicine has conducted a two-year review of consumer messages to our adverse drug experience hotline. The review indicates increasing concern by consumers about risk and benefit of commonly prescribed, approved animal drugs.

The CVM established the hotline, (888) FDA-VETS, in 1996 to receive calls about adverse experiences to approved animal drugs. We expected many of these reports to come from practicing veterinarians, but our review indicates that a majority of the calls in the past few years have come from consumers, particularly dog owners who find our link on the Internet.

The CVM considers the drug label the first source of important facts for veterinarians. The label is the result of considerable scientific regulatory review before CVM approves the drug. It represents known safety and efficacy for any one drug. The label also gives veterinarians important information about whether the drug is suitable for the individual or subgroup within a species of animal. Additionally, whenever manufacturers distribute a client information sheet, this means that either the manufacturer or the CVM wishes to convey more facts about safety or efficacy in lay terms to pet owners.

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The staff at CVM monitors and evaluates adverse drug experience reports and complaints of inefficacy for approved and unapproved, marketed products. For approved products, this evaluation of postmarket safety and efficacy incorporates knowledge gained from the premarket studies as well as from scrutiny of peer-reviewed studies related to the drug, or the disease that the drug is intended to cure or prevent.

From the hotline, we have learned that pet owners increasingly rely on Internet sources for information when their pets have problems. They have told us that, during their Internet searches, they often find label information and client information sheets.

Frequent comments from pet owners who contact the CVM hotline include these:

They did not receive a client information sheet when one was available for a drug that was prescribed for their pet.

The medication they received from their veterinarian was not dispensed in the CVM-approved container but was broken into aliquots that were taken home without the client information sheet or approved label.

The veterinarian did not conduct or recommend blood testing before and after prescribing the drug, even though baseline testing and/or periodic monitoring was recommended on the label. Common examples include heartworm products and nonsteroidal, anti-inflammatory drugs.

After reading client information sheets and labels on the Internet about a drug prescribed for their pet, they discovered that their pet may have fallen into a category of animal for which a precaution or contraindication existed.

Given these findings, we have the following reminders for practitioners:

Drugs that come with client information sheets are intended to be dispensed in the manufacturer's container, with the sheets accompanying the prescription.

Product precautions, contraindications, safety information, and warnings should help identify animal patients that are not good candidates for the medication.

Labels change—if you have a large inventory of a product with a long shelf life, you may want to contact the manufacturer or CVM to obtain the most recent label. A long shelf life makes it likely that some of the product won't be dispensed in the near future. Often, this information is also posted on pharmaceutical companies' official Web sites.

If you have comments or questions about this issue, contact Dr. Victoria Hampshire at (301) 827-0158, or VHampshi@CVM.FDA.GOV .

—Dr. Victoria Hampshire, Adverse Drug Events Coordinator, Office of Surveillance and Compliance, FDA Center for Veterinary Medicine

| Home Page |
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| Action Alerts |

- [illegible]icity In Pets
- Alternative Vaccine
- Homeopathic Nosodes

Pet Vaccinations

Dangers

1. Puppies under three months of age should not be vaccinated.
Vaccinations are much more stressful on the underdeveloped immune system. Also, these vaccinations are much less effective at providing immunity before three months of age. If you feel you must vaccinate, do so with one vaccination of Distemper at three months, followed by a vaccination for Parvovirus at four months of age, and stop with that. If you can't find a single Distemper vaccine use the Distemper-measles combination.

Use killed vaccines ONLY.

2. Kittens should only be vaccinated for Panleukopenia and not before three months of age. All other vaccinations should be avoided. One vaccine is sufficient.

3. Puppies and kittens can be given homeopathic nosodes beginning at three weeks of age, if there is a potential for exposure to Distemper, Parvovirus or Panleukopenia These nosodes can be used until vaccinations are given or continued periodically for the first year of life, if vaccinations are not given.

4. Booster vaccinations are completely unnecessary. Studies are now showing that these vaccinations are effective for many years and most probably for life. Vaccinated animals do not need any boosters. Homeopathic nosodes can be given periodically if you are concerned or if you think your animals live a high risk, life style.

5. Rabies Vaccinations in the USA should be given as dictated by state laws. Lyssin, the homeopathic nosode, should be given within a few hours after the vaccination. Clearly, the rabies vaccination is effective for many years more than state laws require booster vaccination.

6. Booster vaccinations can cause SEVERE set-backs when an animal is being treated homeopathically for chronic problems. They can completely erase any progress that has been made towards improving an animal's health.

7. My personal recommendation is NOT to vaccinate at all.
The best road to good health is feeding a diet rich in fresh foods, raw meats for the carnivores, and avoiding vaccinations and allopathic medications. Antibiotics and other allopathic drugs should only be used in situations where their use is clearly indicated, and this should be only in potentially life-threatening situations. Every time you suppress a symptom the body produces, you are potentially lowering the health status of the body system **(destroy their immune system)** Treating with the correctly prescribed, homeopathic remedy, herbs, or other non-invasive therapies, not of a chemical nature, will enhance your health and your companions health.

8. Commercial diets should be carefully chosen.
Your companion is at the mercy of your good or poor judgment in selecting foods. Cats and dogs which have free access to the outside can to some degree supplement their diet. Otherwise, they are totally dependent on you. **Science diets and Hill's** dog and cat food products **are not good diets.** They use chemical preservatives that have been shown to cause problems in some animals, and they use by-products, which are words on the ingredient label that need to be avoided at all costs. This generally means food not utilized for human consumption. If you feed a carefully selected commercial food, some supplementation with fresh food is necessary to maximize your companions' health. Raw poultry, beef, lamb, or rabbit and occasionally liver should be added to the diet at least three times per week, and fresh vegetables in small amounts should also be offered.

9. The best diet is a RAW FOOD DIET and we have recipes.There are also many good books with recipes for raw diets.

Other Vets Comments on Routine Vaccines

VAFSTF
Vaccine Associated
Feline Sarcoma
Task Force

VET Info & Answers ! - Pet Vaccinations.

Yet, the majority of people really do believe that injecting your pet with a live virus of the disease really works. There is no proof, but if you hear something often enough, it becomes "true" whether it is or not. This is what has happened with vaccinations.

Have you ever asked your veterinarian or your pediatrician before they vaccinated your animal or your child for written medical proof the vaccines work?

The medical community has been brainwashed as well. They are told in medical school that vaccines work, and they take it on faith. Most veterinarians are sincerely interestedin the best care for their patients; however, because new concepts of vaccination are currently being taught in veterinary schools that just continues to perpetuate the veterinarian's belief in them. Western or allopathic medicine is always saying they have to have proof, double-blind studies, and yet, has your veterinarian ever shown you proof that vaccinations work?

Viera Scheibner, Phd, states, "I did not find it difficult to conclude that there is no evidence whatsoever that vaccines of any kind are effective in preventing the infectious diseases they are supposed to prevent. Further, adverse effects are amply documented and are far more significant to publish health than any adverse effects of infectious diseases.

"Immunizations not only did not prevent any infectious diseases, they caused more suffering and more deaths than has any other human activity in the entire history of medical intervention. It will be decades before the mopping-up after the disasters caused by childhood vaccination will be completed. "All vaccination should cease forthwith and all victims of their side-effects should be appropriately compensated.

What Is A Fibrosarcoma?

This odd sounding tumor originates from fibroblasts, the cells that make collagen, and has the potential to metastasize (or spread) to the lungs and other organs. This tumor is often found under the skin where Vaccines are administered, i.e. over the shoulder blades and around the hind legs. Fibrosarcomas have been members of the repertoire of mammalian tumors long before cat vaccines became standard practice. The recent explosion in vaccine technology, combined with better educated pet owners and a more health-conscious public in general, has resulted in regular vaccinations for a significant portion of the cat population. In 1991, the seemingly more-than-coincidental occurrence of tumors at vaccine sites prompted Dr. Mattie Hendrick, pathologist at the University of Pennsylvania Veterinary Teaching Hospital, to suggest a correlation, particularly in cases of fibrosarcomas in younger cats. Since 1991, Dr. Hendricks' questions have prompted the veterinary community to look into different types of vaccines offered by different manufacturers. To date, no single vaccine appears to be responsible for triggering fibrosarcoma. On the other hand multiple vaccines have been associated with these tumors, and the common denominator is the vaccine site. The fibrosarcoma question has become a complex, frustrating issue at the forefront of current veterinary discussion. In November 1996, a group of veterinary medical professionals from the American Veterinary Medical Association, the American Association Of Feline Practitioners and the Veterinary Cancer Society formed the Vaccine Associated Feline Sarcoma (VAFS) Task Force. This task force has three objectives:

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Define the extent of the problem. ** Determine the causes, age of onset and type of vaccines associated with feline fibrosarcomas.
** Educate and inform veterinarians about the findings of the task force. Meeting the last objective resulted in the creation of a standing committee to disseminate information to veterinarians as research uncovers answers about feline vaccine-associated fibrosarcomas and as new vaccines become available.

Who Gets It?

Currently, only an estimated one in 10,000 vaccinated cats develops fibrosarcoma. On the average, this cat is 8 years old, as compared to the 10-year-old cat that develops spontaneous, non-vaccine-

associated tumors. Breed or sex don't appear to influence or predict tumor development, either. In general, researchers have found that vaccine-associated tumors are less likely to metastasize than non-vaccine-associated tumors. The bad news is that the vaccine-triggered tumor is more resistant to treatment. Early diagnosis, then, is very important for a successful treatment outcome.

What Are The Symptoms?

In early tumor development, symptoms are easy to miss because most cats have few reactions to a vaccine. An astute owner may notice a small growth at the vaccine site, usually between the shoulder blades. In later stages, the swelling or growth is obvious. If untreated, this aggressive tumor can be painful and cause lethargy, lameness, weight loss or other clinical illness if it metastasizes to other organs.

Do Certain Vaccine Trigger Tumors?

We don't know for certain what changes a normal swelling following a vaccine into a malignant tumor. Retrospective studies suggest that the adjuvant (the vehicle in which the vaccine is suspended) is associated with fibrosarcoma formation. Certain vaccines produced for rabies and feline leukemia, as well as FVRCP (cat flu), are linked most often to fibrosarcomas and currently are being investigated. Veterinarians are becoming more cautious and meticulous in recording brand of vaccine, lot number and vaccination site so that the profession will be able to reach sound conclusions regarding brand, type of vaccine and routes of administration that are most harmful.

Alternative Vaccines

The biggest advantage of nosodes over vaccines is the fact that they are completely safe. There are no risks or side-effects whatever. And they can be safely given to puppies and kittens much earlier than vaccines can.In fact, the mother can be treated before she gives birth, giving the puppies or kittens protection from the moment they are born. Nosodes, like all homeopathic remedies, are very easy to administer: they are given by mouth, and don't even need to be swallowed. They are also very economical - far less expensive, in fact, than vaccination.

Limitations of Nosodes

There are some limitations to the use of nosodes. Rabies vaccination for dogs is required by law in most counties, (although not in Australia) and the rabies nosode, called Lyssin, will not satisfy that requirement. You should know, however, for the health of your animal, that all vaccines, including rabies are legally and medically approved for use in only very healthy animals! Many dogs and cats who have very abused or emotinally upset, are also at risk of not being able to cope with virus vaccinations.
So if your dog is showing any signs of acute or chronic disease, s/he is exempt from that requirement and should not be vaccinated.

Despite the obvious advantages of nosodes, most boarding kennels and veterinary hospitals will not accept them in lieu of vaccination. If you need to board your dog or cat in a boarding kennel or veterinary hospital, you may be forced to have him/her vaccinated. This is a problem that will hopefully improve with time as more kennel owners and veterinarians become familiar with nosodes.

If you have had your pets vaccinated with the live virus's ....Your vet should ask you to report any unusual development or adverse reaction following vaccination. Veterinarians have been asked to follow the task force's vaccine administration procedures and to report adverse reactions to vaccines to aid this group's investigations. It's difficult to draw conclusions about the relationship between vaccine sites and types when there's such disparity among practitioners in how often and where they give shots. If everyone uses similar techniques and timetables, the task force will be better able to track adverse reactions and draw conclusions about them.

Finally, your vet should encourage you to make a thorough inspection of your cat's body each week, especially around vaccine sites. Small lumps or bumps should be checked out as so possible because early diagnosis is usually related to a better prognosis for a complete cure.

Note: Please refer to your Holistic Animal Therapist for Homeopathic Oral Vaccines

- Never vaccinatean animal with symptoms of acute or chronic health problems, or at the time of surgery or any other physical or emotional stress.
- Vaccinate for one disease at a time that is, avoid multivalent (combination) vaccines. For cats, vaccinate for feline panleukopenia alone. The vaccines for the two upper

respiratory viruses (calicivirus and rhinotracheitis) can be given together. I strongly recommend against vaccination for feline leukemia or feline infectious peritonitis virus. The vaccine is ineffective, and in my opinion, extremely hazardous. For dogs, give parvo separately from distemper. Do not vaccinate for leptospirosis, hepatitis, or parainfluenza. Never give the rabies vaccine at the same time as any other vaccine.

- Avoid modified live virus vaccines whenever possible. Get killed virus vaccines, especially for rabies, canine parvo virus, and feline panleukopenia. (The canine distemper/hepatitis vaccine is not available in a killed virus form).
- For middle ages dogs and cats, vaccinate every 5 years, instead of yearly.
- After vaccination, give a dose of Thuja 30c. Wait one week, then give a dose of Sulfur 6x once daily for 7 days.

Therapeutic Use of Nosodes

In addition to helping prevent specific viral diseases with prophylactic use, nosodes can be used even after exposure to a virus has taken place. If given immediately after exposure, before symptoms develop, these nosodes can prevent the development of clinical disease.

Viral diseases such a feline leukemia, feline infectious peritonitis, canine distemper and canine parvo virus are usually incurable with conventional medical treatment (antibiotics, steroids, etc)

However, they frequently respond very quickly and favorably to homeopathic treatment and Vitamin C (soduim ascorbate acid powder or injectable).

If your pet shows any symptoms of illness, specific, individualized homeopathic treatment will be needed as well as injectable Vit C 3 x daily while in clinic. Due to the potential seriousness of these conditions, you should seek professional help immediately.

Equine / Canine / Feline - IMMUNIZATION NOSODES

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PEOPLE DOING SCIENCE

Ruth Levy Guyer, Ph.D.

VETERINARIAN

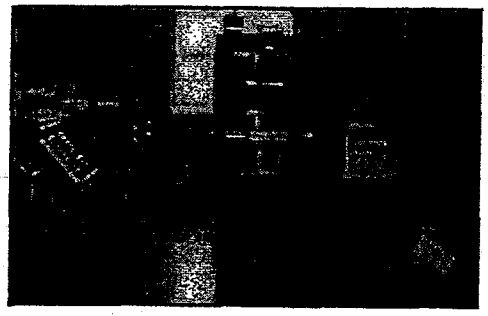
At the clinic, every patient has a chart. The chart includes all the crucial information--when the surgery or other procedure was performed, exactly what was done, what follow-up medical procedures should now be carried out, what exercise routine is appropriate, and what foods the patient should eat and avoid. Some charts include electrocardiogram printouts, which, for some strange historical reason, are called EKGs. Most have records of the patient's blood chemistry and cell counts. All include a billing record. Many charts say "house with a companion."

House with a companion?

These are the charts of Dr. Victoria Hampshire's patients -- sheep, goats, dogs, cats, rabbits, pigs, mice, rats, and ground squirrels. In Hampshire's animal facility at the NIH, the routine is for most animals to live with a buddy or in a larger group. Hampshire finds that the animals are happier that way. And, in times of special stress, such as when a dog is recovering from surgery, Hampshire finds that another animal, specifically a cat companion, is often the best medicine.

Hampshire is a veterinarian at the NIH. She works mostly with large animals. Her charges range from animals who are normal blood donors to those participating in high-risk studies.

[illegible]t thing each morning, technicians at the clinic and another veterinarian visit all the animals who have had s[illegible]gery and assess the status of each. They make decisions about which animals need medical attention and which ones need it fastest. This process is called "triage," the French word for "sorting," a word that came from the battlefield where doctors would evaluate soldiers to figure out which ones had the most severe wounds and needed care most urgently.



When the line-up is set, Hampshire goes on rounds, examining the animals. On any one day, there will be some who are really sick, others who are recovering from consequences of the experiment tha they are participating in, and some who have incidental illnesses or injuries. Hampshire may have to operate on a few, repair surgical stitches on some that were operated on the previous day, and start intravenous fluids for those that have become dehydrated. If animals have been fighting, she will sew up the bite wounds.

By midmorning on most days, all the emergency and basic health needs of the animals are taken care of, and the research activities can begin. In Hampshire's clinic, the protocols are wide-ranging, from brain scans on cats to artificial heart valve research in sheep to day-long medicinal drug tests in several species.

"Pigs are," says Hampshire, "next to humans, the best animals for physiological studies. They can be 'chronically instrumented' with a tube, called an indwelling [illegible]heter, that is connected to a blood vessel. Like patients who are receiving [illegible]motherapy, their blood can be sampled and they can receive medicines through the catheter." A valve that works like a two-way spigot on a sink is attached to the catheter, so that repeated injections and measurements can be made without causing

discomfort to the animal. The animals wear spandex sweaters that hold the tubing in place. "Pigs are not stupid," [illegible]s Hampshire, "they are just tolerant of the instruments."

"The pigs are happy when their comfort needs are met," she says, "and their progress is tremendous when they trust the people working with them." They enjoy food, attention, and toys and like to pile up next to each other in the pen. Most days, staff members play with them, and the pigs pick treats from the treat cart. Hampshire says that the pigs like the company of humans better than they like being with other animals. As we talked, a pig passed by the office on a stroll with a technician.

All animals at NIH are bred on the site or are purchased from "class A vendors," which breed and sell animals for research. The smallest pigs in Hampshire's facility are Minnie, Moe and Max, three black, hairy siblings who were born in December. These "mini-pigs" are hybrids of a Vietnamese Potbelly pig and a Yucatan pig. Hampshire has spent the past two years trying to develop "transgenic" offspring in this breed. If the experiment works, the transgenic pigs will carry the human globin gene and produce its protein product, globin.

Interest in putting new genes -- transgenes -- into animals is high right now, and scientists are taking many different approaches. Another, besides breeding, is to put genes into skin cells and graft the cells onto the animal's back. Pigs, especially the pink ones, are good for these studies, because their skin is very similar to human skin, and skin grafts can be seen easily and watched closely.

[illegible]e of the dogs in Hampshire's clinic are participants in studies of drugs that make blood vessels grow. The issue here is whether the drugs can force new vessels to form at specific locations. If this works in the dogs, it may be a reasonable option for people who need heart bypass surgery but are too sick to survive such an operation.

Other dogs, those in a septic shock study, are considered at "high risk." They need added attention, because the experiments that they are part of can be fatal. Septic shock is a condition that often develops in hospitalized patients as a complication of cancer, diabetes, and a number of other diseases. It kills some 200,000 people in the United States each year and, therefore, is a major problem.

At the opposite end of the risk spectrum is Buster, a dog who came to Hampshire's clinic four years ago to participate in a heart study. During the pre-experiment physical, the doctors found that Buster had a heart murmur that disqualified him from the experiment. He has been a normal blood donor ever since and is comfortable hanging around the clinic offices.

In all experiments that may cause pain to an animal, Hampshire looks for the best approach for lessening or eliminating the pain. She says she is guided by the principle that "if it is painful to a human, it is probably painful to an animal. If we waited for animals to cry before giving them pain relievers," says Hampshire, "we would be underdosing them." When animals cry, their heart rate and blood pressure go up, and they bleed more than usual. These problems can be avoided by early [illegible]eatment with pain killers. Hampshire has found that marcaine and related pain killers (whose names all end in [illegible]ine") are effective drugs in many experiments. She typically starts the drugs well ahead of time, so that the a[illegible]als will not have to experience unnecessary pain.

[illegible]ry experiment that involves animals is classified for its pain category, and these range from "column C" [illegible]periments to experiments in "column E." The animals in column C experiments are expected to experience no pain or minimal pain. Those in column D experiments may experience pain but can be given standard pain relievers, called analgesics. In column E experiments, pain and suffering may be severe, but the animals cannot be given analgesics, because the drugs would mask the purposes of the experiments. Hampshire says that sometimes, through the use of local "blocks," she can "take an animal out of a category," moving it backward up the scale to a category that allows for less pain. She says that acupuncture is another option that she has been considering, because acupuncture is a proven pain reliever for show horses who suffer from back and leg pains. In addition to assessing subjective indicators of discomfort and pain, she measures various serum compounds -- cortisol, prostaglandins, and cytokines -- that are released during pain reactions. These objective measures are adding to her understanding of the animals' pain responses and what can be done to alleviate their suffering.

Hampshire spends most afternoons reviewing proposals by researchers for upcoming experiments. A nine-member committee including veterinarians, scientists, people from the community, safety officers (if radiation is involved), and others evaluates all experiments with animals. With each proposal Hampshire considers whether she "can support it, if it's humane. If not, I indicate what changes need to be made." She helps researchers rethink the designs of their experiments and write appropriate protocols.

Hampshire is constantly "challenging the status quo," looking for ways to enrich the lives of the animals under her care. Years ago, research animals lived in pristine, even sterile, environments, but now "we rely on really good animal husbandry (careful and caring management)" instead. Says Hampshire: "We don't sterilize the hay, but we do look for and remove moldy hay. We stuff the animals' cages full of straw, and, when we began doing this, we stopped seeing animals with sore feet and breeding problems."

"Rabbits in experiments will sometimes go off their feed," says Hampshire. So she began giving the rabbits fresh kale and parsley and dried oatmeal instead of rabbit pellets. By enriching the rabbits' diets in these ways, she says, "we have seen tremendous improvement in stress-related problems."

Hampshire is concerned about the medical and the emotional well-being of the animals under her care and also about the emotional needs of her staff. She says it is a "research risk" when people are upset at work and that it is not easy for people to work with animals that are sick or in pain. All staff members have opportunities to make suggestions for improving conditions for the well-being of the animals. Recently, for example, technicians were disturbed because mice were receiving injections of antibiotics in a rather large volume of fluid. One suggested that, if the antibiotic were injected in half the volume, the mice would experience less stress. The change was made.

Hampshire's daily routine is actually far from "routine," and it got even less so in February and March, 1997, when she packed up 3000 rabies vaccines and traveled for three weeks on a public health mission in Alaska. The team included one other veterinarian and pediatricians, dentists, obstetricians, and other physicians. The plan was to fly in and out of ten remote villages in the Yukon delta; the military transport plane spent nights in an air force hangar and so did the team members, often sleeping on the hangar floor.

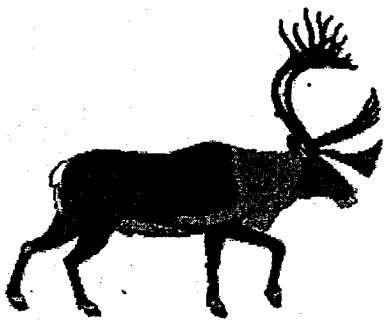
http://science-education.nih.gov/nihHTML/ose/snapshots/multimedia/pds/vet/vet.htm

Hampshire and the other veterinarian immunized 250 domestic dogs and cats against rabies. Rabies is brought to villages by Arctic foxes that come searching for food; they fight with and bite the local animals and, through bites, spread the disease. Hampshire did a radio show and also gave talks in classrooms about rabies prevention and the importance of reporting dog bites.

The trip did not go entirely as planned, in part because snow kept them in some villages longer than they expected and out of others. But the longer stays, says Hampshire, gave the doctors time to "learn of some significant public health problems that might have gone unnoticed."

With no running water and outside temperatures of minus 40, malnutrition and sickness were everywhere in the Yukon villages. Some villagers had giardiasis, a disease caused by the parasite giardia, which enters streams and rivers in the feces of beavers. The villagers get their water from these sources and then develop diarrhea, cramps, nausea and other symptoms of the disease.

Brucellosis, a bacterial disease that causes high fevers, aches, sweats and depression, also comes from contact with animals and is another problem in the villages. Caribou carry the bacteria, and the villagers get the disease either directly, when they slaughter caribou, or indirectly from dogs and wolves that feed on the caribou and then pass the bacteria along.



Another infectious disease that they found is leptospirosis, which is caused by spiral bacteria that normally live in rodents. The Eskimos have an old custom of harvesting and eating mouse food -- seeds and nuts mounded together with mouse saliva and urine. The symptoms of leptospirosis resemble those of alcoholism; because alcoholism is a problem among the Eskimos, the bacterial infection might sometimes be overlooked and thus go untreated.

Hampshire said that they saw dog feces in school yards and everywhere else in the villages. Few dogs passed the physical that was a prerequisite to other procedures -- like spaying and neutering -- that she had hoped to carry out in an effort to control the animal population and improve health conditions for the animals. The village children run around barefoot in the summertime and pick up infections from the feces; in the wintertime, "they simply get feces on their hands." The feces contain hookworms; the children develop larva migrans or "creeping eruption," an itchy skin rash and blisters that mark where the larvae have been moving through human skin.

These and other infections can often be treated, but they have to be recognized first. The team members will be developing a 5-year plan directed toward improving conditions in the villages for both the animals and their owners.

An animal clinic, whether a field station in Alaska or a clinic at the NIH, "is not the typical government workplace nor does it run on a typical government schedule, which is not always compatible with the care of animals," says Hampshire. "We sometimes need someone to stay with an animal all night. So we juggle schedules, and people make accommodations."

Staying with a sick animal all night is nothing new for Hampshire. She grew up on a farm, had her own horse, and, early on, learned to diagnose her horse's health problems. Lots of dogs were also on the scene, because her mother bred basset hounds. Now, when Hampshire goes home at night, it's the proverbial busman's holiday: in addition to her children and husband, she shares her home with two cats and two yellow Labradors.

http://science-education.nih.gov/nihHTML/ose/snapshots/multimedia/pds/vet/vet.htm

All photographs used in this story are courtesy of Dr. Tory Hampshire.

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January 15, 2004

Emerging issues regarding informed consent

Consumers calling hotline with concerns

The staff at the Food and Drug Administration's Center for Veterinary Medicine has conducted a two-year review of consumer messages to our adverse drug experience hotline. The review indicates increasing concern by consumers about risk and benefit of commonly prescribed, approved animal drugs.

The CVM established the hotline, (888) FDA-VETS, in 1996 to receive calls about adverse experiences to approved animal drugs. We expected many of these reports to come from practicing veterinarians, but our review indicates that a majority of the calls in the past few years have come from consumers, particularly dog owners who find our link on the Internet.

"We expected many of these (adverse experience) reports to come from practicing veterinarians, but our review indicates that a majority of the calls in the past few years have come from consumers..."

The CVM considers the drug label the first source of important facts for veterinarians. The label is the result of considerable scientific regulatory review before CVM approves the drug. It represents known safety and efficacy for any one drug. The label also gives veterinarians important information about whether the drug is suitable for the individual or subgroup within a species of animal. Additionally, whenever manufacturers distribute a client information sheet, this means that either the manufacturer or the CVM wishes to convey more facts about safety or efficacy in lay terms to pet owners.

The staff at CVM monitors and evaluates adverse drug experience reports and complaints of inefficacy for approved and unapproved, marketed products. For approved products, this evaluation of postmarket safety and efficacy incorporates knowledge gained from the premarket studies as well as from scrutiny of peer-reviewed studies related to the drug, or the disease that the drug is intended to cure or prevent.

From the hotline, we have learned that pet owners increasingly rely on Internet sources for information when their pets have problems. They have told us that, during their Internet searches, they often find label information and client information sheets.

Frequent comments from pet owners who contact the CVM hotline include these:

- They did not receive a client information sheet when one was available for a drug that was prescribed for their pet.
- The medication they received from their veterinarian was not dispensed in the CVM-approved container but was broken into

aliquots that were taken home without the client information sheet or approved label.
- The veterinarian did not conduct or recommend blood testing before and after prescribing the drug, even though baseline testing and/or periodic monitoring was recommended on the label. Common examples include heartworm products and nonsteroidal, anti-inflammatory drugs.
- After reading client information sheets and labels on the Internet about a drug prescribed for their pet, they discovered that their pet may have fallen into a category of animal for which a precaution or contraindication existed.

Given these findings, we have the following reminders for practitioners:

- Drugs that come with client information sheets are intended to be dispensed in the manufacturer's container, with the sheets accompanying the prescription.
- Product precautions, contraindications, safety information, and warnings should help identify animal patients that are not good candidates for the medication.
- Labels change—if you have a large inventory of a product with a long shelf life, you may want to contact the manufacturer or CVM to obtain the most recent label. A long shelf life makes it likely that some of the product won't be dispensed in the near future. Often, this information is also posted on pharmaceutical companies' official Web sites.

If you have comments or questions about this issue, contact Dr. Victoria Hampshire at (301) 827-0158, or vhampshi@CVM.FDA.GOV.

—Dr. Victoria Hampshire, Adverse Drug Events Coordinator, Office of Surveillance and Compliance, FDA Center for Veterinary Medicine

Return to top

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Victoria Hampshire Company Listing

Animal Healthcare Clinics

Maryland

VETERINARY HOME HEALTH CARE 7307 NEVIS RD BETHESDA, MD 20817-1737 301 871 2175

Source: http://www.petgalaxy.com/health_clinics.html

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Victoria Hampshire Website quotes

It's For The Animals!

WITH HELEN MCKINNON

Which Drugs / Medications are many people concerned about?

How to to report ADVERSE REACTIONS, and why it's IMPORTANT for you to do so.

"The CVM [Center for Veterinary Medicine] established the hotline, (888) FDA-VETS, in 1996 to receive calls about adverse experiences to approved animal drugs."

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"We expected many of these reports to come from practicing veterinarians, but our review indicates that a majority of the calls in the past few years have come

Victoria Hampshire Website quotes, page 2

"When this drug was initially marketed, it was believed to be safe for heartworm positive dogs; then we found that dogs were dying that were heartworm positive," - - Dr. Victoria Hampshire, the FDA's adverse drug events coordinator.

http://www.thepetguardian.com/html/body_proheart_6_info.html

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javmaNews

January 15, 2004

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http://www.avma.org/onlnews/javma/jan04/040115f.asp

—Dr. Victoria Hampshire, Adverse Drug Events Coordinator, Office of Surveillance and Compliance, FDA Center for Veterinary

1: Contemp Top Lab Anim Sci. 2001 Jul;40(4):11-7.

Handheld digital equipment for weight composite distress paradigms: new considerations and for rapid documentation and intervention of rodent populations.

Hampshire V.

Advanced Veterinary Applications, 7307 Nevis Road, Bethesda, Maryland 20817, USA.

Animal care in the third millennium will require a melding of scientific and humane interests to achieve optimal care of genetically engineered mice and to expedite scientific and medical advances by using these mammals. Undoubtedly, rodent patients present certain difficulties for those who wish to assess their daily well-being and to contribute to efficient and successful scientific discovery. High-density housing, large experimental groups, and low-lux room lighting makes the application of large-animal care standards to rodents seem daunting to researchers and veterinary care programs. In addition, great variability in training and experience among those responsible for the direct application of humane care to rodents exists. Most of the direct animal care in small animal facilities occurs in decentralized locales by personnel who have completed obligatory but relatively minimal animal care training. Examples of personnel in this category include postdoctoral fellows, junior-level scientists, summer students, and assistant laboratory animal technologists. Some programs even use the husbandry staff to perform health checks of high-risk populations on a daily basis. For this reason, the extrapolation of performance-based intervention in rodent care is difficult to apply practically. Early efforts to enhance humane outcome in rodents have been published by scientists and veterinarians and are largely directed at singular endpoints, such as weight loss and declining temperatures, in specific models. Scientists often are reluctant to accept such standards because of concern about premature intervention or variability between scorers and to reservations regarding a lack of procedural likeness with their proposed study. This paper highlights a digital method for melding current advanced animal scoring standards using palm pilot user-friendly methods that account for composite weight scoring, behavioral or physiologic attributes, and interventions. Information is rapidly downloaded and results in quick storage of large rodent population monitoring. This minimizes interpretative variability between caregivers and greater standardization of procedures. These considerations facilitate the rapid diagnosis of outliers and make possible intervention that streamlines the delivery of humane care to large experimental populations.

PMID: 11451389 [PubMed - indexed for MEDLINE]

Agency OBtAined

☐ 1: Lab Anim (NY). 2000 Sep;29(8):35-40.

Related Articles, Links

Technical team approaches to rodent care: cost savings, reduced risk, and improved stewardship.

Hampshire V, McNickle C, Davis J.

Advanced Veterinary Applications, 7307 Nevis Rd., Bethesda, MD 20817. Pathology Associates International (contracted to NINDS NIH). Animal Care Section, Division of Intramural Research, National Institutes of Health, Bethesda, MD.

With the increasing decentralization of animal care operations, lack of training and higher-density animal rooms make achieving humane assurances difficult. To offset these problems, some facilities have developed centralized animal care programs, including dispersed teams of qualified animal care specialists.

PMID: 11381234 [PubMed - as supplied by publisher]

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new orleans, louisiana
august 11-15, 2002

WB2: Refinement in Generation and Maintenance of Transgenics: Local Anesthesia, Cryopreservation, and Clinical Assessment of Phenotype
Moderators: Tory Hampshire (USA) and David Morton (UK)

WB2: Refinement in Transgenic Management

David B. Morton[1] and Tory Hampshire[2]. [1]BMSU, University of Birmingham, Edgbaston, Birmindham B31 2EP, UK. d.b.morton@bham.ac.uk. [2]Advanced Veterinary Applications, 7307 Nevis Road, Bethesda, MD 20817, USA. vetcare@msn.com.

Given the exponential growth in the production and use of transgenic animals in research throughout the world and the uncertainty of the impact of such transgenesis and knock-out procedures on the animals, there is an increased awareness of the need for a detailed phenotype assessment of each strain. The establishment of a detailed phenotype will not only be important for animal welfare, but will add to the scientific information base. This could be particularly important when models of human diseases are being generated, as it would be useful to correlate the phenotype with the clinical signs seen in humans with that disease. Moreover, there is an increasing trend to cross genetically modified animals of different strains, as well as with mutant strains. Each genetically modified and hybrid/mongrel animal should have a welfare passport so that the receiving institution is aware of the likely adverse effects, the time at which to expect these effects, as well as how to avoid or alleviate the effects. This workshop aims to provide some approaches and to draw on the experience of all those attending.

Agency 1

ILAR Journal 44(3) 2003
Behavioral Research Outside the Laboratory

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Introduction

Introduction

Victoria A. Hampshire and Lilly-Marlene Russow

Victoria A. Hampshire, V.M.D., is Director of Advanced Veterinary Applications, Bethesda, Maryland. Lilly-Marlene Russow, Ph.D., is Professor in the Department of Philosophy, Purdue University, West Lafayette, Indiana.

Diversity in animal experimentation assumes a number of different meanings depending on the life experiences of laboratory animal veterinarians and the justifications offered by scientists for doing any single experiment. One commonly thinks of technical differences between studies as confounders. Although behavioral and physiological disparities and the humane outcome for the animal(s) have been documented (e.g., Davis 2002), (1) they are much less commonly identified as confounders; and (2) they often depend on phenomena that cannot be easily controlled in the laboratory or, even more problematic, outside the laboratory.

Indeed, one of the greatest difficulties in prospective humane study design is coping with the assumptions that all experiments involving animals can be easily controlled. Indeed, a popular and robust justification offered for the study of drugs, vaccines, and science in living systems is the ability to study processes that occur in or among variable conditions within beings. Konrad Lorenz, one of history's modern animal biologists, addressed such issues in the context of scientific and biological multiplicity as "New Light on Animal Ways" in his book *King Solomon's Ring*. Lorenz was neither a classical zoologist nor a hardened scientist; however, in modern Darwinian fashion, he observed important things about animals and people who work with animals, which we discuss in this issue of *ILAR Journal*.

Herein, Russow and Theran begin by outlining basic ethical and moral theories associated with the use of nontraditional animal species (Russow and Theran 2003). They also explore ways by which the institutional animal care and use committee (IACUC[1]) might better address the impact that research has on animal social structures, as well as those surrounding the sensitivities that humans who work with animals almost inevitably have.

Next, we invite you to step into companion animal hospitals, homes, and research laboratories for a better understanding of work with dogs and cats in nontraditional biomedical research settings. Hampshire introduces readers to the myriad of jurisdictional authority surrounding the use of companion animals in nontraditional settings as well as the procedures that institutions currently follow for coping with ethical and humane care of such animal populations (Hampshire 2003).

In the next article, Hansen describes an example of clinical research studies in dogs (Hansen 2003). He discusses the utility of ethograms or behavioral composites associated with pain management and also highlights his experiences using these composites in evaluating the success of pain management for hospitalized female dogs recovering from ovariohysterectomy (spay) procedures.

Now that our profession has designed strategies for dealing with animal care in the era of genetic manipulation, we have entered a time when phenotypic evaluation of a great many chimers, clones, and models are produced by targeted mutation. More than ever, some programs have issues of competing needs between agricultural production and agricultural research. Field and agricultural veterinary personnel can encounter challenging scenarios while working in nonconventional programs that are more research oriented, especially in studies with genetically altered livestock. Such research may involve returning phenotypically altered animals to an animal society, but one in which hierarchies are changed from what the animal(s) would have typically experienced. Granstrom methodically addresses key recommendations and guidelines that may enable readers to evaluate programmatic compliance with these dueling needs more effectively (Granstrom 2003). His discussion may lend those managers who are presently coping with approval of invasive and critical care procedures in farm animals a greater level of

appreciation for consolidation and collaboration measures that might be achieved across programs and/or institutions to provide more comprehensive care to a relatively select population of animals.

In her article, King provides readers and IACUCs with complementary tools for decision-making related to study design and support in agricultural programs (King 2003). She lends valuable research perspective on the relatively simple but important observations of Lorenz some 30 yr earlier. Taking Granstrom's outline one step farther, King addresses behavioral concepts and approaches to the study of farm animal welfare. We hope the thorough discussion of extrinsic and intrinsic behaviors, the overview of neurophysiological mechanisms underlying animal emotions, and the discussion of animal priorities and lifestyle "costs" (or perhaps value-based decisions) will influence readers to consider very carefully how IACUCs might better approach the design of sociological and environmental provisions within animal care programs as much as they consider the behavioral experiment itself.

We hope that readers find this issue useful for gathering different perspectives and guidelines regarding the care and use of animals outside the customary laboratory setting.

[1]Abbreviation used in this Introduction: IACUC, institutional animal care and use committee.

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Close

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ILAR Journal V44(3) 2003
Behavioral Research Outside the Laboratory

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Regulatory Issues

Regulatory Issues Surrounding the Use of Companion Animals in Clinical Investigations, Trials, and Studies<

Victoria A. Hampshire

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Abstract

Laboratory animal veterinarians sometimes encounter animals with rare conditions and may subsequently become involved in the performance of related animal research outside the laboratory, in homes, in veterinary clinics, or in universities to which owners have donated their animals for study. Similarly, veterinarians may monitor animal companion vaccination studies, performed to optimize preventive health care or minimize physiological variability and research confounders associated with a preventive medicine program for dogs and cats utilized for research procedures. These nontraditional uses of dogs, cats, and other companion animals in research have spurred the establishment of regulations to ensure that the animals benefit from clinical veterinary products and techniques. Included and described are the 2002 Public Health Service Policy, the Animal Welfare Act (AWA), the Federal Food, Drug, and Cosmetic Act, and the regulations of the US Department of Agriculture in response to the AWA. The complexities of clinical research with companion animals outside standard biomedical research [illegible]ities are discussed.

Key Words: companion animal research; regulatory affairs; veterinary clinical research; veterinary drugs; veterinary vaccines

Introduction

A career in laboratory animal medicine involves the care and use of a myriad of animal species as well as numerous and diverse types of experimental protocols, personal contacts, and administrative processes. The majority of laboratory animal veterinarians working in research settings do not usually participate actively in the development of new vaccines, drugs, and treatments targeted for the companion animal, nor do they work in traditional companion animal settings such as animal teaching hospitals, veterinary clinics, and subdivisions of pharmaceutical companies devoted to animal health research. Indeed, most of their efforts are directed at the care and use of animals that ultimately serve as research models for the human biomedical research sector.

It is predictable that as the era of cloning or genetic engineering advances research and treatment paradigms into larger animal species and disease models, these research support veterinarians may well encounter special breeds of dogs or cats that have rare conditions and cause their program of research to conduct interventional treatment regimens on animals outside the laboratory, in homes, in veterinary clinics, or in university research settings to which owned animals have been donated for periods of time. Similarly, vaccination studies are sometimes performed in an effort to optimize preventive health care or minimize physiological variability and research confounders associated with a preventive medicine program for dogs and cats utilized for research procedures. This article provides an overview of regulatory processes associated with these nontraditional uses of dogs and cats in research.

In fiscal year 2000-2001, there were approximately 68 million owned dogs and 73 million owned cats in households within the continental United States. Owners spent yearly averages of $196.00 per dog and $104.00 per cat in veterinary-related expenses (APPMA 2000-2001). These large numbers suggest that the clinical research necessary to bring safe and efficacious vaccines, [illegible]al insecticides, drugs, and medical or surgical treatments into standard practice is also substantial. Equally large is the cu[illegible]t regulatory effort to ensure that animals benefit from such products and techniques and that their owners are sold veterinary medicine and veterinary practices that minimize risk and maximize benefit for their pets.

Laboratory animal veterinarians and animal care personnel receive instruction in Public Health Service (PHS[1]) Policy (PHS 2002), requirements set forth in the Animal Welfare Act (AWA[1]) (AWA 1966), and regulations promulgated by the US Department of Agriculture (USDA[1]) in response to the AWA. However, biomedical research staff less commonly encounter the complexities of clinical research with companion animals outside the standard biomedical research facility.

Differences in Animal Use

The major difference between the use of animals for human benefit and the use of animals for animal benefit is the amount of jurisdictional authority that surrounds each type of study. Companion animal studies are subject to more regulations during the development, testing, and final trials using veterinary procedures and products as well as the close monitoring of their owners' involvement. The regulatory policy surrounding the use of companion animals can be confusing not only to the lay public but also to the laboratory animal specialist because the distinction between what constitutes research, who qualifies as an investigator, and what constitutes clinical discretion is often different from traditional research settings.

Another major difference between human and animal research is the vastly greater number of federal authorities that regulate the use of drugs, vaccines, flea and tick products, and new veterinary procedures in animal research. In the final phases of human health investigations, nearly all clinical trials are ultimately regulated by the Department of Health and Human Services (DHHS[1]). Human vaccines, biologics, drugs, and devices are regulated under rules enacted in response to the Federal Food, Drug, and Cosmetic Act (FFDCA[1]) (FFDCA 2001) under the Food and Drug Administration (FDA[1]). Human Subjects research may also be dually regulated by FDA's parent department, DHHS, through the Office of Human Research Protections.

Animal clinical research, vaccine and drug testing, and the regulation and monitoring of clinical trials may be subject both to regulation from various federal government departments and to institutional-specific policies that may address issues not completely covered by federal rules. The subject of the complex regulations related to laboratory animals is described in a previous issue of *ILAR Journal* (VandeBerg et al. 1999). In short, animal research of any kind is regulated by rules promulgated by the USDA in response to the AWA. These rules establish minimal criteria for humane care and use, and they must be bolstered by strong institutional policies when there are no other rules.

Research at facilities directly or indirectly funded by the DHHS is also subject to rules enacted by US PHS Policy (PHS 2002). Research involving vaccine testing is additionally regulated by rules established by the USDA under the Virus-Serum-Toxin Act (USDA 1913, as amended in 1985). Through the Code of Federal Regulations 21, the FDA articulates regulatory policy regarding drugs, devices, feeds, and feed additives. Flea and tick products are regulated by the Environmental Protection Agency (EPA[1]) in accordance with the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA 1996).

Other products are occasionally regulated under multiple acts of the Federal Trade Commission or the Consumer Product Safety Commission. Vaccine research is predominantly confined to preapproval registration of products based on testing inside the research facility.

A recent increase in feline vaccine-associated sarcomas has catapulted consent for vaccination procedures to the forefront of feline medicine issues (AAFP 1998). However, the trials that go to clinics for testing in client-owned pets are still largely limited either to new clinical treatments and test therapies or to new drugs or new vaccines. These areas are discussed below.

Commonality of Regulatory Intent

Common regulatory roots between research involving animals to derive drugs, devices, procedures, teaching, and testing for human benefit and those developed for animal benefit can be examined in the following publications: (1) the *US Government Principles for the Utilization and Care of Vertebrate Animals Used in Teaching, Research, and Training* (IRAC 1985), and (2) the *Guide for the Care and Use of Laboratory Animals* (NRC 1996). The latter document serves as a foundation for PHS principles, which define the boundaries and other important characteristics of clinical research eligible for federal funding. The following principles are common to the laboratory animal industry and the drug development industry:

- Principle II: Overall relevance of the study to human or animal health
- Principle III: Appropriate species, quality, and number to obtain relevant results
- Principles IV-VI: Appropriate care and housing; and minimization of pain and distress, utilizing measures up to and including humane euthanasia
- Principles VIII and IX: Properly trained and experienced investigators; discretion regarding humane outcome should rest not only with investigators but also with review groups and boards

Testing New Techniques and Veterinary Methods

Advances in companion animal care typically are the result of cutting edge veterinary research at major teaching hospitals. In these cases, the level of the investigators' training and the availability and cost of support staff are typically much higher than in investigative settings or local animal hospitals. Additionally, compared with research laboratories, standard minimal criteria for humane care as described in the AWA and PHS Policy are usually exceeded at veterinary teaching hospitals due to more uniformly experienced personnel who are highly skilled in animal medicine and surgery. Because owners are generally quite desperate to solve problems, concerns arise over client vulnerability. Universities must always devise additional procedures that protect the veterinary/client relationship, shield the pets from unnecessary pain or distress, and safeguard the pet owner from consumer fraud. Such cases almost always involve additional input from ethics panels and board-certified specialists. To accomplish this high standard, institutional care committees in veterinary teaching hospitals must fine-tune their existing national policies and guidelines to adapt to regulations.

Consent Form

The principle of informed consent is common to the use of companion animals both in drug testing and in university experimental, procedural, and testing validation. In contrast to the institutional animal care and use committee (IACUC[1]) review process for a biomedical research animal, clinical studies can proceed with a companion animal only if the owner is willing. Key aspects in the prevention of consumer fraud during the consent process are relevant facts about just how new the procedure or drug in question really is and the chances that the animal in question might not benefit from such a new procedure. Likewise, if there is a high rate of side effects in foundation research with the drug, vaccine, or procedures, that probability should be discussed and defined with the owners before administration.

In September 1999, informed consent issues rose to the forefront of popular press with the case of Jessie Gelsinger (Washington Post 1999). Since then, abuses of the consent process have been the subject of intense public scrutiny. Pet owners have become aware of their need to be informed about risks and benefits of experimental drugs and procedures. Press reports have resulted in the re-examination of what constitutes a fully informed owner or patient (AAFP 1998; Homes-Rovner 2002; Lantos 1993; Silverman 1996). The level of reading skill and comprehension has been especially problematic in addition to how investigators and clinical research committees define lay language (Davis 1998). Procedures for obtaining informed consent before conducting animal clinical studies stem from those developed for human clinical research within the 1976 Belmont Report (NCPHS 1976). In achieving an ethical and humane objective, clinical studies programs within animal hospitals have also tried to emulate these policies. The owner consent form is based on the Belmont Report principle of "beneficence." The underlying premise is that hospital staff and practitioners should treat animals and their owners in an ethical manner, not only respecting their owners' decisions and protecting the animal patient from harm but also making efforts to secure animal wellness. As stated in the report, beneficence is more than a charitable act; it is an obligation. The report further describes objectives of beneficent actions, which do not harm and which maximize possible benefits and minimize possible harms.

Clinical Studies Involving Drugs

The regulation of clinical studies involving companion animals is very comprehensive due to the FDA mission of ensuring the utmost safety and efficacy of new animal drugs. The final phases of drug testing, when clinical trials are initiated, include extensive legal discussions between pharmaceutical companies (sponsors) and the responsible administrative center, the FDA's Center for Veterinary Medicine (CVM[1]). Oversight of clinical research activities involving drug development in dogs and cats also differs in facility, clinical conduct, veterinarian-to-investigator relationships, and reporting of results from studies involving early pharmaceutical development conducted in common laboratory animal species within laboratories or medical schools. Basic research in pharmaceutical development is an activity performed in the following sequence: (1) using in vitro or small mammal models, (2) using dogs or cats held as research subjects by research facilities, and (3) performing single or multiple center clinical trials outside biomedical research structures.

However, before clinical drug trials can be conducted in companion animals outside the laboratory, this preliminary work must be summarized for CVM to establish whether there is a rational basis to allow further development of the drug. Toward this goal, the CVM's Office of New Animal Drug Approval (ONADE[1]) is responsible for reviewing investigational new animal drug applications (INADs[1]) and new animal drug applications (NADAs[1]) stemming from INADs. The INAD usually documents the discovery phases of the drug, the drug manufacturing or drug components, the intended use, the results of any laboratory animal studies, and the results of early pilot studies (e.g., in vitro, teratogenic, toxicological, environmental assessment and human exposure, bioavailability, and pharmacokinetic). The INAD includes the portions of the preliminary work for clinical studies with which the laboratory animal veterinarians are most familiar. Data submitted by the pharmaceutical company (sponsor) to ONADE are then evaluated by the company or sponsor and the FDA reviewers for safety and efficacy. Only

sufficient data permit the design of target animal safety and efficacy work (Vaughn 1998).

FDA's mission also necessitates the study of early detection of adverse drug effects. Humane concerns of the FDA are not bl[illegible]ntly stated, but they appear basically inescapable in the guidelines for very frequent and specific periods of observation with corresponding data collection. These procedures are exceptionally detailed and, if followed by investigators, necessitate prompt detection and relief of pain and distress because they must enable FDA reviewers to determine the earliest possible time of adverse drug effects. Guidelines suggest that study animals be examined twice daily 7 days per week; examinations may include, for example, collection of clinical pathological and histopathological data as well as a timely necropsy (FDA 1997, 2001).

The final phases of new animal drug evaluation involve more investigator controls than are commonly seen in the laboratory setting. Compared with the IACUC requirement that an investigator must have adequate training and oversight to accomplish the research humanely, guidelines from CVM have more comprehensively defined what constitutes investigator adequacy and veterinary oversight. The investigators should be veterinarians or their designates, and they should provide complete details about their research. In contrast to the laboratory setting, the final evaluation of the safety and efficacy of the drugs or techniques are the responsibility of the animals' owners, who have volunteered the animals for participation in the clinical trials outside the confines of biomedical research facilities, sometimes in academic teaching institutions, private veterinary hospitals, or the home. Here, the veterinary role has shifted from one of oversight to one of investigation, which entails additional controls.

In the companion animal clinical drug study, for example, investigators operate largely within federal regulations (sections 511 and 512 of the FFDCA and further defined in Title 21 Code of Federal Regulations [CFR[1]]) (CFR 2002) with oversight from individuals or organizations called clinical trials monitors. The FFDCA does not duplicate any portion of the Animal Welfare Act. Rather, the regulations in CFR Title 21 require compliance with all existing federal regulations in the AWA. Some similarities exist between the Acts. For example, CFR 21 describes requirements for submitting NADAs. Clinical studies must be carried out according to certain criteria described in the FFDCA §512 and further under §514.117of CFR 21 *Adequate and Well-Controlled Studies*. Subparts (a) and (b) require the sponsor to (1) describe key investigators and subordinate personnel, with their qualifications, training, and functions; (2) describe the facilities in which they will work; (3) clearly state the rationale and purpose of the study; and (4) describe the standards of conduct to which the institution will hold such personnel.

A has also published guidelines in documents 58 and 85. Guidance 58, *Good Target Animal Study Practices* (FDA 1997), i[illegible]es additional, very detailed requirements on the investigative study. In addition to the legal requirements (of the AWA, possibly of the PHS, and possibly of the institution), there are requirements regarding the storage, distribution, and disposal of any investigational drug. Guidance Document 85 (FDA 2001) comprehensively describes key professional contacts, conduct, and record-keeping that will be involved in studies. For example, investigators must be masked to treatment identities; animals owned by individuals other than the investigator must be maintained according to the study protocol; investigators must promptly report to the sponsor any adverse drug experience associated with the use of the investigational new animal drug; and investigators must permit a monitor and FDA representative to inspect the facilities used by the investigator for the study and, for the purposes of verifying the validity of the data collected for the sponsor, to inspect and copy records made or kept by the investigator as part of or pertaining to the studies. Records must be much more detailed than is typically the case in protocols subject only to USDA or PHS Policy. Investigators must maintain records to the extent that all contacts with the monitor or other representatives of the sponsor, FDA, and their designees may be contacted. Records must therefore include dates and times of meetings, purpose of meetings, affiliation of individuals involved, and a summary of contact findings.

Monitors

Monitors of clinical trials are required during the investigational and new animal drug approval process. Some veterinary teaching hospitals in which nonpharmacological therapies are tested also establish internal monitoring committees; however, the composition and responsibilities of these members are less detailed and less uniform compared with FDA/CVM Policy. For example, the University of Florida's consent form defines two types of clinical studies. Type 1 studies may involve the following: (1) comparison of a new therapeutic or diagnostic procedure with an accepted procedure or placebo treatment, (2) required collection of additional tissues or fluids during the course of standard treatment, or (3) collection of tissues from a client's animal after it has been euthanized. Such studies generally provide the committee and owners with a rationale or hypothesis, justification for the use of their animals, description of the experimental methods, and anticipated results. The owner must review this information and sign a consent form. Such studies differ from Type 2 studies in which additional blood or fluid samples may be required from what is already considered standard practice. In addition, the size and volume of the fluid collected are usually s[illegible]ndard amounts. The samples or tissues are identified anonymously (UFVTH 2002).

P[illegible] 58 of the CVM policy and procedures (FDA 1997) provides a detailed description of suitable monitors and required documentation during the phases of a study. Monitors must be qualified to oversee the study protocol and to implement quality assurance measures so that the study is consistent with the objectives. Monitors must be unbiased, must personally contact

each investigator, must make frequent trips to the study site to ensure appropriate functioning of the study, and must continually record visits, actions, and correspondence with the investigative staff and sponsor. All study documentation and record keeping must comply with the detailed requirements.

Vaccine Development

The USDA is responsible for the preapproval, licensing, and policy development for companion animal vaccines. The Virus-Serum-Toxin Act of 1913 was amended in 1985 in response to public concern regarding companion animal vaccines, and later associated adverse events (e.g., feline vaccine-induced fibrosarcomas) prompted greater scrutiny of vaccine procedures (AAFP 2000). The Center for Veterinary Biologics, which is part of the USDA's Animal and Plant Health Inspection Service, Veterinary Services, is responsible for the safety and efficacy of marketed US animal vaccines. The Center establishes licensing, testing, and permit requirements and procedures; provides licenses for production facilities and biological products; provides permits for importation of products; and reviews production method, labels, and supporting data involved in the licensing and permit process.

In terms of premarket clinical trials, most vaccine studies take place within the confines of the research organization. Study protocols follow the AWA and subsequent requirements. Because clinical trials are not always performed using privately owned animals, postmarketing surveillance is very important when new vaccines become available. Anecdotal search services frequently provide the best glimpse of safety and efficacy during early vaccine use (Veterinary Information Network 2002). Public concern and a growing body of evidence about vaccine reactions prompted a 2002 working group to examine risk/benefit and public accountability for responsible vaccination use and to recommend strengthened postmarketing surveillance of vaccine reactions (Gaskell et al. 2002).

Postmarketing Surveillance

The postmarketing period of use for common companion animal drugs, vaccines, and new medical treatments is the most useful, yet least well described, monitoring process for animal clinical studies. Most laboratory animal veterinarians will attest that there is no perfect animal study design. Indeed, if it were possible to design a perfect study, little reason would exist for the use of pilots. Just as the IACUC may frequently prescribe pilot protocol review mechanisms to describe risk/benefit of new studies fully, sensible veterinarians and pet owners ask questions about risk/benefit during the first few years of marketed use. During the critical time from clinical study to everyday use, the experimental group of animals suddenly changes from a small study group to the numbers discussed in the Introduction of this article.

Good clinical studies also utilize the benefit of strong postmarketing surveillance in an effort to seek true indices of the safety and efficacy of new products and techniques. Fortunately, new surgical and medical techniques usually must meet the scrutiny and selectivity of academic experts. This requirement and the fulfillment of the high standards shared by peer reviewers preceding publication of new medical techniques serve as ultimate safeguards for their eventual use in veterinary practice. Veterinarians' and pet owners' time and resourcefulness are required to read the pertinent literature on an ongoing basis.

Finding the sources of valuable postmarketing information on drugs and vaccines is often difficult because veterinary medicine programs rarely build these resources into the veterinary teaching program. Each federal agency makes this information available; however, some data are more readily accessed than others. Examples of readily available postmarketing information are provided below.

Adverse drug reactions. The FDA adverse drug reaction database is an enormously useful tool for finding information about common clinical signs associated with drug reactions. The tables are available to the public (http://www.fda.gov/cvm/index/ade/adetoc.htm).

Vaccine reactions. accine reactions are monitored by the USDA Center for Veterinary Biologics through their vaccinovigilance monitoring system (Animal Immunobiolgic Vigilance, USDA/CVM 510 South 17th Street, Suite 104, Ames, IA 50010) or, alternatively, through the United States Pharmacopeia (Tel: 800-487-7776) (http://www.usp.org).

Conclusions

Use of companion animals in nontraditional settings such as animal hospitals, homes, and veterinary teaching hospitals increases channels of approval for clinical studies, drug development, vaccine testing, peer review, and personal malpractice safeguards. Rules and guidelines during review of these procedures have evolved from very complex and thoughtful processes to regulatory systems that still require improvement. It is hoped that future directions will harmonize efforts among the FDA,

EPA, and USDA policies and procedures, the ongoing policy development by the American Veterinary Medical Association in areas related to informed consent, and a growing awareness of the possibilities that exist to provide the consumer with genetically engineered pets. This latter arena is exceptionally difficult to address and will require extensive humane, moral, and ethical deliberation.

Veterinarians in laboratory animal medicine are uniquely trained to collaborate with individuals in nontraditional settings because many of these processes are inherently part of their routine. Such outside administration, particularly with respect to vaccines, is presently in its infancy and can be viewed similarly to pilot programs within research settings. Because many companion animal owners now have access to the internet and cable television involving countless animal special productions, these individuals are more informed about the legal processes surrounding the use of their animals as well as their consumer rights. As a result, it is hoped that more cross-communication, uniformity of administrative monitoring, and postprocedural surveillance will occur within the veterinary profession both in and outside the laboratory animal settings.

[1]Abbreviations used in this article: AWA, Animal Welfare Act; CFR, Code of Federal Regulations; CVB, Center for Veterinary Biologics; CVM, Center for Veterinary Medicine; DHHS, US Department of Health and Human Services; EPA, Environmental Protection Agency; FDA, US Food and Drug Administration; FFDCA, Federal Food, Drug, and Cosmetic Act; IACUC, institutional animal care and use committee; INAD, investigational new animal drug application; NADA, new animal drug application; ONADE, Office of New Animal Drug Evaluation; PHS; Public Health Service; USDA, US Department of Agriculture.

The statements and opinions in this paper represent the understanding, experience, and opinions of the author and not those of the FDA.

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Impact of Noninvasive Technology on Animal Research

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Challenges

Challenges in Small Animal Noninvasive Imaging

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Abstract

The current status and challenges of small animal noninvasive imaging are briefly reviewed. The advantages of noninvasive studies on living animals versus postmortem studies are evaluated. An argument is advanced that even in postmortem situations, noninvasive imaging may play an important role in efficiently characterizing small animal phenotypes as well as pathology. Issues of data interpretation under anesthetized conditions in live animal studies are also reviewed. Five imaging technologies are discussed briefly: magnetic resonance imaging and spectroscopy, ultrasound, computer-assisted tomography, positron emission tomography, and optical imaging. The structural and physiological information content of these different modalities is reviewed along with the ability of these techniques to scale down for use in small mammals such as mice and rats. In general, it was found that most of these technologies scale favorably to the study of small mammals, generally providing more physiological information than when used on the larger human scale. This finding suggests that these types of small mammal imaging capabilities will play a very significant role in the full utilization of these important animal models in biomedical research.

Words: anesthesia; CT; mouse; MRI; optical microscopy; PET; rat; ultrasound

Introduction

Small mammals, namely mice and rats, play an important role in biomedical research. These models are desirable due to low cost of maintenance and housing, short reproductive cycle, availability, and relative ease of transport. Over the last decade, a dramatic increase in mouse utilization has occurred due to the ability to modify the genotype of this animal rapidly. The mouse genotype can be manipulated almost at will, providing a unique tool in evaluating the effects of targeted manipulations on the phenotype of a mammalian system. This study of the "functional genomics" of the mouse will clearly be a major topic of biomedical research over the next decade. However, the methodology to evaluate the physiology or phenotype of the mouse and other small mammal models is still developmental at best. In many cases, a gene is removed, or knocked out, overexpressed, newly expressed, or mutated in an animal with a given hypothesis with regard to the eventual phenotype. Regrettably, it is rare that these genetic modifications have the desired effects on the mouse, and many unexpected phenotypical consequences are realized. This result is simply due to our ignorance in how genes are used in the development and function. Thus, this type of genetic manipulation is quickly being realized to be more an exploratory or discovery-based process rather than a pure hypothesis-driven experiment, which makes the development of screening techniques for the evaluation of animal phenotypes even more critical. By screening, we mean both the ability to evaluate numerous structures and organ systems simultaneously without necessarily targeting one system and the ability to look at large populations of animals frequently required in genetic studies, especially in the area of mutagenesis. Due to the inherent surveillance nature of most noninvasive imaging techniques, these approaches are ideal tools for discovery in evaluating the phenotype of a mouse as they are for discovery of disease in a human patient. In this article, we discuss the application of imaging as a small mammal phenotyping tool with a major focus on the mouse. We focus on the mouse because it will be the dominant mammalian model over the next 5 yr, and its diminutive size provides the greatest challenges and opportunities in the imaging sciences.

When considering using an imaging modality for small mammals, one must consider the changes in scale on both the overall size of the subjects as well as the physiologically relevant imaging volume. For example, in visualizing the resistance arterioles or capillary network of the skeletal muscle, the scale of the target vascular system is the same (150-10 μm). However, the skeletal muscle structures can be several orders of magnitude less when comparing mouse and man. This is a case in which the physiologically relevant imaging volume is nearly fixed between mouse and humans. Other examples of constant physiological volumes are individual neurons or ganglia. In contrast, an important measurement in the heart is the distribution of work and blood flow across the heart wall, or the so-called transmural distribution. In a human, this distribution requires a spatial resolution on the order of 2 × 2 × 7 mm, whereas in the mouse heart, the resolution must approach 0.2 × 0.2 × 1 mm. In this case, an increase in resolution volume of several orders of magnitude is required, similar to the overall scale of the animal. Thus, depending on the questions addressed, the experiment must take into account the required resolution for the physiological or anatomical

measurement and not simply the scale of the animal alone.

The gross scale of the animal and its organs also influence the type and effectiveness of the imaging techniques. Many imaging techniques scale very well with size, permitting higher resolution and signal to noise ratio (SNR[1]) as the sample size becomes s[illegible]ler. One major example of this influence is optics, which can be used to probe the entire adult mouse, but is relatively in[illegible]tive at viewing anything in humans except very superficial structures due to its poor penetration. For each of the modalities de[illegible]bed, a general discussion on the effect of sample scale is presented.

Beyond the consideration of imaging modality, we have found that the basic question of whether living or postmortem studies should be conducted has a significant impact on the effectiveness of the study in terms of cost, time, quality, and, ultimately, scientific value. Based on this observation, a brief comparison of living versus postmortem studies is presented.

Postmortem Noninvasive Imaging

Naturally, when one considers a noninvasive technique, the advantages of performing studies on a living animal come to mind. However, one of the first issues to address when considering an imaging procedure is whether the study should be conducted on a live animal or postmortem. In clinical studies many times the definitive phenotype, or disease, is defined in an autopsy. Noninvasive imaging of morphology can be conducted at the highest level in a cadaver because no physiological motions are present and imaging time is not as critical. Thus, a well designed system for acquiring as much information as possible from postmortem animals may provide many investigators with the morphological and biochemical information they require in a timely and cost-effective manner. Noninvasive techniques are also advantageous compared with conventional gross pathology procedures, which require sectioning the animal and organs. This advantage is realized in cost, speed of acquiring data, and the nondestructive technology permitting follow-up postmortem studies as required. The nondestructive autopsy approach is even gaining favor in the evaluation of human and animal cadavers (Boyko et al. 1994; Ros et al. 1990). Technical development in this area could greatly improve the throughput and quality of these examinations and permit high-resolution (100-μ m isotropic resolution) whole mouse studies on the order of 1 min, seriously competing with many gross pathology studies. The concept that a full three-dimensional image of the soft tissue structure, bones, and vasculature of an animal could be collected in a few minutes and delivered to the investigator's computer for analysis without destroying the animal for further study has many advantages.

A major challenge of this approach is the development of the high throughput systems to evaluate hundreds of animals for s[illegible]eening purposes. With postmortem subjects, one could imagine several robotic solutions to feed magnetic resonance imaging [illegible]) or computer-assisted tomography (CT[1]) devices with scores of animals in series or in parallel. Such devices are in de[illegible]pment around the world. In addition, the automation of image interpretation and analysis must keep up with this data flow as well as just the ability to store and transfer these large data files. For example, a single whole mouse image at a 50-μm isotropic resolution would contain approximately 5×10^8 numbers. This is a remarkable amount of data for a small animal and likely only obtainable on a postmortem study due to the time required and physiological motion interferences at this high spatial resolution.

Live Animal Studies

The major advantage of noninvasive studies is the ability to conduct studies on living animals without significant consequence to the animal or its physiology. However, live animal imaging studies are very difficult to perform because they generally require an anesthetized animal and animal technical support to monitor the animal throughout the procedure and recovery. In addition, the physiological motion, support issues, and limited time available for the scanning generally compromise the quality of the imaging data compared with postmortem studies. For example, current technology applied to MRI of the mouse heart requires at least 1 hr of scan time, not including the anesthetic induction and recovery time, whereas a similar postmortem scan providing information on the entire cardiovascular anatomy of the animal could be conducted in minutes. The reason for this difference is that the heart and lungs are moving in the living animal. Thus, the time available to collect data is severely limited because gating to the two physiological processes is required to freeze the motion of the heart. This is especially true when one is attempting to detect the dynamics of the heart, which requires many high-resolution images. In a postmortem study, the imaging time is nearly 100% in a properly conducted experiment, without the need to correct for flow or gate to physiological parameters that also must be measured in a highly precise fashion in living animal studies. In addition, large improvements in magnetic field shimming are also realized in the postmortem condition. All of these factors contribute to a decrease of a factor of 10 in time. This difference multiplied by several hundred animals becomes highly significant. Similar time constraints exist for other imaging modalities. All issues concerning motion, physiological status, and temperature may play a role in these studies. Due to the high cost and low throughput of these vital imaging techniques, these approaches should be reserved for those studies requiring this type of e[illegible]amination. Some of the types of studies requiring vital measurements are included in Table 1.

L[illegible] animal studies are the most difficult to perform, yet they provide the greatest amount of physiological information. For this reason, these types of noninvasive studies are the focus of the remainder of this discussion. For the different imaging modalities discussed below, the image information content and scaling issues remain basically the same between living and postmortem studies.

Anesthesia Procedures

In vital noninvasive studies of small animals, the use of anesthesia is a major challenge. Active restraint of animals is possible for ultrasound and some other modalities. However, the physiological effects or reproducibility of the physical and mental stress imposed on the animal is unclear, especially in cardiovascular studies. Thus, most studies must be conducted under anesthesia. Regrettably, the impact of this anesthesia requirement is that the imaging data are frequently more profound on the interpretation than the imaging experiment itself. This is especially true with transgenic animals in which the phenotype might be expressed as [redacted]hanced sensitivity to anesthesia; with minimal changes, the phenotype is normal or wild-type.

Because monitoring physiological function is the goal of many imaging studies, from cardiovascular behavior to neurological function, a regime must be picked to minimize the impact on the function of interest. Ultimately, the regime must meet the requirements of the imaging modality both from the perspective of time required for the studies as well as physical access to the animal. Because anesthesia is such an important aspect of small animal imaging, we discuss this major challenge in the field in some detail below.

The small size of the mouse or other small mammal is particularly challenging for maintaining a stable anesthetic plane due to problems with mechanical ventilation and online measures/adjustments of physiological function. Of paramount importance in achieving exact details about physiological changes in models is the need to control homeostatic mechanisms such as fluid and electrolyte balance, blood glucose, and acid/base balance. The most successful anesthetic protocols incorporate considerations for the maintenance of normal packed cell volume, total protein, and osmotic shifts, as well as the minimization of respiratory and metabolic disturbances in pH and normal substrate utilization through the provision of glucose and electrolytes. Naturally, this incorporation requires dynamic monitoring of blood gases and chemistry during an experimental procedure, which is very difficult to obtain from a mouse due both to the difficulty in obtaining vascular samples from these small animals and to the small volumes one can collect without affecting the animal's fluid balance. Thus, not only is microsurgery required for these procedures to monitor the animals, and in some cases deliver imaging contrast agents (MRI, ultrasound, CT, and positron emission tomography [PET[1]]) or tracers (PET), but microanalytical techniques are also required for analysis of the blood samples.

Adequate warmth is of particular importance in small animals because surface area to body weight ratios and metabolic rate are almost 10-fold higher than larger mammalian species, making the extrapolation of large animal procedures to the mouse difficult. For example, the large surface-to-volume ratios of mice require nearly twice the amount of fluid supplementation during anesthesia than most large laboratory animals. In addition, this fluid must be preheated to prevent its contribution to hypothermia during the procedure.

[redacted] regard to ventilation, several significant anatomical and physiological considerations must be understood about rodents b[redacted]one can fully understand acid/base and respiratory balance during imaging procedures. First, because of the relatively larg[redacted]gastrocoele in rodents, thoracic compression is an issue in causing ventilation/perfusion mismatching. Rodents should be positioned at a slight incline, head above tail, to allow maximal costal movement. Additionally, the plane of anesthetic is important, and apnea must be avoided as much as is possible. Investigators can modify standard electrocardiographic equipment with nonmagnetic leads for the purposes of monitoring heart rate to assess depth of anesthetic. Second, large animals tend to adjust minute volume by increasing tidal volume and decreasing respiratory rate per minute. Rodents, however, tend to compensate in rate. The selection of an ideal anesthetic preserves or forces rate stability and preserves maximal costal expansion. Dalkara and colleagues (1995) have described a good example of success in mouse intubation. Several descriptions of small animal ventilator systems for imaging studies have been published (Hedlund et al. 2000; Minard et al. 1998).

The simplest and most consistent anesthetic regime used in MRI and PET procedures usually involves inhalation anesthetics and spontaneously breathing animal models. In these procedures, fast acting induction and recovery inhalation regimes afford greater safety as well as stable physiological effects. Animals are rapidly induced in anesthetic chambers that double as the animal holder for the imaging experiment. In these chambers the animal is continuously bathed in a gas anesthesia. This closed environment also permits the control of the temperature of the animal via the flowing gas as well as the oxygen and carbon dioxide levels for physiological perturbations. These simple nonventilated animal protocols have been very successful especially in studies that focus mostly on structure and not physiological function.

Magnetic Resonance Imaging (MRI) and Spectroscopy (MRS[1])

MRI and MRS are based on the detection of the oscillating magnetic field induced from a special set of nuclides that posse a net spin in the presence of a strong magnetic field. A detailed discussion of MRI and MRS appears elsewhere in this volume (Chatham and Blackband 2001). MRI generally refers to the determination of the distribution of one molecule, such as water or fat, within a tissue at high spatial resolution. MRS generally refers to maintaining the spectral information in the magnetic signals from the nuclides, which permits the determination of the molecules or metabolites containing a given nuclide. The collection of this [redacted]tional information in MRS along with the fact that metabolites are generally at low concentration results in the MRS e[redacted]iment having a low SNR. These combined effects make any images collected with MRS very poor in spatial and temporal re[redacted]tion. MRI and MRS must be conducted in a strong homogeneous magnetic field, which requires a specialized magnet as well as receiver coils to detect the nuclide signals. Because the absorption of these oscillating magnetic fields is relatively low in biological tissues, the penetration of these signals is excellent in most studies. The detection of the naturally occurring nuclide ^{1}H found in water and fats is usually used for MRI studies providing an adequate SNR to create images with submillimeter resolution in vivo. The MRI signal from water protons is rich in information about the physiology and function of tissues because it is the solvent of the cell with very little occurring without some impact on the magnetic properties of this molecule (Balaban 1998). This

information includes a diverse amount of information on blood flow and oxygenation as well as macromolecular composition and motion, tissue structure, temperature, contractile activity, nerve and muscle fiber orientation, and edema. A few other nuclides are present in adequate concentration to be used in natural abundance MRI, including ^{23}Na (Christensen et al. 1996; Winter et al. 1998; Wolff et al. 1990; Xia et al. 1996) (total Na distribution, some information on intracellular and extracellular distribution), ^{31}P (H[illegible]eh and Balaban 1987) (metabolite distribution and metabolic rates), and ^{2}H (Eng et al. 1990; Ewy et al. 1988) (structural and [illegible]mical information). These studies usually have much lower spatial and temporal resolution than ^{1}H due to their relatively low concentration and magnetic signal intensity per mole compared with ^{1}H. However, unique information can be obtained even on this spatial scale. Usually any tracer nuclide added to the animal is in a concentration too low to permit a reasonable MRI experiment to be conducted. The exceptions to this are inhaled superpolarized gases (Cremillieux et al. 1999; Viallon et al. 1999) (lung volume imaging, perfusion imaging) and ^{2}H- (Ewy et al. 1988; Robinson et al. 1998) and ^{19}F-labeled fluorocarbon blood substitutes (Zimmermann et al. 2000).

MRS maintains the spectral properties of the nuclides permitting the determination of the chemical species with in tissues. The nuclear magnetic resonance (NMR[1]) spectral properties of a given metabolite are a function of the local magnetic interactions within the molecule providing, in most cases, a unique spectral fingerprint. Using this fingerprint, investigators can determine the concentration of a given metabolite, noninvasively. In some metabolites, the physiological milieu (e.g., temperature, pH, or free Mg^{++} concentration) can modify the molecular interactions and resulting NMR spectral properties, providing unique information on these more global parameters. The lower concentration of these metabolites or ions generally results in poorer SNR and lower spatial resolution than conventional MRI procedures on water protons. MRS can be used on some natural abundance nuclides to good effect, monitoring several important metabolic reactions including ^{1}H (Gadian et al. 1986; Nielsen et al. 1999; Sebrie et al. 1998) (e.g., lactate, fat, glutamate, choline, inositol, glucose), ^{13}C (Artemov et al. 1998; Hassel and Brathe 2000; Peled-Kamar et al. 1998) (e.g., fats, glycogen), and ^{31}P (Holtzman et al. 1997; in't Zandt et al. 1999; Lukes et al. 1997; Robinson et al. 1998) (e.g., ATP, *creatine phosphate, glucose-6-phosphate, free phosphate). More extensive studies in MRS have been conducted with a* number of tracer molecules permitting the analysis of the intracellular milieu, metabolite kinetics, drug distribution and metabolism, ion fluxes, and metabolite dynamics. These nuclides used as tracers in MRS include ^{133}Cs (Schornack et al. 1997), ^{2}H (Eng et al. 1990), ^{15}N (Kanamori and Ross 1997; Meynial-Denis et al. 1997), ^{17}O (Arai et al. 1990; Fiat et al. 1992; Ronen et al. 1998; Sibson et al. 1998), ^{13}C (Bhujwalla et al. 1994; Pascual et al. 1998; Peled-Kamar et al. 1998; Sibson et al. 1998), ^{87}Rb (Cross et al. 1995; Deslauriers and Kupriyanov 1998; Syme et al. 1990), and ^{19}F (Hees and Sotak 1993; Mason et al. 1993; McSheehy et al. 1997).

Contrast agents in ^{1}H MRI are usually metal-based agents (including free Mn) that modify the magnetic relaxation properties of [illegible]. This permits the elimination or enhancement of the water depending on the agent and detection scheme. Specifically, a[illegible] to enhance the vascular bed or distribute in the interstial space have been very useful in angiography (Bogdanov et al. 199[illegible] Lauffer et al. 1998) as well as perfusion (Ikehira et al. 1988; Lyng et al. 1998), tumor detection (Maurer et al. 2000; Saini et al. 1995), and neuronal fiber tracking (Pautler et al. 1998).

As can be seen from just the number of nuclides that can be detected, the information content of MRI is remarkable. An incomplete summary of this information is included in Figure 1. From these data, one can gather information ranging from structure to the chemical composition of some elements. Physiological information of blood flow, oxygenation, and volume is available along with the metabolism that is supported by these processes. Finally, information on the extracellular and intracellular milieu, including ion concentrations, pH, and temperature, can also be obtained.

MRI and MRS methods have been successfully applied to the mouse and rat due to the advantageous scaling factors that occur in magnetic resonance (Dubowitz et al. 2000; Fayad et al. 1998, Jacobs et al. 1999; Maxwell et al. 1998; Slawson et al. 1998; Wiesmann et al. 1998). The mouse embryo has been extensively characterized (Smith 2000). Indeed, many of the pioneering biological applications of MRI were first performed on small mammals due to the availability of appropriate-sized magnets. Small animals also permit the use of small magnetic resonance receiving coils, which increase the sensitivity to the magnetic fields generated by the nuclides. In other words, the closer a coil can be physically placed to a target organ, the better the SNR of the measurement. This is analogous to the improvement in reception of a radio signal in your car as you approach the transmitter in your destination city. Smaller subjects also mean that smaller magnets with higher magnetic fields can be used. The SNR of the MRI experiment roughly increases linearly with the magnetic field when the sample noise dominates. At the time of this writing, mouse studies can be conducted on 11.7-T or even higher field systems in comparison to the 1.5-T systems used in humans (T = Tesla or 10,000 gauss earths field is 0.5 to 1 gauss). This means that an approximate factor of 10 or more increase in SNR can be realized using these small high-field magnets. However, the imaging experiment is a three-dimensional problem, and the cube root of this factor of 10 must be taken to evaluate the net effect of this increase in SNR on image resolution. For example, if an imaging voxel is 2 × 2 × 20 mm at 1.5 T, the voxel can only be reduced isotropically to ~0.9 × 0.9 × 9 mm at 11.7. Thus, both the magnetic field and coil proximity issues must be used to optimize the MRI experiment on a small mammal. It is our opinion that the r[illegible]ction in coil size is the greatest gain in MRI/MRS experiments, especially when superconducting coils (Hurlston 1999; Miller et a[illegible]99) may be used to eliminate the coil as a source of noise that may result in a stepper increase in SNR with magnetic field.

Finally, the small size of mice also permits the use of very high-powered imaging gradients, which makes it possible to obtain >100 gauss/cm at very high switching rates. This permits the high spatial resolution required as well as a reasonable desired speed of acquisition without causing neuronal stimulation in these small subjects. This high rate of acquisition can contribute to increases in SNR via true fast imaging with steady state procession ("FISP"), with short time to repeat values and reduced in-homogeneity effects via shorter time to echo values. The sum of these advantages results in the acquisition of images in mice that

are very comparable to those of humans, taking into account the physiologically important voxel size. Examples of a human and mouse heart are shown in Figure 2.

It is apparent from the progress in small animal MRI and MRS studies that much of the utility of these approaches in man will translate to the evaluation of small animal physiology.

Ultrasound

Ultrasound relies on the modification of an induced acoustic wave traveling through tissue. Ultrasound studies are conducted using a probe to project sound into the animal and recording the time and magnitude of the reflected sound wave using the same probe. The analysis of this acoustic echo permits the imaging and measurement of tissue acoustic properties. A detailed discussion of ultrasound appears elsewhere in this volume (Coatney 2001).

Ultrasound is used primarily for monitoring tissue structure and motion. The amount of tissue characterization that can be accomplished with ultrasound is limited. Because acoustic waves do not penetrate bone, ultrasound is not very useful in the developed brain with an intact skull. Another limitation of ultrasound is the fact that the acquisition of data is very user dependent in finding the appropriate acoustic "windows" for access of internal organs. Thus, a skilled technologist or investigator is required for these studies. Despite these limitations, ultrasound has been the mainstay in the evaluation of cardiac wall function, blood flow, and valve performance as well as an important tool in monitoring fetus development. The advantages of ultrasound include its ease of use, portability, and relatively low cost compared with MRI, CT, and PET. Due to its portability and the rapid frame rate that is relatively insensitive to motion, it is conceivable that nonanesthetized imaging studies could be conducted on restrained animals if the stress on the animal were not too great or influenced the results significantly. The portability and relative low cost suggest that these units could be housed in the animal holding facility permitting on-site data collection.

Recently, the development of bubble-based contrast agents (Calliada et al. 1998; Lindner et al. 2000) has improved the amount and quality of information in ultrasound imaging. Agents are now being developed for specific adhesion to useful markers in tissue that could expand the use of ultrasound in tissue analysis (e.g., Villanueva 1998). Another important contribution in this area has been harmonic-based ultrasound echo analysis (Forsberg et al. 1996, 2000), permitting higher tissue and agent-generated contrast. Real-time three-dimensional ultrasound (Linney and Deng 1999) performed on small animals may also remove some of the operator limitations as well as provide rapid whole animal studies. These approaches provide a significant opportunity in ultrasound in small animals to develop approaches to improve the specificity and physiology information content of this approach.

Ultrasound does scale appropriately with small animals. The resolution of the ultrasound experiment is roughly proportional to the frequency of operation. Smaller animals with a shorter path-length requirement for the ultrasound wave permit the use of higher frequencies that cannot adequately penetrate into larger animals or humans. The SNR of ultrasound is roughly constant, because the noise is a coherent "speckle" from internal reflections. However, as in magnetic resonance, the SNR of ultrasound is increased by the proximity of the probe to the region of interest. Thus, in smaller animals the target organ is much closer to the probe, which increases the inherent SNR. These factors permit the spatial resolution of the ultrasound instrument track with the size of the animal.

Again, using the heart as a comparison, the mouse images provided at 25 mHz and even higher frequencies are approaching the utility of human scale instruments. Numerous investigators have begun to use them in the evaluation of adult (Takeishi et al. 2000; Yokosawa et al. 2000) and fetal heart anatomy and function (Linask and Huhta 2000; Turnbull 2000). An example of an ultrasound image at 45 mHz is shown in Figure 3.

Compared with MRI, challenges in ultrasound imaging are tissue contrast and SNR. It is hoped that the advent of specific contrast agents will improve the utility of ultrasound beyond the structure/function studies now under way in animals. Regardless, ultrasound remains one of the least expensive and easiest to use of the imaging tools available for small animal evaluations concerning heart function and soft tissue structure outside the brain. Its ability to monitor fetal development under nonanesthetized conditions is also a valuable asset to the evaluation of development in transgenic animals.

CT

CT is basically a three-dimensional x-ray technique that is sensitive to the x-ray absorption of the tissue. Contrast can be generated by the differences in tissue absorption, with bone providing the most striking intrinsic contrast, or by using contrast agents to enhance the vasculature or specific tissues and conditions. The inherent SNR of CT is very high. Smaller animals provide some advantage in CT by permitting the use of low energy irradiation that can penetrate the mouse without significant attenuation. The low-energy irradiation is more sensitive to the tissue absorbance, which provides a higher contrast image. The use of low-energy irradiation in larger animals is prohibited due to the power deposition required to obtain an adequate flux through large structures. Finally, the size of the device can be greatly reduced, decreasing price, ease of shielding, and siting within an animal facility. Using current technology, full three-dimensional mouse images with 100 × 100 × 100 μm resolution can be obtained in a few minutes (Graichen et al. 1998; Kennel et al. 2000; Paulus et al. 2000; Yamashita et al. 2000) with higher resolution studies approaching potentially 50-μ m isotropic resolution with the one limitation being that the amount of energy absorbed by the animal may approach "invasive" levels. A coronal CT section of a mouse is shown in Figure 4. The skeletal

system highlighted in this CT image has been the focus of most of the initial work with small animal CT.

The high speed and high resolution of CT will clearly make it a valuable tool in the screening of large mouse populations. High-throughput systems for both vital and postmortem studies must be interfaced to these scanners to expedite the population screens envisioned for functional genomics. Contrast agents to improve soft tissue contrast as well as directly observe the vascular anatomy may also prove useful in the optimization of this approach to small animals, again requiring vascular access in the small animal. The major limitation of CT for use in small animals is the lack of information on tissue characterization and physiological function. Of all of the methods, CT will likely provide the greatest challenge in terms of data processing and data interpretation. As discussed above, a single data set from an isotropic 50-μm CT scan will approach 10^9 values. Due to the rather inefficient image reconstruction algorithms available for CT, these data will require a considerable amount of time just to convert into a useable image, not including any image processing or artificial intelligence to automate the interpretation of the images.

PET

PET relies on detection of radioactive probes emitted in the body. Imaging of this emission is performed using a combination of detector geometry along with the timing of the emissions detection. A detailed discussion of PET appears elsewhere in this volume (Cherry and Gambhir 2001). PET is one of the most sensitive imaging techniques and is capable of detecting vanishing small amounts of radiolabeled material. The short-lived isotopes (Ingvar et al. 1991) used in this approach include ^{11}C (Kuge et al. 2000; Levchenko et al. 2000), ^{13}N, ^{15}O (Magata et al. 1995; Yamamoto et al. 2000), and ^{18}F (Ingvar et al. 1991; Yamamoto et al. 2000) isotopes, which are extremely useful in the evaluation of biological processes. The clever use of these PET tracers and tracer chemistry is rivaled only by MRI/MRS in information content in an imaging modality (Phelps 2000). In addition to flow and metabolism markers similar in both PET and MRI, the sensitivity of PET has resulted in a unique ability to monitor receptor ligand interactions in humans and animals with remarkable success. This sensitivity has resulted in PET being one of the primary targets in the development of gene expression markers as well as the detection of early cancer (Phelps 2000). One of the major drawbacks of PET is the requirement for a local cyclotron to generate the probes and synthesis unit to produce the biologically useful probes. However, most major medical centers already have such facilities where the tiny quantities required for small animal imaging can be easily obtained. Because radioisotopes must be used in these studies, vascular access or direct injection of the tracers into the organ of interest is required.

PET has been demonstrated in the mouse and other small animals (Chatziioannou et al. 1999; Gambhir et al. 2000; Yu et al. 2000) using devices that can generate >5-fold higher overall spatial resolution than conventional human scanners (Cherry et al. [illegible]). For receptor binding in the brain, where the density of receptors may be similar in mice and humans, this resolution may still be inadequate for some studies. The major improvements in these small PET systems include the ability to design detectors that could more completely enclose the entire animal and collect a higher fraction of the emitted photons. In addition, for a given radioisotope, the small size of the animal results in less scattering and attenuation of the photons resulting in higher collection efficiency. These combined effects have resulted in very successful application of PET to the study of small animals. An example of the detection of reporter gene (herpes simplex virus 1 thymidine kinase) in the mouse using a 18-F labeled metabolite is shown in Figure 5 (Gambhir et al. 1999) from the UCLA group.

With these early demonstrations in small animals and the commercial availability of high-resolution PET instruments, the use of PET in the characterization of mice will certainly increase. The major advantage of PET is high sensitivity without the penetration limitations of optical techniques. The successful application of this approach will depend on the development of appropriate probes that will determine the specificity and sensitivity of the measurements.

Optical Imaging

Optical imaging is an extremely sensitive measurement that can detect a single molecule using fluorescence techniques. Optical imaging is usually performed in two modes: simple transmission absorption imaging and fluorescence imaging. In simple transmission absorption imaging, either transmitted or reflected light is used with tissue or optical probes, providing differential absorption to generate useful tissue contrast. The most common technique used here is optical coherence tomography (Chen et al. 1998; Kehlet et al. 1999; Roper et al. 1998). Fluorescent imaging is performed by irradiating the tissue with a frequency of light lower than the emission frequency exciting fluorescence from intrinsic or extrinsic probes under investigation. Fluorescence imaging is the most sensitive approach, and it has gained great interest with the development of genetically encoded highly efficient fluorescent probes based on green fluorescence protein. Optical imaging in large animals has mostly been limited to the study of skin, eyes, surface vessels, and epithelial tissues accessible to visible light (Barton et al. 1999; Chen et al. 1998; Kehlet et al. 1999; Knuttel and Boehlau-Godau 2000; Masters et al. 1998; Roper et al. 1998). Some spectroscopic studies with limited imaging resolution have been conducted with infrared light (IR[1]). These studies have been mostly focused on imaging structures using the natural differential optical absorbance of tissues. Most notable have been the direct observations of blood cell motion using the high extinction of the hemoglobin. Some naturally occurring probes including myoglobin, hemoglobin, and cytochromes can provide biochemical information within the tissue specifically dealing with oxygen delivery and mitochondrial energetics (Steen et al. 1989; Steinberg et al. 1997; Ueda et al. 1988). However, most of the activity in optical imaging focuses on the use of exogenous or genetically engineered optical probes. Probes are being created to evaluate everything from structure to intracellular milieu to protein function in vivo with unparalleled sensitivity and spatial resolution. Like all newly introduced probes, the adverse effects of these molecular manipulations must be carefully followed to ensure that the measurement or probe is not interfering with the background phenotype or physiology (Huang et al. 2000).

The major limitation of light is the high absorption and scattering that occur in biological tissues and limit the penetration of the light through the body. However, in small animals the required path-length of light is much shorter, which makes the use optics much more feasible. Multiphoton (so-called two- or three-photon confocal microscopy) fluorescence microscopy has also improved the depth of resolution and quality of fluorescence imaging in intact tissues by limiting the excitation field. Using this latter approach with specific protein fluorescence probes, the morphology and plasticity of neurons have been directly observed in v[illegible]sing two-photon confocal microscopy in rats (Figure 6) (Lendvai et al. 2000). The feasibility of using this approach on entire em[illegible]s without significant physiological effects on development has also been demonstrated (Squirrell et al. 1999). On a larger scale, whole adult animal screening has recently been shown using whole body IR fluorescence (Weissleder et al. 2000). An example from this study is shown in Figure 7 in which a tumor that trapped a polymer containing a near-IR fluorescence probe was localized in the intact mouse.

The optical detection of molecular events is the most sensitive molecular imaging tool available in vivo. Due to the small size of the mouse and the ability to create optical markers for monitoring a wide variety of gene functions or even simple physiological and anatomical questions, it is clear that this approach will play a growing role in the noninvasive evaluation of the mouse phenotype.

Summary

Most of the standard imaging modalities used in clinical evaluations scale favorably to the size of a mouse or rat. These improvements in performance result in the maintenance of the physiologically relevant information in these images even though the size of the subjects has been reduced by several orders of magnitude. Due to its high sensitivity and specificity coupled with the ability to create genetically coded probes, optical imaging is likely to play a growing role in small animal imaging. Major challenges in this approach are the maintenance and monitoring of an appropriate physiological state while conducting these studies. All of the modalities must be further modified to optimize their performance in the study of small animals; however, as noted in this review good progress is being made. Potentially, the largest technical challenge involves handling and processing the enormous amount of data provided by the approaches. One of the advantages of studying small mammals is that large numbers can be evaluated for genetic or mutant screening. Imaging these large numbers will result in the mandatory development of computational systems capable of handling these large data sets. In addition, analysis of these data must be automated in some form to reduce the need for the investigator to screen each of these images. These automated image interpretation systems are also under development in the clinical radiology community where useful approaches may already be undergoing evaluation. With the growing interest in the function of genes in development and function as well as the study of intact biological systems in m[illegible]mals, it is clear that these screening imaging tools will play a critical role.

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[1]Abbreviations used in this article: CT, computer-assisted tomography; IR, infrared light; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NMR, nuclear magnetic resonance; PET, positron emission tomography; SNR, signal-to-noise ratio.

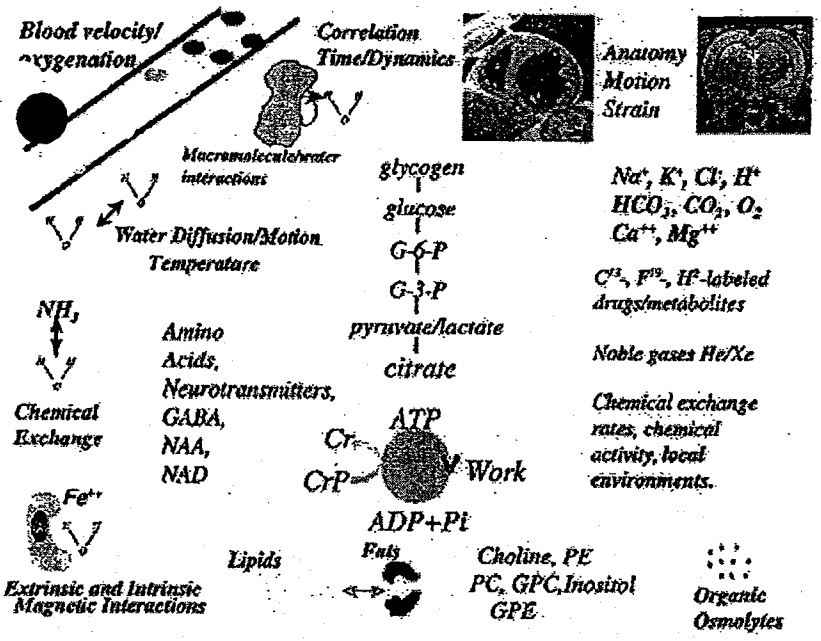

Figure 1 Schematic diagram of information content of magnetic resonance imaging (MRI)/magnetic resonance spectroscopy (MRS). Italicized text is information extracted from water proton imaging (MRI). Most of the other information is gathered using MRS techniques. ATP, adenosine 5c-triphosphate; GABA, aminobutyric acid; GPC, glycerolphosphorylcholine; GPE, glycerolphosphorylethanolamine; NAA, N-acetylaspartate; NAD, nicotinamide adenine dinucleotide; PC, phosphorylcholine; PE, phosphorylethanolamine.

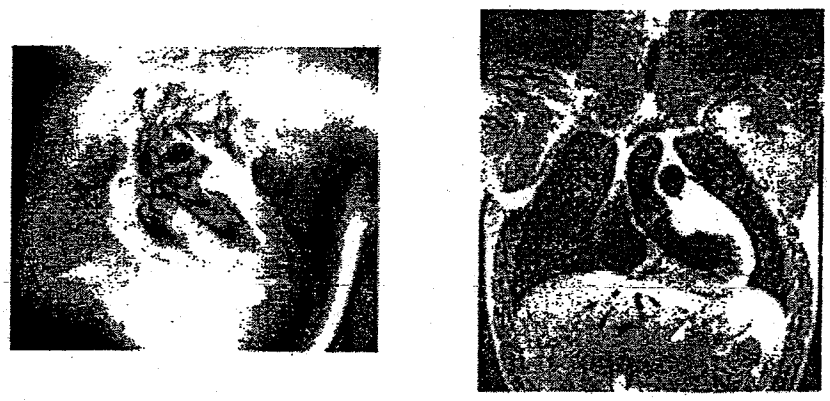

Figure 2 Proton magnetic resonance images of the mouse (left) and human heart (right). The mouse heart image was collected in a 4.7-T system using a surface coil placed around the chest of the mouse. The human image was collected at 1.5 T using a whole body coil and a similar inversion recovery sequence as used in the mouse to result in the "black-blood" image. Both images were collected in less than 5 min.

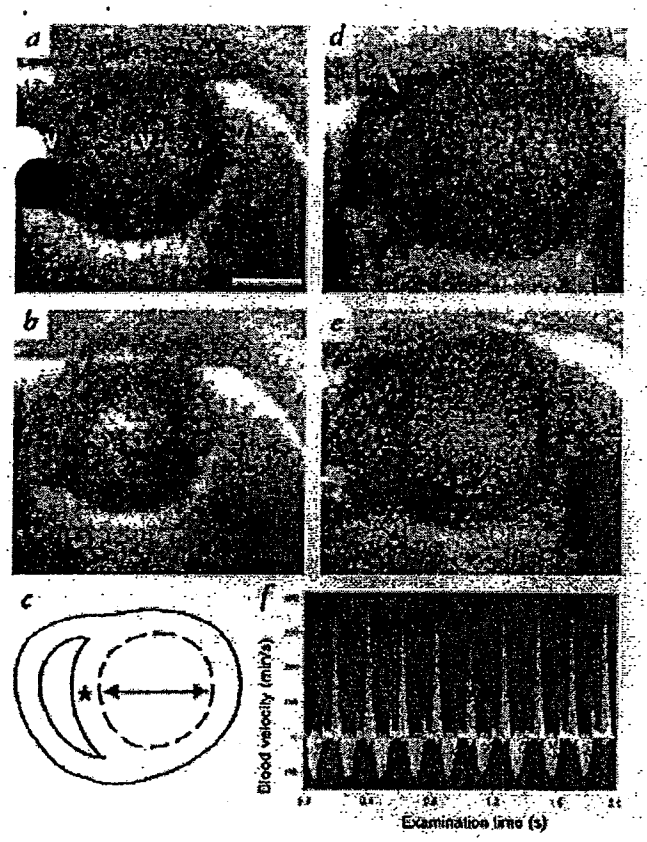

Figure 3 45-MHz ultrasound images of the mouse heart. Data used with permission from Fatkin D, Christe ME, Aristizabal O, M[illegible]onnell BK, Srinivasan S, Schoen FJ, Seidman CE, Turnbull DH, Seidman JG. 1999. Neonatal cardiomyopathy in mice he[illegible]rgous for the Arg403Gln mutation in the alpha cardiac myosin heavy chain gene. J Clin Invest 103:147-153.

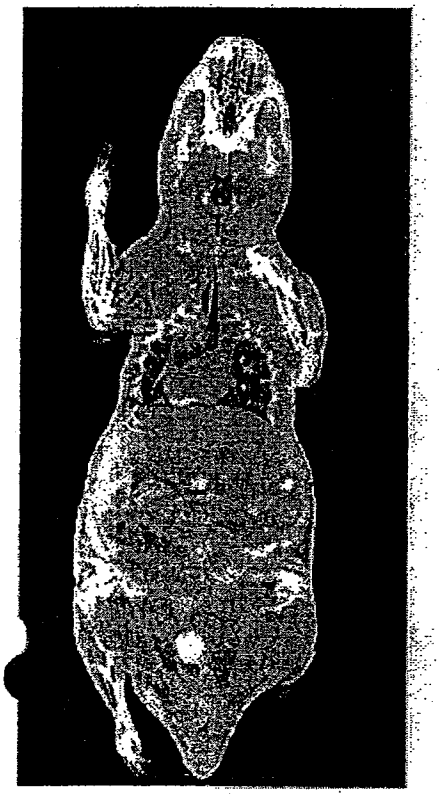

Figure 4 Computer-assisted tomography coronal section through a whole mouse. Image courtesy of Oak Ridge National Laboratories, Oak Ridge, Tennessee.

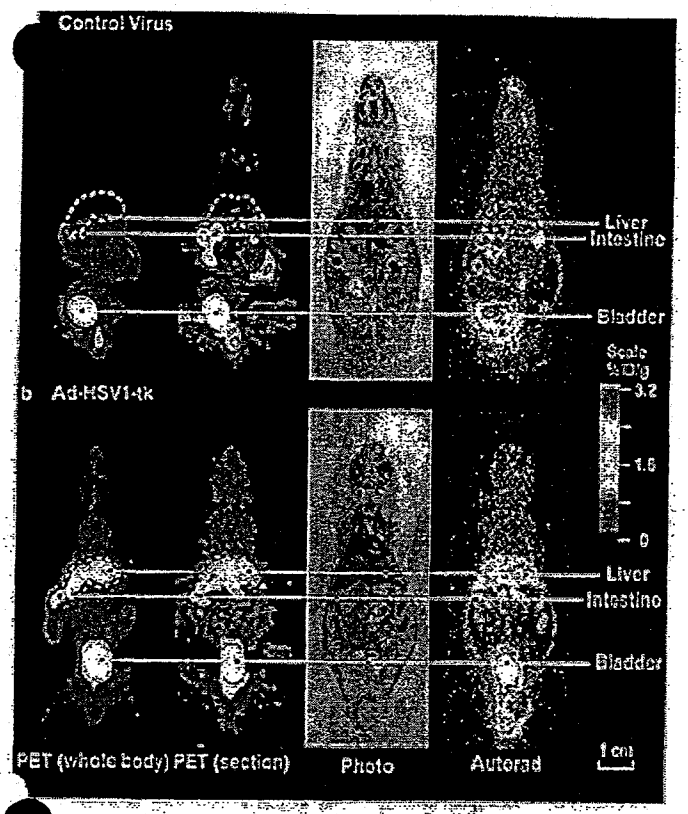

Figure 5 18-F positron emission tomography (PET) images of a mouse after virus infection with the HSV1-tk reporter gene. 8-(^{18}F) fluoroganciclovir was used as the active metabolite. (a) Control images. (b) Active virus. The labeling in the liver and intestine was found to be enhanced in the presence of the viral infection. *ID/g, infectious dose per gram.* Data used with permission from Gambhir SS, Herschman HR, Cherry SR, Barrio JR, Satyamurthy N, Toyokuni T, Phelps ME, Larson SM, Balatoni J, Finn R, et al. 2000. Imaging transgene expression with radionuclide imaging technologies. Neoplasia 2:118-138.

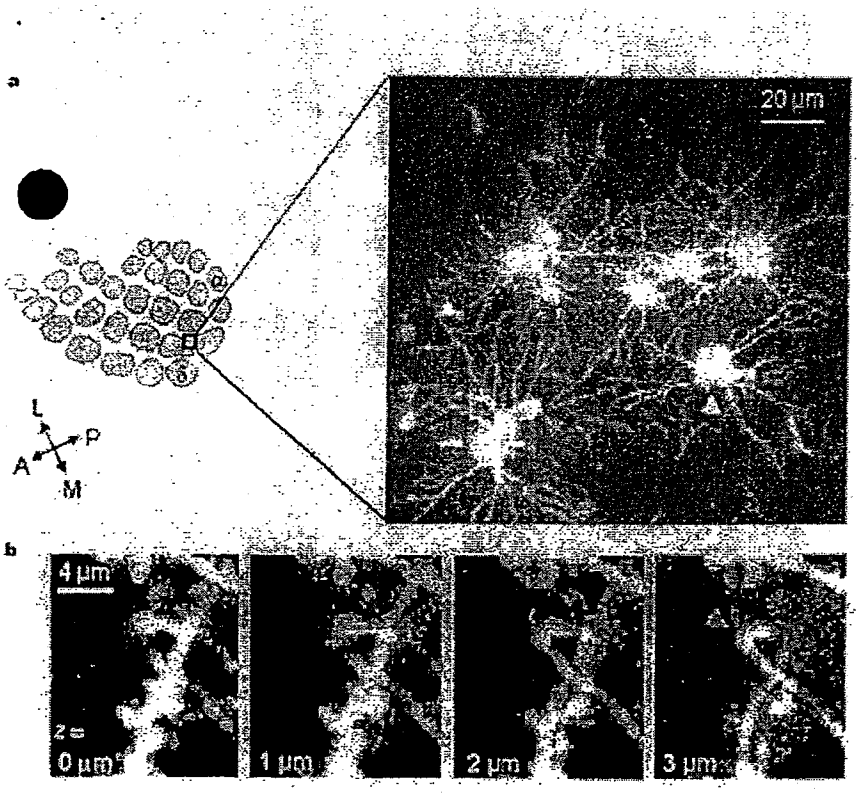

Figure 6 (a) Green fluorescence confocal microscopy of dendrites in developing rat brain. (b) Images of barrel cortex neurons that were enhanced by the expression of green fluorescence protein DNA introduced by the selective injection of engineered Sindbis virus. Data used with permission from Lendvai B, Stern EA, Chen B, Svoboda K. 2000. Experience-dependent plasticity of dendritic spines in the developing rat barrel cortex in vivo. Nature 404:876-881.

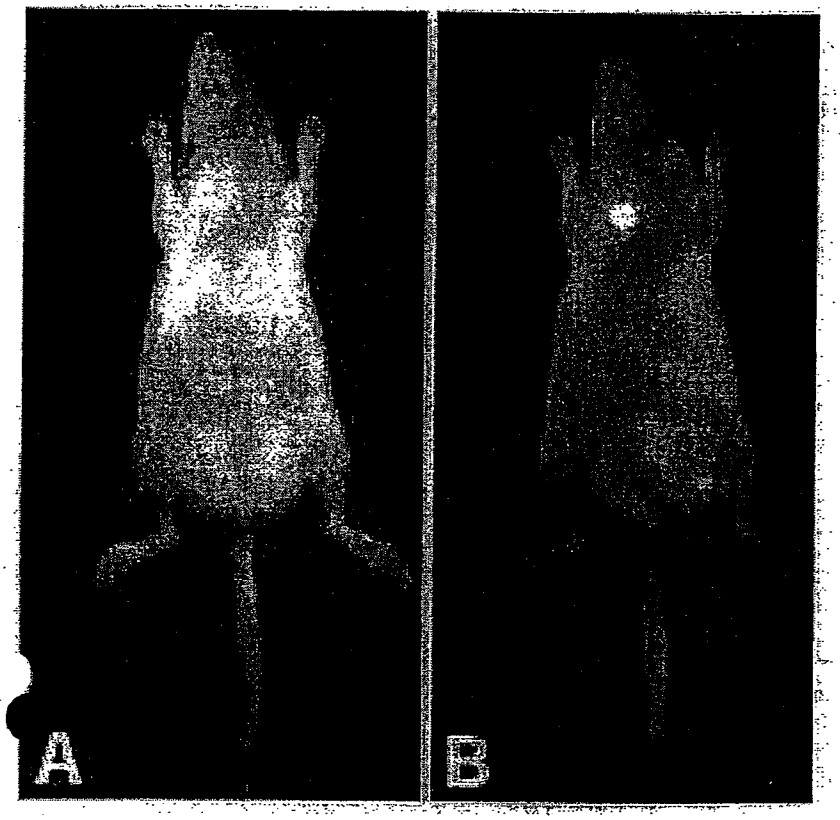

Figure 7 Whole body near infrared (IR) fluorescence image of a mouse. (A) Mouse reference image. (B) Whole body infrared

fluorescence. A polymer containing a self-quenched fluorescent probe was administered by injection into the animal and trapped in the tumor (bright structure in infrared image). The fluorescence was enhanced in the tumor by the activity of lysosomal proteases, which cleaved the polymer and reduced the self-quenching of the probe by releasing it from the polymer. Data used with permission from Weissleder R. 1999. Molecular imaging: Exploring the next frontier. *Radiology* 212:609-614.

Table Justifications of vital imaging studies

- Need for dynamic physiological data or labile biochemical/structural information
- Need for internal longitudinal controls
- Animals are valuable breeding stock or difficult to produce or maintain
- Monitoring and adjustments of drug treatments or other experimental protocols
- Use of imaging technique to screen for inclusion in another protocol

Close

Definition of Pain and Distress and Reporting Requirements for Laboratory Animals: Proceedings of the Workshop Held June 22, 2000 (2000)

Institute for Laboratory Animal Research (ILAR)

Personal Experiences with Clinical Pain Management, Study Design, Mitigation of Scientific Confounders, and Long-term Gains to the Researchers and Public

Victoria Hampshire

Advanced Veterinary Applications
Bethesda, Md.

It is truly an honor to be invited here to the National Academy of Sciences and to have the opportunity to be associated with all of you. As a newcomer to this arena, you might say that I am well qualified and have come of age on the front line in mammoth research programs where I have collaborated with scientists to reduce distress in animal models within scientific constraints of the protocols.

EXPERIMENTAL EFFECTS ON ANIMALS

Animal models of human disease and physiology are becoming exceedingly complex. Experimentation is not neatly packaged. Pain and "altered states" of physiology leading to distress can be acute or chronic in duration and any combination. It is a mistake to state, as many have, that animals do not suffer during experimentation simply because they have not been observed to suffer. Lack of observation is particularly relevant because only small numbers of programs, if any, provide more than 8 hours of care over the workday. It is also a mistake to dwell on costs associated with increased provisions for monitoring and intervention programs because the relative savings are well known in terms of

higher animal yields, smaller interanimal variability due to management of stressors, and shorter time from bench-to-bedside human trials. Thus, quality pain management programs result in more observations during experimentation and public assurances that are immeasurable.

OCR for page 78

78 DEFINITION OF PAIN AND DISTRESS AND REPORTING REQUIREMENTS Results of Cumulative Minor Events It is my clinical opinion that most animals in research suffer from cumulative and minor events that, when combined, amount to distress. In other words, the animal is not feeling well enough to normally ambulate, eat, or drink. It then becomes a bit dehydrated, a downward trend develops, and more serious stressors result. early detection provides the greatest gain in terms of control of variables and pain and distress management. Current endpoints such as loss and low body temperature are instituted long after distress and stress or pain are encountered and are useless to refinements that are ei pragmatic or benefi- cial. Viewed prospectively, however, a variable such as weight can be very use- ful for finding that particular instance when results become negative. Time is therefore essential in pain management if one hopes to reach beyond a paper program and create one of substance. The importance of time is more dramatic in smaller animals as metabolic rate is known to be roughly 10 times higher in mice than man. Other species fall somewhere between. The best way to describe this early detection of weight loss and other variables contributing to physiological stress is to describe the following example. Multidimensional Risk An excellent example of multidimensional risk is that of canine myocardial ischemia (Banal and others 1991,1994; Lazarous and others 1996; Rajanayagam and others 2000; Shou and others 1997; Unger and others 1990, 1991, 1993a,b; 1994~. The dog patient received a left lateral thoracotomy incision to create a left anterior descending coronary artery event. In this example, I shall discuss veteri- nary support surrounding a decade of research involving hundreds of canine patients on which human trials were eventually predicated. The instrumentation utilized to constrict arteries over a 3-week period of time is a silastic balloon ameroid placed over the artery and tunneled through the ribs into the subcutaneous space. The dog, pig, or rat (as are today's models) is then recovered overnight with oxygen, warmth, analgesics, and antibiotics; it also must receive constant monitoring for ventricular arrythmias, infection, electrolyte imbalance, and glucose disturbances. The model then undergoes the additional stress of serial MRI or angiographic episodes under general anesthesia. Then add the additional experiment whereby the investigator wishes to administer viral-mediated gene therapy using adenoviral vascular endothelial growth factor, and have a singular experiment within a multidimensional risk project. The risks to distress include infection, dehydration, electrolyte disturbances, arrythmias and angina, poor wound healing, and increased catabolic demand at a time when animals do not feel particularly well. Within this one model, you may look at one possible risk such as infection or septicemia. Septic animals undergo an initial systemic inflammatory response.

OCR for page 79

PERSONAL EXPERIENCES WITH CLINICAL PAIN MANAGEMENT 79 The body is then riddled with the events associated with hyperdynamic shock, leaky blood vessels, pulmonary edema, and glucose and electrolyte disturbances. Such events must be detected within hours to provide symptomatic relief as well as to stabilize the experiment. Therefore, an 8-hour or singular monitoring scheme is worthless to the animal, the model, and, ultimately, extrapolation to public medicine and benefit. PROVISION OF NECESSARY IMPROVEMENT In 1989, when I first joined NIH, this model received only a few hours of intensive care and was put back in a kennel. The mortality rate was 55%. During my first 5 years there, I had supportive program directors who encouraged the augmentation or magnification of veterinary presence. I made steady improve- ments, which included acquisition of an overnight technical staff, clinical chem- istry and complete blood count analyzers that gave results instantly at the cageside, and the provision of scoring systems that augmented analgesic adminis- tration. Survival rates increased to 95%. Deaths were always associated with sudden ischemia and closure of the ameroid rather than with other complications. I was very proud of this progress and other changes, and the scientists noted a more expensive short-term solution with long-term benefit. Over the next 5 years, I continued to make similar improvements across all species and all projects. Although the scientists initially viewed this as expensive, they eventu- ally understood the benefit. Scheme of Veterinary Care In my view, the way to achieve this outcome is to suggest a scheme more like a good veterinary teaching hospital or te clinic for animals in these risk groups. We thus need small teams to cover large amounts of ground and high rodent density housing for less groups in an effort to discover outliers. Such management is accomplished by the hiring of clinically astute veterinarians and roaming te al teams. The emergence of large numbers of genetically altered rodents can also be monitored in this manner by central dispersion of tea of technologists under the line command of clinical veterinarians. Successful monitoring has already been achieved in some places and was recently described in Lab Animal (Hampshire and others 2000a,b). Shifting Responsibility for Performance Standards Additionally, it is not reasonable to expect today's scientist to be clinically knowledgeable or experienced about veterinary medicine; therefore the develop- ment and

line accountability of such teams of clinical veterinarians and technologists

OCR for page 80

EFINITION OF PAIN AND DISTRESS AND REPORTING REQUIREMENTS are absolute requirements for accomplishing this task. In the context of ch budgets, this approach is easily achieved by a shift from engineering standards toward greater emphasis on veterinary performance s ards. However respon- sible, the scientists can be unrealistically expected to understand or have time to fully manage such key animal populations. There must be responsibility, col- laboration, and authority of clinical veterinary staff. ESTABLISHMENT OF PREREVIEW Finally, part of ILAR' s directive today was to provide guidance to USDA' s inclusion of alternative searches in Policy 11. I have not heard anyone call this a similarities search, but having performed such searches, I believe the existing directive does not enhance science or animal care. The current policy and enact- ment drive away scientists rather than enlisting their cooperation because it is described and viewed as a barrier rather than an opportunity. A better solution is to require a prereview in which the attending veterinary staff search human and animal-similar literature for the purposes of seeking answers to confounding variables, stress and pain outcomes, and case management of human or animal- similar patients. Alternatives, in my opinion, are most beneficial when viewed as refinements to animal care and study design. If such a search were undertaken prospectively for these purposes, compliance with responsible use of animals would often develop naturally. SCIENTIFIC JOURNALS AS FACILITATORS I must mention literature because methods that describe adequate animal care and monitoring are frequently not part of scientific journal reporting. Many investigators argue that their science does not need refinement because the methods they are utilizing have been reproduced time and again according to proven methods. Many will also try to pool controls from previous work in which no pain and distress management schemes were utilized. I contend, how- ever, that many methods are missing from such papers. A preponderance of papers reviewed, do not mention analgesic programs and leave the reader to wonder if compliance really existed at all. One must understand that the recalcitrant scientist will continue to ignore Policy 11 directives but will still cater to the scientific journals under today's "publish or perish" conduct. If the majority of exemplary publications were also to include a section specifically describing pain and distress monitoring, dura- tion, and intervention criteria, the mainstay of scientists would also conform to that standard. A commensurate education in Policy 11 guidelines and journal management would be very useful for achieving this goal.

OCR for page 81

PERSONAL EXPERIENCES WITH CLINICAL PAIN MANAGEMENT CONCLUSION 81 I have attempted to describe a pain classification system that is substantive when viewed retrospectively. It assumes strong veterinary action in prereview, the design of a pilot, and retrospective adjustment of protocols not only so that accurate reporting is performed, but also so that the public can be made more aware of which relief measures were meaningful. This system of veterinary col- laboration, pilot design, and retrospective refinements and reporting affords more efficient experimental conduct with more accurate reporting of results and animal pain classification. REFERENCES Banai S., M.T. Jaklitsch, W. Casscells, M. Shou, S. Shrivastav, R. Correa, S.E. Epstein, and E.F. Unger. 1991. Effects of acidic fibroblast growth factor on normal and ischemic myocardium. Circ Res 69:76-85. Banai S., M.T. Jaklitsch, M. Shou, D.F. Lazarous, M. Scheinowitz, S. Biro, S.E. Epstein, and E.F. Unger. 1994. Angiogenic-induced enhancement of collateral blood flow to ischemic myocar- dium by vascular endothelial growth factor in dogs. Circulation 89:2183-2189. Hampshire V.A., C. McNickle, and J.A. Davis. 2000a. Red-carpet rodent care: Making the most of dollars and sense in the animal facility. Lab Anim 29:40-45. Hampshire V.A., C. McNickle, and J.A. Davis. 2000b. Technical team approaches to rodent care: Cost savings, reduced risk, and improved stewardship. Lab Anim 29:35-39. Lazarous D.F., M. Shou, M. Scheinowitz, E. Hodge, V. Thirumurti, A.N. Kitsiou, J.A. Stiber, A.D. Lobo, S. Hunsberger, E. Guetta, S.E. Epstein, and E.F. Unger. 1996. Comparative effects of basic fibroblast growth factor and vascular endothelial growth r on coronary collateral development and the arterial response to injury. Circulation 94:1074-1082. Rajanayagam M.A., M. Shou, V. urti, D.F. Lazarous, A.A. Quyyumi, L. Goncalves, J. Stiber, S.E. Epstein, and E.F. Unger. 2000. Intracoronary basic fibroblast growth factor e es myo- cardial collateral perfusion in dogs. J Am Coll Cardiol 35:519-526. Shou M., V. Thirumurti, S. Rajanayagam, D.F. Lazarous, E. Hodge, J.A. Stiber, M. Pettiford, E. Elliott, S.M. Shah, and E.F. Unger. 1997. Effect of basic fibroblast growth factor on myocardial angiogenesis in dogs with mature collateral vessels. J Am Coll Cardiol 29:1102-1106. Unger E.F., S. Banai, M. Shou, M.T. Jaklitsch, E. Hodge, R. Correa, M. Jaye, and S.E. Epstein. 1993a. A model to assess interventions to improve collateral blood flow: Continuous adminis- tration of agents into the left coronary artery in dogs. Cardiovasc Res 27:785-791. Unger E.F., S. Banai, M. Shou, D.F. Lazarous, M.T. Jaklitsch, M. Scheinowitz, R. Correa, C. Klingbeil, and S.E. Epstein. 1994. Basic fibroblast growth factor enhances myocardial collateral flow in a canine model. Am J Physiol 299(Pt 2):H1588-H1595. Unger E.F., C.D. Sheffield, and S.E. Epstein. 1990. Creation of anastomoses between an extracardiac artery and the coronary circulation. Proof that myocardial angiogenesis occurs and can provide nutritional blood flow to the myocardium. Circulation 82:1449-1466. Unger E.F., C.D. Sheffield, and S.E. Epstein. 1991. Heparin promotes the formation of extracardiac to coronary anastomoses in a canine model. Am J Physiol 260(Pt 2):H1625-H1634. Unger E.F., M. Shou, C.D. Sheffield, E. Hodge, M. Jaye, and S.E. Epstein. 1996. Extracardiac to coronary anastomoses support regional left ventricular function in dogs. Am J Physiol 264(Pt 2):H1567-1574.

Representative terms from entire chapter:

fibroblast growth factor, endothelial growth factor, clinical pain management, growth factor enhances, basic fibroblast growth, growth factor, vascular endothelial growth, pain management, fibroblast growth, clinical pain, enhances myocardial collateral, factor enhances myocardial, collateral blood flow, endothelial growth, animal care, basic fibroblast, vascular endothelial, myocardial collateral, veterinary staff, collateral blood, distress management, clinical veterinarians, animal models, pain classification, enhances myocardial, myocardial angiogenesis, coronary artery, coronary anastomoses, accurate reporting,

Science Blog

2000

From: Humane Society of the United States

HSUS news conference

HSUS to launch effort to end research animal pain and distress at Washington news conference

WHO:
Andrew Rowan, Ph.D., senior vice president, The Humane Society of the United States (HSUS)

Martin Stephens, Ph.D., vice president, Animal Research Issues, The HSUS

Alan Goldberg, Ph.D., director, The Center for Alternatives to Animal Testing, Johns Hopkins University

Barbara Orlans, Ph.D., professor, The Kennedy Institute of Ethics, Georgetown University

Victoria Hampshire, VMD, director, Advanced Veterinary Applications

WHAT:
News conference to launch The HSUS' efforts to end pain and distress in research animals by the year 2020.The HSUS will release a report documenting that substantial numbers of animals used in research in the United States endure pain and distress that is neither reported nor alleviated despite federal Animal Welfare Act mandates. The report also contains The HSUS' blueprint for ending pain and distress in research animals over the next 20 years.

Other panel participants will discuss the legislative framework for addressing pain and distress, public concern on this issue, the recognition and alleviation of pain and distress, and problems with the existing system for reporting pain and distress.

Agenda OBT

WHEN:
Thursday, April 27, 2000 10:00 a.m.

The week of April 23 is World Week for Animals in Laboratories

WHERE:
First Amendment Room National Press Club Washington, DC

A light breakfast will be served.

Contact: Rachel Querry at 301-258-8255

Victoria Hampshire Article

ANIMALNET OCTOBER 12, 2000

http://131.104.74.73/archives/animalnet/2000/10-2000/an-10-12-00-01.txt

Farm plan angers estates residents: hog operation seen as potential
Walkerton
Alberta's feedlot alley
Outbreak of rift valley fever --- Saudi Arabia, August--October, 2000
In defence of animal research
Poorly conducted(or reported)animal tests put humans at risk
House backs year's delay in extra care for lab rats
Water buffalo win reprieve: Ottawa gives archers another month
Indonesian official orders mammals killed to stem spread of rabies
"Geese in space - the next generation" takes off with Ducks Unlimited
Animal-rights group says it may target Burger King
Endangered and threatened wildlife and plants: 90-day finding on a petition to list the California spotted owl as threatened or endangered
Fisheries of the northeastern United States; Atlantic surf clam and ocean quahog fishery; suspension of minimum surf clam size for 2001
Anacapa island restoration plan, final environmental impact statement, channel islands national park, Ventura County, Ca; notice of availability
Fisheries of the exclusive economic zone off Alaska; Bering Sea and Aleutian Islands area; amendment 58 to revise the Chinook salmon savings areas
Fisheries of the northeastern United States; scup fishery; Commercial quota harvested for winter II period

AnimalNet is produced by the Centre for Safe Food at the University of Guelph, and is supported by the Ontario Cattlemen's Association, the U.S. National Pork Producers, U.S. National Food Processors Association, Pfizer Animal Health Group, Pioneer Hi-Bred Limited (Canada), Canadian Animal Health Institute, Meat & Livestock Australia, Canadian Pork Council, Ontario Egg Producers, Ontario Farm Animal Council, U.S. National Cattlemens Beef Association, the Rutgers Food Risk Analysis Initiative, Ag-West Biotech, Land O' Lakes Feed, Capital Health, Animal Industry Foundation, American Feed Industry Assn., the Ontario Soybean Growers Marketing Board, Food Industry Environmental Network, Canadian Poultry and Egg Processors, Chicken Farmers of Canada, MDS Nordion, American Meat Institute, AdCulture, USDA Veterinary Services (Fort Collins) Alberta Farm Animal Council, and the Agricultural Adaptation Council (CanAdapt Program).

Agency Obtain

archived at:
http://www.plant.uoguelph.ca/safefood/archives/animalnet-archives.htm

POORLY CONDUCTED (OR REPORTED) ANIMAL TESTS PUT HUMANS AT RISK

October 12, 2000

Nature 407, 671 (2000)

Victoria Hampshire of Advanced Veterinary Applications in Bethesda, Maryland writes that animal clinical research paradigms are part of the mechanism for assessing the risks of new drugs in humans. To extrapolate the results to humans requires that animal experiments are designed adequately and conducted properly, with the methods fully reported. But, says Hampshire, these goals are often not met, either because collection of equivalent clinical parameters is held to be too difficult or time-consuming, or because of an effort to over-simplify complex biological systems in animals that are not identical or close to the human paradigm [1]. This problem needs rectifying.

Hampshire says that the sort of information that should be recorded and reported includes means and standard deviations for weight, electrolytes and glucose, and the exact time of day of key treatments (including weekends). This would reveal whether such variables were kept constant throughout the experiment, and would show whether failures were due to failure of treatment or of support care.

Another area requiring more detailed reporting is that of pain detection and alleviation, where is not evident in publications of studies supported by the US Public Health Service (PHS). The PHS and the US Department of Agriculture require alleviation of pain in animals, but this information isn't appearing in the methods sections of publications.

Hampshire says that in order to provide information about the dynamic nature of the success or failure of treatment, clinical pathological data should be used, from tests such as complete blood counts, clinical chemistries and organ profiles carried out on living animals at specified times during a disease. Pathological data alone (from tests carried out after death, such as liver biopsies) are not adequate.

Omissions in reporting are prevalent.

Hampshire goes on to say that scientists and the public need access to correct information about clinical protocols in animals. We need more of the right kind of clinical study design, and more collaborative reporting from inside animal facilities.

Such partnerships between veterinarians and scientists are sticky; they require a change in thinking. Scientists need to stop viewing veterinary care as a burden and see it as a quality assurance for studies that are destined for human use. As well as allowing more accurate risk/benefit analysis for human drug trials, introduction of such reporting standards in non-human experiments could also reduce the amount of costly regulation required at the later stages of commercialization of drugs.

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i.e. subscribe animalnet -L Wendy Powell

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For more information about the AnimalNet research program, please contact:
Dr. Wendy Powell
wpowell@uoguelph.ca
http://www.plant.uoguelph.ca/safefood

archived at:
http://www.plant.uoguelph.ca/safefood/archives/animalnet-archives.htm

Contents

Pain & Distress Report

Fall 2000
Volume 1, Issue 1

A report from the Pain & Distress Initiative of The Humane Society of the United States

Policies & Perspectives

USDA Seeks Comments on Pain and Distress Issues

The U.S. Department of Agriculture (USDA) has announced its intention to revise the regulation and reporting of pain and distress in laboratory animals under the Animal Welfare Act. As part of this process, the USDA sought public comments on defining "distress" and revising the current reporting system for pain and distress.

The USDA's request for comments was published in the July 10, 2000 *Federal Register,* Vol. 65, No. 132 and on the USDA website, *www.aphis.usda.gov/ppd/rad/webrepor.html.* The comment period ended on November 7, 2000. Comments were requested about the following issues.

▶ Would the addition of a definition of "distress" help animal research institutions recognize, minimize, and report animal distress?

▶ If a definition for "distress" is created, what elements should be included in the definition?

▶ What are the benefits and limitations of the current pain and distress classification system?

▶ Should the current classification system be revised or replaced? If so, what specific classification systems should be considered?

▶ Should animal pain and distress be reported prospectively (amount of pain and distress *predicted* beforehand) or retrospectively (*actual* pain and distress observed)?

Changes to USDA Policy #12—Alternatives to Painful/Distressful Procedures

On June 21, 2000, the USDA announced changes to Policy #12, which [illegible] consideration of alternativ[illegible] procedures [illegible] pain and di[illegible] This policy [illegible] researchers [illegible] in order to [illegible] that addre[illegible] and refiner[illegible]

Agency Obtained

The researcher was to provide a written narrative of the database search to the Institutional Animal Care and Use Committee (IACUC), and specify what alternatives, if any, were available.

The new version of the policy allows other sources to be used in lieu of the databases: "conferences, colloquia, subject expert consultants, or other sources may provide relevant and up-to-date information regarding alternatives." If these other sources are used, the researcher should explain why the sources are valid. "Regardless of the alternatives source(s) used, the written narrative should include adequate

continues on page 2

continued from page 1

information for the IACUC to assess that a reasonable and good faith effort was made to determine the availability of alternatives or alternative methods." The revision specifies that "[w]hen other sources are the primary means of considering alternatives, the IACUC and the inspecting Veterinary Medical Officer should closely scrutinize the results."

For more information, see *www.aphis.usda.gov/ac/policy/policy12.*

AALAS Issues Position Statement on Pain and Distress

The American Association for Laboratory Animal Science (AALAS) issued a position statement in spring of 2000 on the recognition and alleviation of pain and distress in laboratory animals. The statement (available at *www.aalas.org*) addresses technical aspects of pain and distress as well as policy issues such as the USDA reporting system. Regarding the latter, AALAS states that the "current USDA reporting categories have been in use for many years and would benefit from revision and expansion to improve their utility" (p.1).

The AALAS position statement notes the following: The evaluation of potential pain or distress is a complex process and varies amongst species and individuals; determining what constitutes pain or distress in animals is made more difficult by the lack of agreed-upon criteria and definitions; the alleviation of pain and distress requires that multiple methods be applied from anesthetics, analgesics, environmental enrichment, to significant alterations in research protocols; and ways of alleviating pain and distress may interfere with the production and/or collection of accurate data. The statement argues that the current USDA pain and distress reporting categories are not reflective of animal states, nor do they provide useful data. Possible policy changes may create less accurate information.

The AALAS statement offers the following recommendations, among others: The current USDA reporting categories need to be revised to reflect the complexity of evaluating animal pain and distress; the IACUC's reporting of pain and distress should be done in conjunction with a qualified veterinarian; training of all personnel must be of the highest standard and the IACUC should ensure that training includes recognition and alleviation methods of animal pain and distress; qualified veterinarians should be involved in every step of a research protocol, and any projected painful or distressing procedure should be carefully monitored by the veterinarian and animal health care staff; prospective plans should be created for administering analgesics and tranquilizers and monitoring the animals; analgesics should be administered prior to any known painful procedures; death as an endpoint should be avoided; and additional research is needed in the area of the recognition and alleviation of animal pain and distress.

Assessing the Quality and Effectiveness of IACUC Oversight in Investigator Compliance

A recent paper describes the process that an IACUC used to determine the success of its research oversight and its facilitation of researcher compliance. The process was carried out by an outside consultant and involved two steps: individual interviews and a written survey (based on the findings of the interviews). Confidential interviews were conducted with the IACUC chair, attending veterinarian, IACUC members, and principal investigators. Interview questions addressed issues such as the influence of IACUC operations on research efforts, the process of protocol review and approval, and possible reasons for resistance to the review process.

The results identified three areas to be improved. The largest number of respondents agreed that the software used for completing the "Animal Procedure Statement" was difficult and inadequate. Second, both the interviewees and survey respondents expressed a need for an "extensive technical training program on the care and use of laboratory animals." Finally, respondents felt that an IACUC education and outreach program aimed at the research community should be developed and implemented.

The survey method proved to be an objective means of assessing IACUC-investigator interactions and determining which areas needed improvement.

—*Contemporary Topics,* January 2000, pp. 28–31

New Policy at *Veterinary and Comparative Orthopaedics and Traumatology*

G. Sumner-Smith, editor-in-chief of *Veterinary and Comparative Orthopaedics and Traumatology,* has stated in an editorial that no papers will be accepted for publication in this journal without a paragraph describing the post-operative care given to the patients (either human or animal). The paragraph must have the heading "Post-operative care" and should include both drug dosages and regimes. Sumner-Smith states that "if authors are required to include such material in a submission, they are more likely to carry out the protocol." Manuscript referees "will also be requested to state their opinion as to the scientific validity of the material in that paragraph."

In an unusually candid statement for the scientific literature, Sumner-Smith states: "Most journals require authors to quote

the regulations in force in the country of origin of the manuscript submitted. It has come to our knowledge that, regrettably, in many institutes only lip-service is paid to those regulations. A deplorable situation and one which this journal finds to be totally unacceptable."

—*Veterinary and Comparative Orthopaedics and Traumatology,* November 1998, 11(4):5

Blind to Distress?

The Protocol Review column in *Lab Animal,* June 2000, raises the often-overlooked issue of distress. In a hypothetical scenario, an IACUC grapples with the issue of whether an investigator should be permitted to temporarily blind rabbits in one or both eyes as part of an ocular globe manipulation. Bilateral blindness would mean that each animal could serve as its own control and consequently, fewer animals would be used. Unilateral blindness would presumably cause less distress to each animal but entail use of more animals.

Some of the (fictitious) IACUC members and (real) *Lab Animal* commentators noted that humans would experience significantly more distress with bilateral (vs. unilateral) blindness. Rabbits, not comprehending that the blindness would reverse in a few weeks, would perhaps experience even more distress. Consequently, the weight of the deliberations favored unilateral blindness and the use of more animals. One commentator urged the IACUC to explore the efficacy of distress-relieving drugs, regardless of whether one or both eyes were blinded.

—*Lab Animal,* June 2000, pp.19–21

Software for Scoring Rats and Mice

Advanced Veterinary Applications has developed software programs that enable technicians to easily score mice and rats during daily health checks. The software is for PalmOS® compatible handheld electronic devices. The scoring systems, AVASelect Forms, became available in September 2000.

The new scoring systems can be readily adapted to specific protocols or to programs using telemetry or barcode readers. Technicians can use the general, cardiovascular, neurologic, gastrointestinal, dermatological, and tumor scoring systems. A general husbandry checklist is included and can be customized to meet facility-specific requirements. Additionally, a Veterinary Treatment and Intervention Form and a Short Rodent Room Technical Box Checklist are provided to rapidly score large rodent holding areas that require minimal detection and intervention.

The forms are downloadable with the click of a mouse into user-group domains. The system also allows IACUC evaluation of large populations at annual or three-year renewal time; graphing of data such as weight, body temperature, mean pain and distress scores; digital notification of caretakers and technicians to "call the vet now" or "daily average priority vet check"; and easily archived rodent clinical records. Also upon request, scoring systems and download versions may be customized. Demonstrations can be scheduled with Victoria Hampshire, V.M.D., Director, Advanced Veterinary Applications, 301-221-5086, *vetcare@msn.com.*

Monoclonal Antibody Production

This past spring, the Alternatives Research and Development Foundation (ARDF) mailed a packet of materials on monoclonal antibody (MAb) production to all IACUCs in the United States. The packet included a guidance document, written by Louis DeTolla, V.M.D., Ph.D., and Joanne Smith, D.V.M., to assist IACUC members and scientists in evaluating the need for the use of in vivo MAb production rather than in vitro methods.

Also included are the proceedings of a 1999 workshop on MAb production, a current list of custom contract MAb producers who offer in vitro options, and a copy of *Lab Animal* magazine's 1999 MAb special supplemental issue.

The ARDF can be reached at 14280 Golf View Dr., Eden Prairie, MN, 55346 or via e-mail at *ardfjmc@aol.com.*

—IACUC mailing from ARDF

Test Kit Available for Acute Phase Proteins

Cardiotech Services is marketing a test kit for Alpha Acid Glycoprotein (AGP), an acute phase protein that, when elevated, is said to be an early indicator of background illness or other stressors. Continued high levels of the protein indicate a poor prognosis. Acute phase proteins such as AGP are elevated during acute or chronic periods of inflammation or infectious disease, following surgery, and when malignant tumors and autoimmune diseases are present. AGP testing can provide an early indicator of adverse change in condition, before antibodies are developed and clinical symptoms are apparent.

AGP is manufactured in the liver and found in blood of humans and animals. The Cardiotech assay, the SRID plate test, requires only 5ug/ml of plasma or serum applied to separately identified wells, which are then stored for 24 hours and interpreted. This assay was originally created to monitor the impact of chemotherapy treatments on human patients' immune system responses. The kit has been reconfigured to monitor

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continued from page 3

and identify stress responses in animals. Cardiotech Services (Louisville, KY) can be reached via their website at *www.hot1.net/cardiotech/APP.htm* or by phone at 502-473-7066.

Recent Publications

Allen, T. 1999. *Information Resources for Institutional Animal Care and Use Committees 1985–1999,* USDA [AWIC Resource Series No. 7], Beltsville, MD.

Kreger, M. 2000. "The Search for Refinement Alternatives: When You've Just Got to Use Animals," *Lab Animal* 29 (4 April), pp. 22–29.

Silverman, J., Suckow, M.A., and Murthy, S., eds. 2000. *The IACUC Handbook,* CRC Press, New York.

From the Technical Literature

Guidelines for Assessing the Health and Condition of Mice

Charmaine Foltz, D.V.M., of Oak Ridge National Laboratory, and Mollie Ullman-Cullere, M.S., of Massachusetts Institute of Technology, present guidelines on the care and use of transgenic and mutant (knockout) mice, which often have debilitating phenotypes. The authors cite the Three Rs of refinement, reduction, and replacement, but call for a fourth "R": investigator responsibility. Investigators should monitor and manage colonies of transgenic and mutant mice in order to assess and maintain the health of these animals. Research protocols should clearly identify endpoints for early intervention in cases of substantial pain and/or distress.

The authors recommend criteria for assessing animal health and endpoint determination. These criteria include examining body condition, obvious health problems, more subtle health problems, and additional health issues.

▶ Body Condition Scoring: In addition to monitoring body weight and temperature, "body condition" should be examined by scoring body mass along the sacroiliac bones on a scale that ranges from 5 (obese) to 1 (advanced muscle wasting);

▶ Obvious Health Problems: These include excessive grooming (barbering) or fighting, malocclusion, rectal prolapse, tumors and masses, ulcerative dermatitis, and vaginal or uterine prolapse;

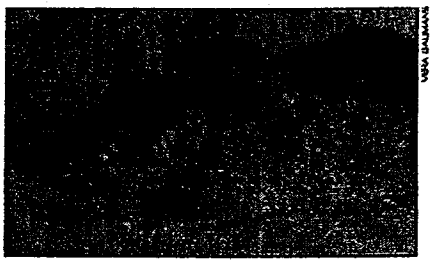
▶ Subtle Health Problems: These include alterations in activity and behavior, as well as anemia, dehydration, diarrhea, hypothermia, icterus, preputial or vaginal discharge;

▶ Additional Health Issues: These can include abnormal breathing patterns, abnormal locomotion, eye inflammation or abnormality, tilted head, hyperactivity, lethargy, paresis, paralysis, ruffled fur, and tremors.

Foltz and Ullman-Cullere strongly recommend supplementing general criteria for assessment with specific criteria for specific research models in order to accurately judge the health and well-being of transgenic mice.

—*Lab Animal,* April 1999, pp. 28–32

Transgenic and mutant mice need closer monitoring of their health.



Red Carpet Rodent Care: Making the Most of Dollars and Sense in the Animal Facility

Authors Victoria Hampshire, V.M.D., Judith Davis, D.V.M., and Christine McNickle borrowed methods commonly used in veterinary hospitals in order to design rodent care and use programs that enhance animal welfare and science, yet are practical and cost-effective. Seven areas of care were improved or implemented; these include extended work shifts, intense investigator training, a scoring-and-treatment system for distressed rodents, maintenance doses of fluids and analgesics, a high-calorie supplement, portable thermoregulation devices, and anesthetic refinements (use of isofluorane versus pentobarbital). The new program led to "a survival rate to endpoint of 95% or greater for all rodents used in experiments" versus approximately 50% in previous years.

—*Lab Animal,* May 2000, pp. 40–45

Do Fish Feel Pain?

This article by Neville Gregory, Ph.D., closely examines neurological, pharmacological, and behavioral studies of fish and concludes that fish do feel pain. The author proposes that there are three ways of attempting to establish if fish can feel pain: determine if fish have neurotransmitters, neuron types, and brain structures that are known to mediate pain; assess the physical responses of fish who are exposed to noxious stimuli (and also see if

here is a difference in the presence of an analgesic); and condition fish to a painful stimulus and observe whether they show aversion to the conditioned stimulus.

Past studies have shown that fish do have neurotransmitters, neuron types, and brain structures similar to those in mammals that mediate and influence pain. The author indicates that some areas require further testing. Various behavioral studies concluded that fish show many physical responses to noxious stimuli that involve conscious perception. The author concludes that "the appropriate question appears not to be *do fish feel pain?* But rather, *what types of pain do fish experience?*" and, furthermore, which types of stimuli provoke pain responses in fish.

—*ANZCCART News*, December 1999

Upcoming Conferences

Alternative Toxicological Methods for the New Millennium

- Coordinated by the Department of the Army
- Location: National Library of Medicine, Bethesda, MD
- November 28–December 1, 2000
- For more information, send an e-mail to [illegible]

IACUC Issues and Research Animal Welfare

- Coordinated by the Scientists Center for Animal Welfare
- Location: San Antonio, TX
- December 4–5, 2000
- For more information, go to [illegible]

Pain & Distress Statistics

Canada's 1997 Statistics on Animal Use

The Canadian Council on Animal Care (CCAC) has released statistics on the use of animals in research, teaching, and testing in Canada during 1997. These statistics are broken down according to Categories of Invasiveness. In 1997, 36.2% of the animals experienced little or no discomfort or stress (category B), 25.9% experienced minor stress or pain of short duration (C), 30.9% experienced moderate to severe distress or discomfort (D), and 7.0% experienced severe pain near, at, or above the pain tolerance threshold of unanesthetized conscious animals (E). Categories D and E are roughly equivalent to the "Column E" category of the U.S. Department of Agriculture (USDA) system, yet the USDA reported only 7.9% of regulated animals in Column E, whereas Canada reported 37.9% in Categories D and E.

The total number of animals used during the year was 1,471,611, a 24.6% decrease from 1996. (The Canadian system counts all vertebrate animals, unlike in the United States, where only some mammals are counted.) This decline from 1996 to 1997 may be the beginning of a trend or a temporary decrease. The most commonly used species included mice (32.8%), fish (20.9%), rats (20.6%), and chickens (13.0%).

—*CCAC Resource*, 1999, 23(2)

New Zealand's 1998 Pain and Distress Statistics

New Zealand arguably has the most sophisticated classification system for pain and distress in laboratory animals. The system uses five categories and focuses on the concept of suffering, which is typically avoided in discussions of laboratory animal welfare in the United States. According to New Zealand's latest report (National Advisory Ethics Committee: 1998 Annual Report, Ministry of Agriculture and Forestry, Wellington, NZ), the figures covering warm-blooded vertebrates used in 1998 are as follows:

No Suffering	94,311	(46%)
Little Suffering	75,898	(37%)
Moderate Suffering	27,560	(13%)
Severe Suffering	1,244	(1%)
Very Severe Suffering	6,740	(3%)
	205,753	(100%)

Overall, 17% of these animals were reported as experiencing moderate to very severe suffering. Most of the animals in the severe and very severe categories were mice. There was a 27% reduction in the number of animals in the severe and very severe categories from 1997 (approximately 10,900) to 1998 (approximately 8,000). Institutions in New Zealand are required to take all possible steps to reduce or ameliorate the suffering of animals, and special attention is given to those projects that cause severe or very severe suffering to the animals.

Attitudes & Public Opinion

U.K. Public Opinion Survey on Animal Experimentation

A recent survey on animal experimentation demonstrates that many factors influence British public opinion about this issue. Some of these factors include the amount of pain and suffering the animal is subjected to, the use of alternatives to animals, the species of animal, and type of research. The overall conclusion of the survey was that "[o]ver 80% [of those surveyed] accept that [animal experimentation] is necessary as long as suffering is minimised, if it is for medical purposes or for life-threatening diseases, and/or if alternatives are fully considered."

continues on page 6

Attitudes & Public Opinion continued from page 5

Pain and suffering were found to be a major criterion in forming an opinion about animal research. Seventy percent of those surveyed indicated that they "can only accept animal experimentation so long as there is no unnecessary suffering to the animals." Many also questioned how pain levels are measured and what is considered to be an "acceptable" level of pain. The results demonstrate that acceptance of animal experimentation is not a clear-cut issue; it is complex and conditional, and can seem contradictory.

Market & Opinion Research International conducted the study of 1,014 people, aged 15 and older, for the United Kingdom's Medical Research Council last year. For more information about the survey, go to: *www.mrc.ac.uk/whats_new/MORI_animals.html.*

Desensitization in Vet Schools

A recent British survey has shown that, similar to medical students, over the course of their studies, veterinary students become less compassionate toward their animal patients. Also noted was a decrease in their perception of the sentience of dogs, cats, and cows, i.e., the animals'

More female vet students may mean more empathy for animals.

ability to experience pain, distress, and negative emotional states, such as fear, boredom, anxiety, and depression. On a slightly more positive note, female students had higher levels of empathy and are in the majority.

Researchers concluded that the students' emotional detachment was necessary to ensure that as veterinarians they would be better able to deal with distressing situations. However, critics point out that such distancing leads to less consideration of the animals' welfare, pain, and distress, and note that considerations about the welfare of animals are central to a vet's job.

The full text of this article is available in the *Veterinary Record*, March 2000; a summary may be found at *http://news.bbc.co.uk./hi/english/sci/tech/newsid_673000/673033.stm.*

Helpful Websites

▶ A compilation of literature on the assessment of animal welfare and animal distress: [illegible]

▶ *Lab Animal* online: [illegible]

▶ Animal Welfare Information Center (AWIC) Workshop Online—Meeting the Information Requirements of the Animal Welfare Act: [illegible]

The online version of AWIC's popular workshops.

▶ Sharing and Collaboration Across Borders: Information on Alternatives Databases: [illegible]

This website links to 26 databases and organizations that have websites and sorts them by reduction, refinement, and replacement.

▶ IACUC.org: [illegible]

This website is produced by AALAS and is an online resource for IACUCs.

Introducing the Pain & Distress Report

The Animal Research Issues section of The Humane Society of the United States introduces the *Pain & Distress Report*, which provides IACUCs and others with up-to-date information on issues regarding pain and distress in laboratory animals.

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Weight Loss References

Int J Eat Disord. 2001 Sep;30(2):193-203.

Binge eating disorder and night eating syndrome: psychological and behavioral characteristics.

N litano MA, Head S, Babyak MA, Blumenthal JA.

Centers for Behavioral and Preventive Medicine, Brown Medical School and The Miriam Hospital, Providence, Rhode Island 02903, USA.

OBJECTIVE: The present study was designed to examine the psychological and behavioral characteristics associated with both night eating syndrome (NES) and binge eating disorder (BED) in 42 males and 41 females who were enrolled in a university-based weight loss center. METHOD: Individuals were classified into one of four groups: NES only (N = 23), BED only (N = 13), both NES and BED (N = 13), or no diagnoses of an eating disorder (N = 34). Analyses of covariance (covarying for age and gender) were conducted to compare patients with BED and NES. RESULTS: NES patients scored lower on disinhibition than BED patients ($p < .01$). Also, individuals who met criteria f scored higher than NES only patients on state anxiety ($p < .01$), disinhibition ($p = .08$), and trait anxiety DISCUSSION: These results suggest that NES represents a subcategory among the obese, which also binge eaters. In addition, anxiety distinguished individuals who met criteria for both disorders from pat diagnosed with either NES or BED. Copyright 2001 by John Wiley & Sons, Inc.

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http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11449453&dop

Acta Neurochir Suppl. 2000;76:277-8.

Plasminogen activator inhibitor-1 in patients with ischemic stroke.

Ha niemi E, Tatlisumak T, Soinne L, Syrjala M, Kaste M.

Department of Neurology, Helsinki University Central Hospital, Helsinki, Finland.

Low fibrinolytic activity may increase the risk of thrombosis. Plasminogen activator inhibitor-1 (PAI-1) is an inhibitor

of the fibrinolytic system. We examined the PAI-1 levels in patients with ischemic stroke. Plasma levels of PAI-1 were measured using enzyme-linked immunosorbent assay (ELISA) in 55 consecutive patients (age 60.2 +/- 11.4, 40 males and 15 females) with ischemic stroke. The PAI-1 assessments as well as neurological examinations using validated stroke scales were conducted at admission and 1 week, 1 month, and 3 months after stroke. Sex- and age-matched controls (+/- 4 years) underwent plasma PAI-1 measurement once. Etiology of the stroke was classified using the Trial of [redacted]10172 in Acute Stroke Treatment (TOAST) criteria. All pertinent stroke risk factors were recorded. All patients were contacted 3 years after stroke for recurrent vascular thrombotic disease. The plasma PAI-1 levels were 17.2 +/- 7.8 IU at admission, 11.2 +/- 9.2 IU at 1 week, 14.4 +/- 7.9 IU at 1 month, and 17.8 +/- 7.8 IU at 3 months among patients and 11.8 +/- 9.5 IU among controls (p values are < .002, .7, .12, and < .0005, respectively). As a rule, the neurological scores did not show a correlation to the PAI-1 levels. Presence of diabetes, hypertension, obesity, smoking, anticoagulant treatment, and sleep apnea did not affect the PAI-1 levels at any time point. Females had slightly higher PAI-1 levels. Age was a strong determinant for PAI-1 levels being higher in younger patients at every sampling time point (p values .02, .02, .02, and .03 respectively). The etiology of the ischemic stroke did not have an impact on PAI-1 levels. In 16 patients recurrent thrombosis had occurred. The high PAI-1 levels at admittance may reflect either an acute phase response or a chronic state. Normalized levels at 1 week and 1 month may be due to hospital diet, antithrombotic medication, weight loss, active physical therapy, and better care for diabetes. PAI-1 levels at 3 months after stroke did not predict recurrent thrombosis.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11450024&dopt=Abstract

Contemp Top Lab Anim Sci. 2001 Jul;40(4):11-7.

Handheld digital equipment for weight composite distress paradigms: new considerations and for rapid documentation and intervention of rodent populations.

E. [redacted]pshire V.

Advanced Veterinary Applications, 7307 Nevis Road, Bethesda, Maryland 20817, USA.

Animal care in the third millennium will require a melding of scientific and humane interests to achieve optimal care of genetically engineered mice and to expedite scientific and medical advances by using these mammals. Undoubtedly, rodent patients present certain difficulties for those who wish to assess their daily well-being and to contribute to efficient and successful scientific discovery. High-density housing, large experimental groups, and low-lux room lighting makes the application of large-animal care standards to rodents seem daunting to researchers and veterinary care programs. In addition, great variability in training and experience among those responsible for the direct application of humane care to rodents exists. Most of the direct animal care in small animal facilities occurs in decentralized locales by personnel who have completed obligatory but relatively minimal animal care training. Examples of personnel in this category include postdoctoral fellows, junior-level scientists, summer students, and assistant laboratory animal technologists. Some programs even use the husbandry staff to perform health checks of high-risk populations on a daily basis. For this reason, the extrapolation of performance-based intervention in rodent care is difficult to apply practically. Early efforts to enhance humane outcome in rodents have been published by scientists and veterinarians and are largely directed at singular endpoints, such as weight loss and declining temperatures, in specific models. Scientists often are reluctant to accept such standards because of concern about premature intervention or variability between scorers and to reservations regarding a lack of procedural likeness with their proposed study. This paper highlights a digital method for melding current advanced animal scoring standards using palm pilot user-friendly methods that account for composite weight scoring, behavioral or physiologic attributes, and interventions. Information is rapidly downloaded and results in quick storage of large rodent population monitoring. This minimizes interpretative variability between caregivers and greater standardization of procedures. [redacted] considerations facilitate the rapid diagnosis of outliers and make possible intervention that streamlines the delivery of humane care to large experimental populations.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11451389&dopt=Abstract

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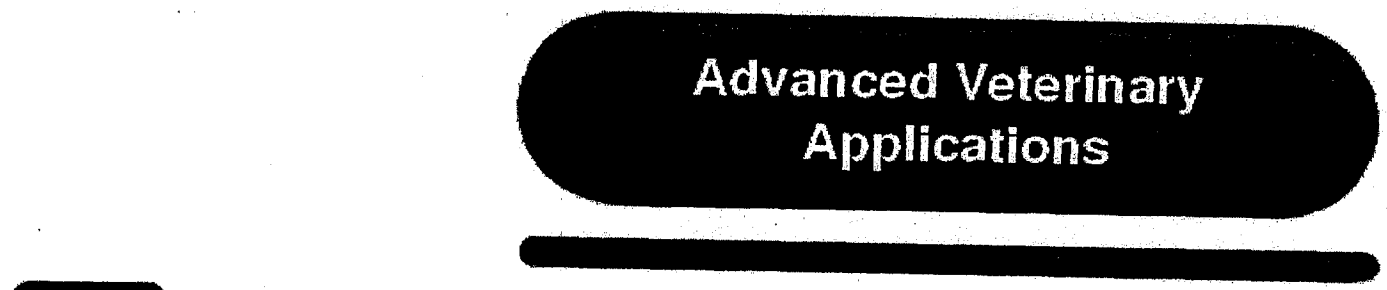

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Lick granuloma.

Addison's Disease
Addison's disease

Adrenal Gland Disease, Ferrets
Cushing's disease of ferrets

Anal Sac Disease, Canine
Impacted anal sacs, infection of the anal sac, abscessed anal sac

Anemia, Canine and Feline
Anemia, low red blood cell count

Bladder Stones, Feline
Urinary bladder calculi, bladder stones

Blastomycosis
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Bots, Equine
Bots

Bovine Postparturient Paresis
Milk fever

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Bronchoscopy, airway scoping

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Heart disease, Heart muscle failure

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Cat scratch disease or fever
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Kidney failure, renal insufficiency, renal disease
Coccidiosis, Canine and Feline
Coccidia
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Colic
Corneal Ulcers, Canine and Feline
Corneal ulcer
Coronavirus Disease, Canine
Coronavirus disease, Viral inflammation of the small intestine
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Ruptured cruciate, Ruptured ligament, Ruptured anterior cruciate ligament (ACL), Torn ACL, Torn ligament
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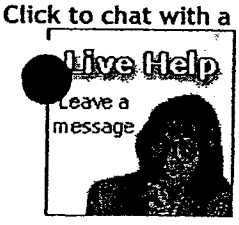

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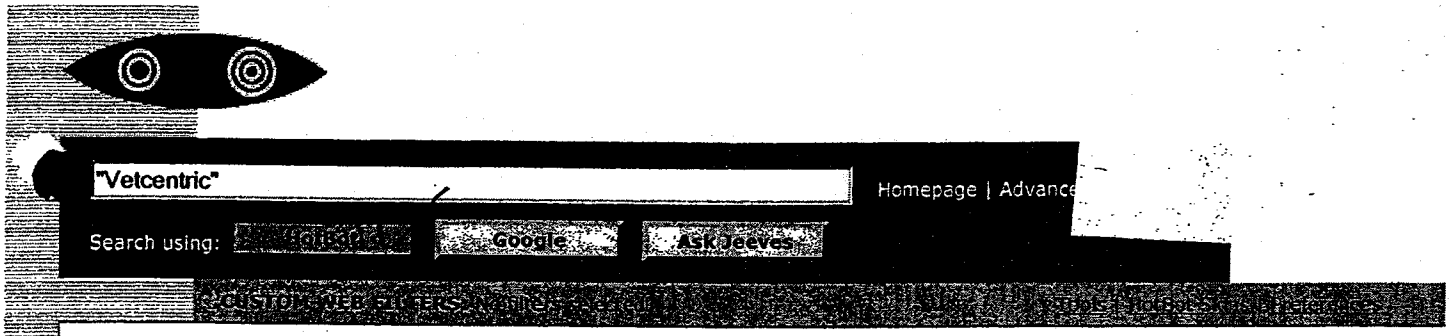

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October 11, 2004	Newsday.com	Medical advice, one dog at a time
September 23, 2004	KPHO-Phoenix, AZ	Vets May Not Warn You About Potentially Deadly Pet Drugs

"A Few of the Statistically Insignificant"

IMPORTANT: Adverse Reaction Survey!

Lawsuit Over Veterinary Drug Settled

Issued by the EPA: Retailers and Counterfeit Pet Products (Frontline & Advantage)

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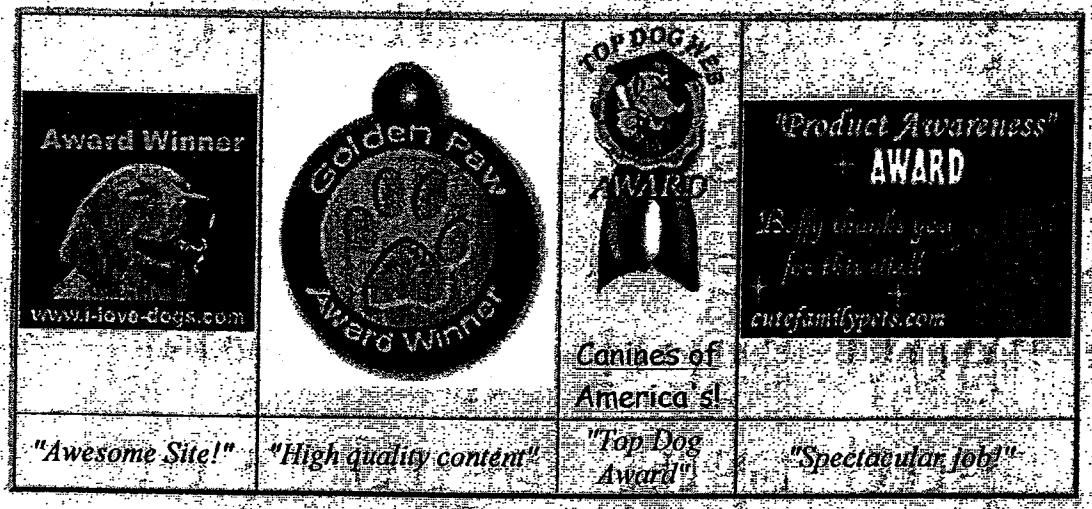
The Poison Control Hotline is there to assist vets in dealing with adverse drug reactions and other poisonings.



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~Margaret Mead~

FDA/CVM definition of 'Adverse Reaction'

Top two symptoms of an 'adverse reaction' appear to be:

Vomiting and Diarrhea

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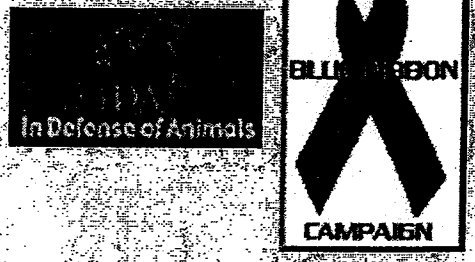

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FDA/CVM: October 8, 2004 - Questions and Answers Regarding the FDA Recall of ProHeart®6

News in South Carolina: **The State.com:** Drug suspected in wolf's death

Post & Courier: Heartworm Drug May Have Killed Endangered Red Wolf <must be registered>

September 13, 2004 Letter to Veterinarians Important Drug Information about Proheart®6 from the FDA

September 2004 - Letter to Veterinarians from manufacturer

2004 Heartworm Concerns

September 23, 2004	**KPHO-Phoenix, AZ**	**Vets May Not Warn You About Potentially Deadly Pet Drugs**
Oct 11, 2004	NewsDay.com NY	Medical advice, one dog at a time
Oct 3, 2004	WMAZ Macon, GA	Harmful Medicine for Pets?
Sept 28, 2004	NewsDay.com NY	DEADLY VACCINE Heartworm drug

		recalled
Sept 28, 2004	KPRC Houston, TX	Heartworm Medicine Recalled After Animal Deaths
Sept 27, 2004	WJRN Tulsa, OK	***Woman sues manufacturers of heartworm medicine***
Sept 10, 2004	WFRV Green Bay WI	Proheart 6 Nationwide Recall
Sept 9, 2004	KOTV, Tulsa, OK	Concerns Over A Heartworm Medicine For Dogs
Sept 8, 2004	WOI TV, Des Moines, IA	Follow Up: What's Killing Your Family Pet?
Sept 8, 2004	CBS4-Denver, CO	Popular Heartworm Medicine Recalled
Sept 6, 2004	WLUC MI UP	Fort Dodge Animal Health to Voluntarily Recall ProHeart(R)6
Sept 4, 2004	WZZM Grand Rapids, MI	Popular Heartworm Medication Recalled
Sept 3, 2004	CBS 2 Chicago	Popular Heartworm Medicine Recalled

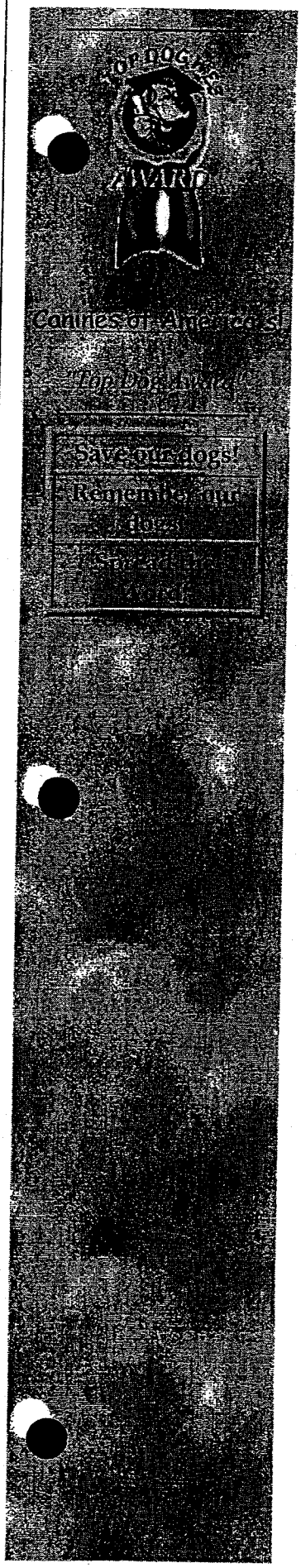
Previous News Stories

Avid Sues Banfield Over Microchip Program

IMPORTANT: Adverse Reaction Survey!

The Animal RescueSite is having trouble getting enough people to click on it daily to meet their quota of getting free food donated every day to abused and neglected animals.
It takes less than a minute to go to their site and click on "feed an animal in need" for free. This doesn't cost you a thing. Their corporate sponsors/advertisers use th numbers of daily visits to donate food to abandoned/neglected animals in exchange for advertising.

http://www.theanimalrescuesite.com
Please go there now..... and send it to everyone you know



Chances are that you have arrived at this site due to your dog receiving a six month heartworm injection, which has led you to seek additional information other than what is listed within the manufacturer's site. Hopefully, you may also have arrived here due to desiring to become more educated about this product, before you allow it to be administered to your dog.

Please read on and make your own decisions.

Those of us that were able to, did..... but some of us were not that lucky.

Older News:

NEWS: May '04 Letter sent to vets regarding recall/warning letter

5/13/04 Proheart® 6 (moxidectin)Recall

4/27/04 Proheart® 6 (moxidectin)Recall

3/31/04 Warning Letter from FDA to Fort Dodge Animal Health

Subject: GMP in Mfr, Processing, Packing, Holding Drugs/GMP for Finished Pharmaceuticals/Adulterated

February '04 Iverharat® Plus Recall

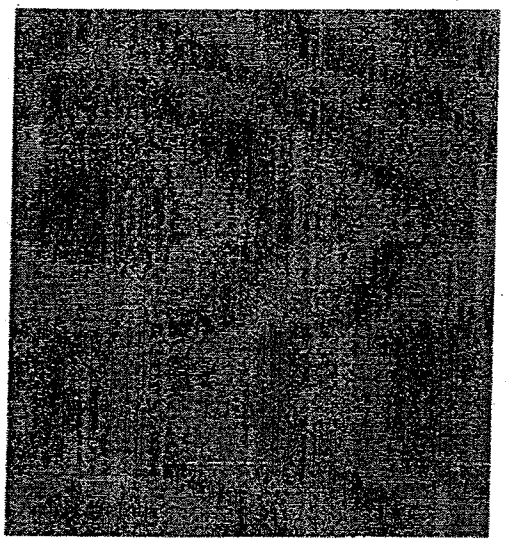
October '03 Iverhart Plus® Recall

EPA: Retailers and Counterfeit Pet Products

Special Note from the FDA **- Confirmed 2/17/04 - as of Dear Doctor letter of 2003 - NOT approved for *heartworm positive dogs!***

Editors Note: *Please! If you haven't already done so, at least check out the Petition. It covers much more then just drugs. It covers Rights that we think we automatically have.*

http://www.dogsadversereactions.com/moxidectin/moxidectinpage.html



For a true story on hope please read the ***"Mircale Worker"*** by Meridith Moore

PLEASE NOTE:

This website, it's contents, or any reference to enities or other links...are ***not affiliated with, sponsored by or associated with any product, manufacturer or other retail business.***

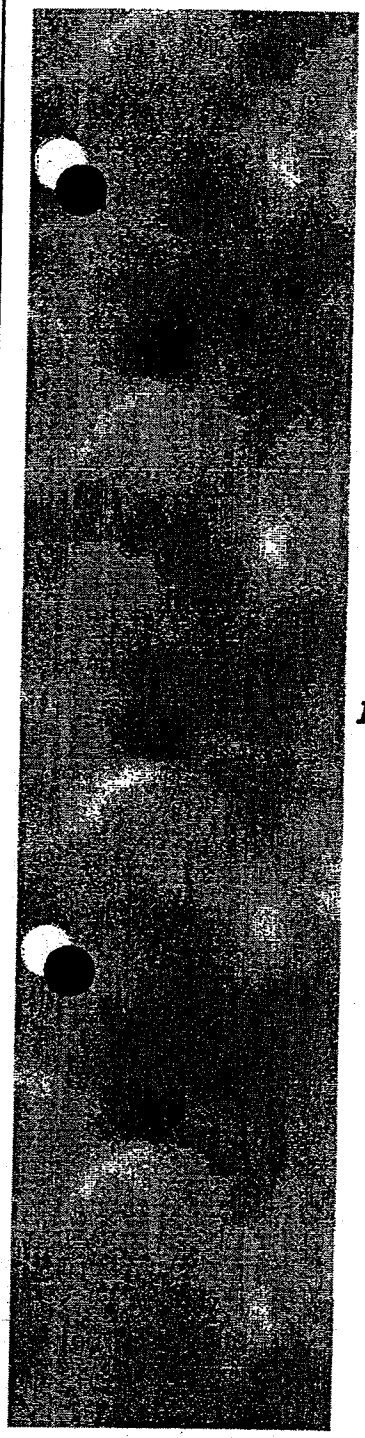
We're sorry, for legal reasons we can no longer supply the manufacturers of products links.
PLEASE read this Disclaimer CAREFULLY - - BEFORE USING THIS SITE
By using this site, you signify your consent to this disclaimer.
If you do not agree to this disclaimer, please Do Not use the site.

Due to the Federal Drug Administration requiring the manufacturer of this product to submit Dear Doctor Letters to ALL Veterinarians nationwide, we felt that we should post those letters here. In addition, we have received numerous e-mails from dog guardians that feel "in their opinion" that the six month heartworm injection has made their dog ill or led to their dogs death.

Therefore, we have taken the time to create this site for people to perform their own conclusion about this product.

While not all can be proven or disproven, that this product is harming any dog(s), we feel that the 4771 (as of 10/1/04) possibly related adverse reactions reported to the Federal Drug Administration plus the 555 deaths.... warrants the creation of this web site.

We're Missing Dogs!!!



According to the label: "Approximately 1% will have an adverse reaction.

According to the manufacturer in February '04 they had sold into vet clinics 16.1 million doses.

That is 161,000 dogs.

Only approximately 5000 have been reported to the FDA.

What happened to approximately 156,000 dogs??

Message from Web Creators:

Since this site is information and opinions only,
we authorize anyone to forward it, print it or link to it, giving credit to the source..

If you would like your story told, good or bad, please contact us!

Any and all communication is considered private,

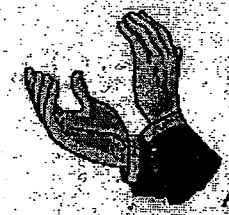
and all transmissions become the property of DOGS Adverse Reactions..

Since 3/15/04

Old Site: 10,906 hits from 12/4/03-3/15/04

Contact Us	NSAIDs	**DOGS**	Moxidection	Site Map

Organization



All members of DOGS ... In no special order....

Many Hugz and lots of sloppy kisses! to the following:

The Internet!!! and Jim and I-Dog!! and American Heartworm Society!

Special Thanks to our 'others' ... who without
their support, we couldn't have done this.

Al Simpson, Davy, Sandi Herman

Janice Storey
Demitry Herman
Dr. Bob Rogers, DVM
Dr. Larry Pearson, DVM
Dr. Hampshire
Myra Kirkland
Kim Willliams
Sandra Slayton
Robert Reynolds
Kim Russ
Norita
Barbara (Ike)
Golden Doxie
Audry Laskey
Linda Molaison
Kristen Perez
April Andrade
Griffin Hill
JeanBrudd

Laurryn Simpson
Jean Townsend
North Rhode Island Animal Hospital
David J. Andrix, DVM
Dr. W.E.Guthrie, DVM
Stacy Lege' - Strickland
Eric Williams
Stan Vidmar
Linda Reynolds
Tim Russ
Darren
Jeff Pulice
Dyan K
Jeff
Pat Labone
Chris Le Duc
Jeanne Andrade
S.K.Dauria
John M.

June M.
Joanne Plumer
Sue
Judy Reilly
Stan Kubacki
Lloyd Cole
Jean Whitfield
Gina
Donna S.
Kim Smith
Bonnie Pearson
Denise Schwartz
Kristin Moore
Melissa Patrick
Scott Brainerd
Kelli Yount
L.Latinette
Fracesca
Flygirl
Suresh Kumar
Pam Pickett
Laurie and Jim R.
Christine Zattolo
J.Dickson

Addieford
Joan Mickey
Duane
Billy Folks
Norma Kubacki
Amber H.
Wilda Jones
Jason
Joyce Parry
Sue
Kay Nelson
John Skalet
Ed Murray
Wanda Scott
Donna Summer
Barbi
Laura
Linda & Tom
Joanne Amoroso
Lynnie
Gary Rogers
Sandy Faut
Dawn Prentiss

Senior Dogs Project
Florida Pets
IDA (In Defense Of Animals)
BARKS
Its For The Animals
NZYMES
Furry Friends
Veterinary Malpractice
YahooGroups

RainBow Bridge
Shirley's Wellness Cafe
Guardian Campaign
BowChow
AdoptingaDog
CAPS
Jim Lemon, POMCA Director
petEmpawrium.com/

Guest Book	Table of Contents	Contacts
Classes 101	Organization List	If You Suspect an Adverse Reaction

Moxidectin Section	DOGS Editorial	NSAID Section
Moxidectin List	Changing Times	NSAID List
Six Month Injection	Other Drugs	Arthritis/Pain Medication
	Dog Food Information	
Flea Products	Veterinarian Oath	Miscellaneous Warnings
Who Am I?	DOGS Info Links	Our Mission
Newsletters	DOGS Good Reading	Monthly Poll
.	Puppy Mills	.

http://www.dogsadversereactions.com/organization.html

Myra Kirkland:

PROHEART 6 SHOT CONTINUES TO BE SUSPECT! ....people to contact if you think your dog has suffered from this shot....

ProHeart6
(moxidectin)

Last month we posted information about the possible dangerous side effects of the ProHeart6 shot. ProHeart6 is a long-lasting heartworm preventative, intended to prevent heartworm for six months. Reports of deaths associated with the shot have continued to arrive at the Senior Dogs Project. We have also been asked to help establish communication among people who suspect their dogs have been negatively affected by the shot. Here is the E-mail message we received

- "My name is Janice Storey. My dog, too, became ill because of the ProHeart6 shot and died on October 17. Along with Myra Kirkland, I am on a mission to save other dogs and making it mandatory that veterinarians present the ProHeart6 label for review prior to a consumer making a decision about this shot. My dog, Trouble, received his annual vaccinations along with the ProHeart6 shot. He began coughing shortly thereafter and was dead within weeks. If you would like to know Trouble's story, please notify me at my E-mail site and I will be happy to forward the document to you."
- If you suspect your dog has had an adverse reaction to the ProHeart6 shot, and you would like to be in touch with others like you, here are the people to contact:

Myra Kirkland, MKirkland@cardinal.tr.com

- Janice Storey, **jstorey1@swbell.net**
- You may also wish to join the "doghealth2" E-mail list, which has ongoing discussions about canine medications and health. **doghealth2@yahoogroups.com**

http://www.srdogs.com/Pages/news.oct.nov2.html

Jan Townsend

Myra Kirkland continued:

I am extremely elated that the FDA has pulled the Profilcat 6 shot from the market. It has taken Many individuals Many hours to achieve this goal. Thanks to A.J. who had a hand in this. We must continue however to be sure that the individual veterinarians stop giving this drug and that dog owners still report reactions to the FDA on the Profilcat 6 shot. A special thanks to FDA who has been a vital part in the adverse drug surveillance on Profilcat 6. Dean, Janice and I now know our dogs DID NOT DIE IN VAIN & We will continue to spread the word on this dangerous shot. Thanks to all. Myra

http://www.dogsadversereactions.com/newsletterSpecial.html

The Pet Guardian

Vaccinations | Pet Nutrition | Heartworms | Emergency Care | Pet Insurance

Last Modifed on Sunday, September 26, 2004

ProHeart 6 Complaint Form
Click Here

NEW - **"Lawsuit Filed Against Manufacturer of ProHeart 6 Heartworm Medication."**

NEW - **"FDA Talk Paper: Fort Dodge to Comply with FDA's Request to Recall ProHeart 6 Injectable Heartworm Product from the Market Due to Serious Health Concerns." September 3, 2004**

NEW - **"FDA Letter to Veterinarians: Important Drug Information about ProHeart6." September 13, 2004**

NEW - **Fort Dodge Letter to Vets, September 2004**

"My major concern about using ProHeart 6 is not simply the dangerous potential side effects - all medications have potential side effects. It is the fact that these occur significantly more often when using ProHeart 6 than when using one of the many other equally effective heartworm preventatives currently on the market." - "A Concerned Vet"

Know the Facts about ProHeart 6
Click Here

- **Vets and ProHeart 6 - Is it about the money? You decide.**
- **Is ProHeart 6 Really Safe? A Vet Speaks Out.**
- **Fort Dodge Recall Notice of ProHeart 6 April 27, 2004**

- **Letter to Vets Regarding the product recall of ProHeart 6 April 2004**
- **Dear Doctor letter to Veterinarians July 2002**
- **Dear Doctor letter to Veterinarians June 2003**
- **Dear Doctor letter to Veterinarians August 2003**
- **FDA orders label changes for ProHeart 6**
- **Proheart label 2001**
- **Proheart label 2002**
- **Proheart label 2003**

- **Warning letter to Fort Dodge - March 31, 2004**
  On December 1-12, 2003 Food and Drug Administration (FDA) Investigators performed an inspection of your veterinary pharmaceutical manufacturing operation known as Fort Dodge Laboratories, Inc., located at 800 5th Street, N.W., Fort Dodge, Iowa 50501. This inspection revealed serious deviations from the current Good Manufacturing Practice...

---

*"The verdict is still out on ProHeart 6. Case documentation and research are in progress. To be safe - **just don't use ProHeart 6**. To be fair and the devil's advocate many, many, many, dogs have had the shot without consequences, however, there were dogs with blood clots in their lungs that were in oxygen tents - they are tragic - not where you want your dog to be." - "Anonymous Vet"*

"When this drug was initially marketed, it was believed to be safe for heartworm positive dogs; then we found that dogs were dying that were heartworm positive," - - Dr. Victoria Hampshire, the FDA's adverse drug events coordinator.

2/14/03

I am indeed quite leery of the 6-month ProHeart shot. At the conventional allopathic practice I work at, my colleagues do use it more than I certainly have, and, fortunately, I have yet to see a severe life-threatening reaction yet, although I do feel that there have been certainly a number of milder acute reactions. I do feel that when you INJECT medications or vaccinations that there will always be those who react with sensitive immune systems, as

by injecting things, you bypass all of the ways the immune system evolved to ward off microbes and other chemical invaders, which are unfortunately in the adjuvants of many injectables and vaccinations . . .

The problem with this Fort Dodge shot is that there is no specific antidote to it, and once you inject the stuff, it's there for a minimum of 6 months . . . So if a patient is uniquely sensitive to it, then what is one supposed to do?

You see, the problem with all of these products and vaccinations is that they are not studied CHRONICALLY over months or years of use in either pets OR CHILDREN. Their safety studies are done in a very limited population of individuals and for only short periods. There is no market in allopathic medicine for chronic safety studies done by INDEPENDENT researchers (not the drug companies), as they are too busy putting time, finances and resources in new drug development.

I know several of my homeopathic colleagues have indeed seen life-threatening reactions to the ProHeart shot, and in my opinion, there should be a legal consent form required before a veterinarian does inject this stuff, as most veterinarians inject it while not citing any immune reactions, which Fort Dodge does acknowledge occur. - Michael Dym, VMD

Questions or Comments? Send E-mail to
info@thepetguardian.com

ATTACHMENT 27

Catherine Couch

From: B R [retake@erols.com]
Sent: Thursday, October 21, 2004 10:11 PM
To: Germider, L
Cc: Catherine Couch
Subject: Real Property Search - Individual Report.htm

Importance: High

Real Property Search - Individ...

property record v.hampshire BALABAN, ROBERT S & VICTORIA A HAMPSHIRE Use: RESIDENTIAL
Principal Residence: NO
Mailing Address: 5608 MADISON ST Deed Reference: 1) /10752/ 232
BETHESDA MD 20817-3728

ATTACHMENT 28

Catherine Couch

From: B R [retake@erols.com]
Sent: Saturday, October 23, 2004 10:53 AM
To: Germider, L
Cc: Catherine Couch
Subject: just for clarification re: record

Importance: High

HAMPSHIRE, VICTORIA
ADVANCED VETERINANY APPLICAHIONS
7307 NEVIS ROAD
BETHESDA, MD 20817

Active:
This unincorporated entity is legally active and present in Maryland.

ATTACHMENT 29

Catherine Couch

From: B R [retake@erols.com]
Sent: Monday, October 25, 2004 3:36 PM
To: Germider, L; Catherine Couch
Subject: Regarding Entity Search Results.htm

Importance: High

Entity Search Results.htm (6 K...

Catherine,
Entity Search Results.htm, I am not certain but it seems you couldn't open the link I'd sent?? I have attached it. Let me know if you have a problem opening it.

Below are the responses I'd rec'd as of the close of business today. I have written them several further follow-ups. If need be, I will call MD.

We shall persevere!

In reading their responses, I'd say a 'TYPO' is very possible.

Best,
D

-----Original Message-----
From: Charterhelp [mailto:Charterhelp@dat.state.md.us]
Sent: Monday, October 25, 2004 2:23 PM
To: retake@erols.com
Subject: Request for your assistance RE: Business Record

L Number are unicorporated are number for personal property return. You can call 410-767-4991 .

-----Original Message-----
From: Charterhelp [mailto:Charterhelp@dat.state.md.us]
Sent: Monday, October 25, 2004 4:19 PM
To: retake@erols.com
Subject: RE: Need your assistance RE: Business Record

I show no record of this entity

-----Original Message-----
From: Charterhelp [mailto:Charterhelp@dat.state.md.us]
Sent: Monday, October 25, 2004 1:44 PM
To: retake@erols.com
Subject: Need your assistance RE: Business Record

did you register name by filing a tradename application.

ATTACHMENT 30

Catherine Couch

From: B R [retake@erols.com]
Sent: Monday, October 25, 2004 11:32 AM
To: Germider, L; Catherine Couch
Subject: RE: Entity Search Results.htm

Importance: High

Catherine,

I have sent the enclosed inquiry to MD, DAT (Dept of Assessments and Taxation). I will notify you of any response ASAP!!

Let's see what they have say.

Best,
D

Hi

Could you kindly advise me if the entry reflected in your available records, is accurate? Upon inspection it appears that a manual transcription error, may possibly be indicated: ADVANCED VETERINANY APPLICAHIONS(L05436670)?? I am attempting to locate a business entity indicated as 'ADVANCED VETERINARY APPLICATIONS', Bethesda MD 20817. For some reason I can't seem to locate them other than on the internet. I'd like to determine and verify their legitimacy. I greatly appreciate any assistance, related information or clarification, you may be able to provide.

The following is indicated in your available records:

Charter Search Results for Dept ID #: L05436670
(L05436670)

(L05436670) HAMPSHIRE, VICTORIA
(L05436670)ADVANCED VETERINANY APPLICAHIONS

Active: This unincorporated entity is legally active and present in Maryland.

Can you tell me if this means the entity is a DBA??

Thank you in advance for your time and attention, I shall look forward to your reply.

Sincerely,

-----Original Message-----
From: Catherine Couch [mailto:catherinec@germinder.com]
Sent: Monday, October 25, 2004 12:02 PM
To: 'B R'
Subject: RE: Entity Search Results.htm

Donna, for some reason there's no information listed on the website. Thanks, Catherine

-----Original Message-----
From: B R [mailto:retake@erols.com]
Sent: Saturday, October 23, 2004 9:59 AM
To: Germider, L
Cc: Catherine Couch

ATTACHMENT 31

Maryland Department of Assessments and Taxation 1

Taxpayer Services Division
301 West Preston Street ☐ Baltimore, Maryland 21201

Taxpayer Services Division

Charter Search Results for: HAMPSHIRE, VICTORIA%

Page 1 of 1

(Dept. ID) Entity Name	Entity Detail	Status
(L05436670) HAMPSHIRE, VICTORIA	Personal Property	ACTIVE

Click here for a plain text ADA compliant screen.

Maryland Department of Assessments and Taxation
MONTGOMERY COUNTY
Real Property Data Search

Go Back
View Map
New Search
Ground Rent

Account Identifier: **District - 07 Account Number -** 00612618

Owner Information

Owner Name: BALABAN, ROBERT S &
VICTORIA A HAMPSHIRE

Use: RESIDENTIAL

Principal Residence: YES

Mailing Address: 7307 NEVIS RD
BETHESDA MD 20817-4737

Deed Reference: 1) /11429/ 53
2)

Location & Structure Information

Premises Address
7307 NEVIS RD
BETHESDA 20817

Legal Description
BANNOCKBURN

Map	Grid	Parcel	Sub District	Subdivision	Section	Block	Lot	Group	Plat No:
GM42				72		5	17	81	Plat Ref:

Special Tax Areas **Town**
Ad Valorem
Tax Class 38

Primary Structure Built	Enclosed Area	Property Land Area	County Use
1957	1,554 SF	69,629.00 SF	111

Stories	Basement	Type	Exterior
1	YES	STANDARD UNIT	BRICK

Value Information

	Base Value	Value As Of 01/01/2002	Phase-in Assessments As Of 07/01/2004	As Of 07/01/2005
Land:	294,810	294,810		
Improvements:	208,280	208,280		
Total:	503,090	503,090	503,090	NOT AVAIL
Preferential Land:	0	0	0	NOT AVAIL

Transfer Information

Seller:		**Date:** 06/03/1993	**Price:** $420,000
Type: IMPROVED ARMS-LENGTH		**Deed1:** /11429/ 53	**Deed2:**
Seller:		**Date:**	**Price:**
Type:		**Deed1:**	**Deed2:**
Seller:		**Date:**	**Price:**
Type:		**Deed1:**	**Deed2:**

Exemption Information

Partial Exempt Assessments	Class	07/01/2004	07/01/2005
County	000	0	0
State	000	0	0
Municipal	000	0	0

Tax Exempt: NO
Exempt Class:

Special Tax Recapture:

* NONE *

Annual Sales $170,000
Total Employees 3

Key Person
Owner David Burghard

US SIC Code
7389 Business services, nec

(3)Vetcentric Inc
Physical Address
839 Bestgate Rd
Annapolis, MD 21401-3013 (Map)Phone: 410-571-6790

Key Information
D-U-N-S Number 106442267
Line of Business INTERNET SERVICE FOR VETERINARY & ANIMAL INFORMATION
Location Type SINGLE LOCATION

Key Numbers
Annual Sales $1,300,000
Total Employees 60

Key Person
President John Dwyer

US SIC Code
0752 Animal specialty services

Maryland Department of Assessments and Taxation 1

Taxpayer Services Division
301 West Preston Street ☐ Baltimore, Maryland 21201

Main Menu | **Security Interest Filings (UCC)** | **Business Entity Information (Charter/Personal Property)** **New Search** | **Get Forms** | **Certificate of Status** | **SDAT Home**

Taxpayer Services Division

Entity Name: VICTORIA HAMPSHIRE, VMD, P.A.
Dept. ID #: D06047849

Principal Office (Current):	7307 NEVIS RD BETHESDA, MD 20817
Resident Agent (Current):	VICTORIA HAMPSHIRE 7307 NEVIS RD BETHESDA, MD 20817
Status:	INCORPORATED
Good Standing:	Yes
Business Code:	Professionals
Date of Formation or Registration:	11/15/2000
State of Formation:	MD
Stock/Nonstock:	Stock
Close/Not Close:	Not Close

Link Definition

General Information	General information about this entity
Amendments	Original and subsequent documents filed
Personal Property	Personal Property Return Filing Information and Personal Property Assessments
Certificate of Status	Get a Certificate of Good Standing for this entity.

Click here for a plain text ADA compliant screen.

Maryland Department of Assessments and Taxation
MONTGOMERY COUNTY
Real Property Data Search

Go Back
View Map
New Search
Ground Rent

Account Identifier: **District - 07 Account Number -** 00513160

Owner Information

Owner Name:	BALABAN, ROBERT S & VICTORIA A HAMPSHIRE	**Use:**	RESIDENTIAL
		Principal Residence:	NO
Mailing Address:	5608 MADISON ST BETHESDA MD 20817-3728	**Deed Reference:**	1) /10752/ 232 2)

Location & Structure Information

Premises Address
5608 MADISON ST
BETHESDA 20817

Legal Description
HUNTINGTON TERRACE 6
739-865

Map	Grid	Parcel	Sub District	Subdivision	Section	Block	Lot	Group	Plat No:
HN13				32		7	29	80	Plat Ref:

Special Tax Areas **Town** **Ad Valorem** **Tax Class** 38

Primary Structure Built	Enclosed Area	Property Land Area	County Use
1940	1,128 SF	6,875.00 SF	111

Stories	Basement	Type	Exterior
1 1/2	YES	STANDARD UNIT	FRAME

Value Information

	Base Value	Value As Of 01/01/2004	Phase-in Assessments As Of 07/01/2004	As Of 07/01/2005
Land:	155,870	305,870		
Improvements:	135,510	161,820		
Total:	291,380	467,690	350,150	408,920
Preferential Land:	0	0	0	0

Transfer Information

Seller:		**Date:** 10/20/1992	**Price:** $0
Type: NOT ARMS-LENGTH		**Deed1:** /10752/ 232	**Deed2:**
Seller:		**Date:**	**Price:**
Type:		**Deed1:**	**Deed2:**
Seller:		**Date:**	**Price:**
Type:		**Deed1:**	**Deed2:**

Exemption Information

Partial Exempt Assessments	Class	07/01/2004	07/01/2005
County	000	0	0
State	000	0	0
Municipal	000	0	0

Tax Exempt: NO
Exempt Class:

Special Tax Recapture:
* NONE *

Maryland Department of Assessments and Taxation

Taxpayer Services Division
301 West Preston Street Baltimore, Maryland 21201

Main Menu | Security Interest Filings (UCC) | Business Entity Information (Charter/Personal Property) New Search | Get Forms | Certificate of Status | SDAT Home

Taxpayer Services Division

Entity Name: VETERINARY HOME HEALTH CARE
Dept. ID #: T00069152

Status:	FORFEITED
Owner (Primary)	HAMPSHIRE, VICTORIA ANNA 7307 NEVIS ROAD BETHESDA, MD 20817
Location:	VETERINARY HOME HEALTH CARE 7307 NEVIS ROAD BETHESDA, MD 20817
Renewal Notice Date:	08/22/2003
Expiration Date:	02/11/2004

ATTACHMENT 32

Maryland Department of Assessments and Taxation

Taxpayer Services Division
301 West Preston Street ☐ Baltimore, Maryland 21201

Taxpayer Services Division

Charter Search Results for: VETCENTRIC%

Page 1 of 1

(Dept. ID)	Entity Name	Entity Detail			Status
(F05482039)	VETCENTRIC, INC.	General Info.	Amendments	Personal Property	REVIVED
(F05482039)	VETCENTRIC.COM, INC.	General Info.	Amendments	Personal Property	OLD NAME

Maryland Department of Assessments and Taxation 4

Taxpayer Services Division
301 West Preston Street Baltimore, Maryland 21201

Taxpayer Services Division

Entity Name: HAMPSHIRE, VICTORIA
Dept. ID #: L05436670

Personal Property

Mailing Address

HAMPSHIRE, VICTORIA
ADVANCED VETERINANY APPLICAHIONS
7307 NEVIS ROAD
BETHESDA, MD 20817

Personal Property Filings

Asmt. Year	Filing Date	Extension	Penalty Amount	Penalty Paid Date
2004		No		
2003		No		
2002		No		
2001		No		
2000	02/14/2000	No		

Personal Property Assessments Summary

Asmt. Year	Date Assessed	County Base	Town Base	Date Certified
2004				
2003				
2002				
2001				
2000	05/09/2000	0	0	

Personal Property Assessments Certification Information

Asmt. Year	Location	County	License	Town	Date Certified

Maryland Department of Assessments and Taxation 4

Taxpayer Services Division
301 West Preston Street Baltimore, Maryland 21201

Main Menu | Security Interest Filings (UCC) | Business Entity Information (Charter/Personal Property) New Search | Get Forms | Certificate of Status | SDAT Home

Taxpayer Services Division

Charter Search Results for Dept ID #: L05436670

Page 1 of 1

(Dept. ID)	Entity Name	Entity Detail		Status
(L05436670)	ADVANCED VETERINANY APPLICAHIONS		Personal Property	ACTIVE
(L05436670)	HAMPSHIRE, VICTORIA		Personal Property	ACTIVE

ATTACHMENT 33

Catherine Couch

From: B R [retake@erols.com]
Sent: Wednesday, October 13, 2004 3:06 PM
To: Germider, L; Catherine Couch
Subject: As Discussed: D&B
Importance: High

(1)Vetcentric Co
Physical Address
Enid, OK 73702 (Map)
Phone: 580-446-5555
Mailing Address
P O Box 700
Enid, OK 73702-0700

Key Information
D-U-N-S Number 859134343
Line of Business VETERINARY SERVICES
Location Type SINGLE LOCATION

Key Numbers
Annual Sales $48,000
Total Employees 1

Key Person
Owner Phil Steiner

US SIC Code
0742 Veterinary services, specialties

(2)Vetcentric Co
Physical Address
75 Verona Rd
Pittsburgh, PA 15235-1426 (Map)
Phone: 412-243-2401
Mailing Address
P O Box 17498
Pittsburgh, PA 15235-0498

Key Information
D-U-N-S Number 859915170
Doing Business As "Verntz Memorial Animal Hosp"

Line of Business BUSINESS SERVICES, NEC, NSK
Location Type SINGLE LOCATION

Key Numbers

ATTACHMENT 34

10/20/04

To: Brent Standridge

From: Lea-Ann Germinder

Cc: C.T. Newsum, Craig Wallace (verbal)

Accompanying this package are two boxes of product and paperwork from Advanced Veterinary Applications per your request.

Attached is the latest correspondence and documentation in attempting to order Heartgard from Advanced Veterinary Applications.

We have yet to receive the email notification and paperwork on the Heartgard ordered through Dr. Levy's prescription. It still appears you are unable to order a script from Advanced Vet but we have one more avenue to try.

ATTACHMENT 35

October 27, 2004

C.T. Newsum
Vice President Division Counsel
Fort Dodge Animal Health
9225 Indian Creek Parkway, Suite 400
Overland Park, KS 66210

Re: ProHeart®6 Recall Interim Research Report - Additional Materials

C.T.,

Per Brent Standridge, included in this package are the requested research materials regarding the recall of ProHeart®6 which came from a second source. Please note that the agency received these documents after the ProHeart®6 Recall Interim Research Report was submitted to Fort Dodge on October 12, 2004.

Also included in this package are the VetCentric materials sent to us from Dr. Steve Levy. The VetCentric Services Guide explains the procedure for becoming a VetCentric partner practice, provides information on product pricing and details the benefits veterinarians will receive in prescribing animal health medications and OTC products through VetCentric's website.

Finally, please find in this package the product and receipt information from the Heartgard order placed by a pet owner through VetCentric. As you can see, there is no paper trail to Advanced Veterinary Applications.

I will follow-up with Brent via phone to discuss these research materials in more detail.

Regards,

Lea Ann Germinder
Germinder & Associates, Inc.
6201 Brookside Blvd.
Kansas City, MO 64113

cc: Brent Standridge
Senior Vice President, Fort Dodge Animal Health

ATTACHMENT 36

From: Geoffrey Levitt
To: Corcoran, Tom; Essner, Robert; Rhudy, Marily H.; Stein, Lawrence
Date: 11/5/2004 1:18:24 PM
Subject: Call with Dan Troy

** Confidential **

I just spoke with Dan Troy to follow up on Bob's call to Les Crawford. I noted the apparent conflict of interest issue, etc., as per our talking points. Dan's response was that FDA of course takes any conflict of interest issue seriously and would be willing to hear us out, but that we should not assume this would necessarily lead to a reversal of the agency's position on ProHeart 6. That position was the result of a thorough internal review by a large group under Dr. Sundlof's supervision, so that bias on the part of any one individual - unless it were Sundlof himself - would be unlikely to be determinative. I said we had information to show not only that there was a strong appearance of conflict and bias, but also that these issues had influenced the data and analysis on which FDA's positon was based such that a completely fresh review of the data would be warranted. Dan commented that our presentation at the meeting with Dr. Crawford in Sept. had appeared unfocused and had not made a strong impression. He emphasized the importance of bringing to the next meeting a short and sharply focused presentation that would make clear why we thought the merits of the matter needed to be re-opened on the basis of the alleged conflict and bias. He asked if the individual in question had been central to the FDA's activity on the issue. I said that we felt it would not be appropriate to identify the individual in advance of our meeting, but could confirm that the person had been very heavily involved in the matter.

Geoff

CC: Burke, Cecilia; Newsum, C.T.

ATTACHMENT 37

Five Giralda Farms
Madison, NJ 07940

Douglas A. Dworkin
Vice President
Deputy General Counsel
973 660 6803 tel
973 660 7050 fax

Wyeth

December 16, 2005

The Honorable Charles E. Grassley
Chairman, Committee on Finance
United States Senate
Washington, DC 20510-6200

Dear Senator Grassley:

Thank you for the opportunity to respond to your November 17, 2005 inquiry regarding the circumstances of our voluntary withdrawal of the heartworm preventative medication ProHeart® 6, and the conflict of interest question we subsequently raised with the Food and Drug Administration (FDA). Wyeth is committed to cooperating with your investigation and answering the Committee's questions.

Our responses are set forth below:

1. *State how Wyeth concluded that Dr. Hampshire had an "apparent conflict of interest." In complying with this request, describe in detail the actions taken by Wyeth, including but not limited to whether or not Wyeth subsidized, either directly or indirectly, an investigation of Dr. Hampshire. Additionally, provide copies of all communications, documents, and records related to Wyeth's conclusion that Dr. Hampshire had an "apparent conflict of interest," including but not limited to, payments associated with one or more investigation(s) of Dr. Hampshire.*

As discussed below, Wyeth first identified Dr. Victoria Hampshire's apparent conflict of interest as an issue in September of 2004. To put that issue in context, earlier in 2004, Fort Dodge (Wyeth's animal pharmaceuticals subsidiary) had become concerned that our competitors might be manipulating adverse events reporting and media coverage regarding ProHeart 6. In an effort to determine the source of seemingly coordinated negative reports and internet stories, several Fort Dodge employees ran online searches related to ProHeart 6. Fort Dodge also asked its public relations firm, Germinder & Associates,

Wyeth

Inc. (GAI) to conduct online research, and, given the possible litigation issues, also retained the consulting firm ICG, Inc. (ICG) to do internet research. Through this research regarding ProHeart 6, Fort Dodge learned that Dr. Victoria Hampshire – then the lead ProHeart 6 reviewer and Adverse Drug Events (ADE) Coordinator at the Center for Veterinary Medicine – was quoted and thanked on several websites devoted to asserting that ProHeart 6 was dangerous.

During roughly the same period of time, Fort Dodge independently became concerned about what we considered misleading interpretations by CVM reviewers of ProHeart 6 adverse event reports and data. For example, in several instances advanced cases of cancer were attributed to ProHeart 6 even though the dogs had received their first dose of the medication only days before. In another case, a dog fell off the back of a truck after having been given ProHeart 6. The autopsy showed that the dog ruptured its liver from falling off the truck, but the CVM reviewer blamed the dog's death on ProHeart 6. In yet another case, a dog came into a veterinarian several days after treatment with ProHeart 6 with severe bleeding. High levels of rat poison were found in the dog's liver on autopsy, but the reviewer linked the death to ProHeart 6.

Fort Dodge's concerns about the objectivity of the CVM review process increased during Dr. Hampshire's September 1, 2004 presentation on ProHeart 6 adverse events. In that presentation (which led to the decision to withdraw ProHeart 6 from the market), she showed the initial adverse events reports for the product as trending upward for June, July and August 2004. In actuality, however, the initial reports were trending downward. Upon closer review of the data, we concluded that Dr. Hampshire had combined the follow-up reports with the initial reports to show an upward trend, in effect double-counting the adverse events. Dr. Hampshire also insisted that there was "an increasing severity and frequency of life threatening chronic systemic signs," despite clear data to the contrary. Dr. Hampshire also was quoted at that meeting as stating she did not trust veterinarians to report ProHeart 6 associated reactions to the FDA as "veterinarians know that owners cannot buy ProHeart 6 over the internet and thus want to protect their income by not reporting any adverse events." (See Wyeth 11/19/04 presentation at 18.)

Wyeth

Subsequent to the September withdrawal of ProHeart 6, Fort Dodge learned through an employee's Google search that Dr. Hampshire appeared to be affiliated with Advanced Veterinary Applications (AVA), an internet pharmacy business that marketed a range of veterinary products, including products that competed with ProHeart 6. In fact, the AVA pharmacy website prominently featured pictures and text promoting HeartGard®, a competitor product. Dr. Hampshire's business venture thus appeared to present a financial conflict of interest in the context of her review of ProHeart 6. We confirmed Dr. Hampshire's ownership of AVA by reviewing public records for the internet pharmacy business and Dr. Hampshire, and also requested that GAI place an order for products through the AVA website to confirm that AVA was an active business.

Once we received the products ordered through Dr. Hampshire's AVA website, Wyeth and its outside counsel (including attorneys specializing in FDA law at Covington & Burling) reviewed the regulations governing ethical conduct of government officers and employees. Among other applicable rules, the general standards of ethical conduct for federal employees prohibit an employee from participating personally and substantially in an official capacity in a particular matter in which he/she has a financial interest, if the particular matter will have a direct and predictable effect on that interest. 5 C.F.R. Sec. 2635.402(a), citing 18 U.S.C. 208(a). *See also* August 1, 2001 FDA document, entitled "*Conflict of Interests Basics for New HHS Employees*" which, in giving an example applying the financial interest rule, states that "if you work at FDA, for example, you cannot work after hours managing a retail drug store . . . ."

Based on the facts and the regulations, we concluded that Dr. Hampshire's operation of a website selling and featuring a competing product could constitute a financial conflict of interest and possibly affect the objectivity of FDA's review of ProHeart 6. In view of FDA's prohibitions against employees' conflicts of interest and to help assure that the integrity of the FDA regulatory process was not threatened by the fact or appearance of impropriety, we asked for a meeting to discuss our concerns with FDA officials. That meeting took place on November 19, 2004, when we delivered the Power Point presentation (to which you referred on November 17, 2005) to the FDA Chief Counsel Daniel Troy, and Acting Commissioner Dr. Lester Crawford.

Wyeth

See also the enclosed documents, which constitute our initial production of non-privileged responsive documents, which we are providing pursuant to the Committee's request, and for its exclusive use. We are still in the process of collecting and reviewing documents and will produce additional responsive documents as soon as is practicable. Many of the documents the Committee requested are privileged, either as work product or confidential attorney-client communications. Disclosure of privileged documents to a third party, such as the Committee, could constitute waiver of that privilege in other contexts, such as ongoing litigations regarding overlapping subject matter.

2. *Identify all individual(s) and/or agent(s) (including full name, title, and contact information) employed by and/or associated with Wyeth, either directly or indirectly, who were involved in any way with an investigation(s) of Dr. Hampshire. In the event that any individual(s) and/or agent(s) is/are no longer associated with Wyeth, identify that individual(s) and/or agent(s) as well.*

The following individuals and entities provided information and documentation with respect to the review of a possible conflict of interest involving Dr. Hampshire:

Dr. Rami Cobb
Vice President of Pharmaceutical Research
Fort Dodge Animal Health
Princeton, New Jersey
Phone: (732) 631-5800.

Dr. Deborah Chaleff
Director Regulatory Affairs & Quality Assurance
Fort Dodge Animal Health
Princeton, New Jersey
Phone: (732) 631-5800.

Brent Standridge
Senior Vice President North American Sales & Marketing
Fort Dodge Animal Health
Overland Park, KS
Phone: (913) 664-7036.

Wyeth

Craig Wallace
Vice President North American Marketing
Fort Dodge Animal Health
Overland Park, KS
Phone: (913) 664-7059.

C.T. Newsum
Senior Vice President & Chief Counsel
Fort Dodge Animal Health
Overland Park, KS
Phone: (9130 554-7004

Marta K. Porwit
Project Manager
ICG, Inc.
Princeton, NJ
Phone: (609) 806-5000.

Lea Ann Germinder
President
Germinder & Associates, Inc.
Kansas City, MO
Phone: (816) 822-0192.

Doug Todd
Phillips McFall McCaffrey McVay & Murrah, P.C.
One Leadership Square, 12th Floor
211 North Robinson
Oklahoma City, OK 73102
Phone: (405) 235-4100

3. *Identify all individual(s) and/or agents(s)(including full name, title, and contact information) employed by and/or associated with Wyeth, either directly or indirectly, who were involved in any way with the research supporting and the preparation of the Power Point presentation entitled, "ProHeart 6 Apparent Conflict of Interest," dated November 19, 2004. In the event that any individual(s) and/or agent(s) is/are no longer associated with Wyeth, identify that individual(s) and/or agent(s) as well.*

Wyeth

Dr. Rami Cobb
Vice President of Pharmaceutical Research
Fort Dodge Animal Health
Princeton, New Jersey
Phone: (732) 631-5800.

Dr. Deborah Chaleff
Director Regulatory Affairs & Quality Assurance
Fort Dodge Animal Health
Princeton, New Jersey
Phone: (732) 631-5800.

Brent Standridge
Senior Vice President North American Sales & Marketing
Fort Dodge Animal Health
Overland Park, KS
Phone: (913) 664-7036.

Craig Wallace
Vice President North American Marketing
Fort Dodge Animal Health
Overland Park, KS
Phone: (913) 664-7059.

C.T. Newsum
Senior Vice President & Chief Counsel
Fort Dodge Animal Health
Overland Park, KS
Phone: (9130 554-7004.

Geoffrey Levitt
Vice President & Chief Counsel, Regulatory and Research
Wyeth Pharmaceuticals
Collegeville, PA
Phone: (484) 865-8598

Doug Todd
Phillips McFall McCaffrey McVay & Murrah, P.C.
One Leadership Square, 12th Floor
211 North Robinson
Oklahoma City, OK 73102
Phone: (405) 235-4100.

Wyeth

Robert Kelner
Partner
Covington & Burling
1201 Pennsylvania Avenue, NW
Washington, DC 20004
Phone: (202) 662-6000

Richard Kingham
Partner
Covington & Burling
1201 Pennsylvania Avenue, NW
Washington, DC 20004
Phone: (202) 662-6000

Eugene Lambert
Partner
Covington & Burling
1201 Pennsylvania Avenue, NW
Washington, DC 20004
Phone: (202) 662-6000

Jeannie Perron
Counsel
Covington & Burling
1201 Pennsylvania Avenue, NW
Washington, DC 20004
Phone: (202) 662-6000

4. *Provide copies of all documents and records, including but not limited to communications and email, related to the Wyeth Power Point presentation entitled, "ProHeart 6 Apparent Conflict of Interest," dated November 19, 2004.*

See enclosed production, which constitutes our initial production of non-privileged responsive documents.

5. *State whether or not Wyeth provided notice to the FDA that it was initiating or conducting a private investigation into an FDA employee? If so, provide the name(s) of any individual at the FDA who received notice prior to the initiation of the*

Wyeth

investigation. Provide copies of all records, including but not limited to communications and emails between Wyeth and the FDA related to the investigation of Dr. Hampshire.

Wyeth first notified the FDA in detail of this issue in a November 19, 2004 meeting with Daniel Troy, FDA Chief Counsel and Acting FDA Commissioner, Dr. Lester Crawford. (The meeting itself was requested in early November.)

6. *How many times has Wyeth investigated an FDA employee(s) and/or presented information to the FDA related to an FDA employee's apparent conflict of interest? Additionally, describe in detail the facts associated with each investigation and/or presentation.*

The above-referenced research and contacts with the FDA regarding Dr. Victoria Hampshire is the only instance we have been able to identify in which Wyeth has collected information regarding an apparent conflict of interest involving an FDA employee and/or presented such information to the FDA.

7. *Provide complete contact information for Mr. Clint "C.T." Newsum, Vice President for Wyeth Pharmaceuticals. Additionally, please make Mr. (8) Newsum available for an interview with my staff to take place no later than December 23, 2005.*

Mr. Clint Newsum
Senior Vice President & Chief Counsel
Fort Dodge Animal Health
9225 Indian Creek Parkway, Suite 400
Overland Park, KS 66210
Phone: (913) 664-7004

Wyeth will make Mr. Newsum available for an interview with your staff at a mutually convenient time and date.

9. *Provide complete contact information for Mr. [redacted] a Senior Territory Manager for Fort Dodge Animal Health, a division of Wyeth Pharmaceuticals. Additionally, please make [redacted] available for an interview with my staff to take place no later than December 23, 2005.*

Wyeth

[redacted]

Wyeth will make Mr. [redacted] available for an interview with your staff at a mutually convenient time and date.

10. *Provide complete contact information for Mr. Tom O'Hare of Copiague, New York. Identify the relationship Mr. O'Hare has with Wyeth Pharmaceutical, including but not limited to, any financial relationship. State whether or not Wyeth is able to make Mr. O'Hare available for and interview, and if so, please make Mr. O'Hare available for an interview with my staff to take place no later than December 23, 2005.*

Mr. O'Hare has no relationship, financial or otherwise, with Wyeth and Wyeth is unable to make him available for an interview. Wyeth has been informed that Mr. Hare is a relative of LeAnn Germinder of Germinder & Associates, Inc. and that he resides at 40 East Gate, Copiague, NY 11726.

Sincerely,

Douglas A. Dworkin

Enclosure

ATTACHMENT 38

Memorandum of Meeting
November 19, 2004
Rm. 14-71, Parklawn

Wyeth:

Bob Essner, Chairman, President, and Chief Executive Officer
Jeff Levitt, V.P. and Chief Counsel, Regulatory and Research
Gerald Fisher, Senior V.P., Drug Safety and Metabolism

FDA:

Lester M. Crawford, Acting Commissioner
Dan Troy, Chief Counsel
Dana Delman, Policy Analyst

Wyeth representatives discussed issues surrounding the September 3, 2004, withdrawal from the market of ProHeart®6, an approved injectable sustained-release heartworm prevention product for dogs. Fort Dodge Animal Health, a division of Wyeth, has ceased production of the product until FDA's questions about adverse reaction reports associated with ProHeart®6 can be resolved.

Wyeth representatives conveyed their concerns with the FDA assessment of adverse reaction data, and a potential conflict of interest issue. They specifically asked for a reexamination of that data prior to an advisory committee meeting scheduled for January 2005 at which all available data on ProHeart®6 will again be evaluated.

Dana Delman

ATTACHMENT 39

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

The Honorable Charles E. Grassley
Chairman
Committee on Finance
United States Senate
Washington, D.C. 20510-6200

JUN 7 2006

Dear Mr. Chairman:

Thank you for your letter of April 18, 2006, regarding your Committee's ongoing review of the Food and Drug Administration (FDA) and events surrounding the investigation of Dr. Victoria Hampshire. You requested certain records and communications about this investigation.

We have enclosed documents that we have identified as responsive to your request along with an index of documents in each of the enclosed tabs. We have not included documents that were previously provided to Committee staff in the November 10, 2005, briefing with the FDA's Office of Internal Affairs (OIA). Some documents may be responsive to multiple items of your request. For these, we have placed the document under the tab in which it seemed most responsive. We restate your requests below in bold type, followed by our responses under each item.

By way of background in FDA, all enforcement activity is conducted by the Office of Regulatory Affairs (ORA). Within ORA, the Office of Criminal Investigation (OCI) conducts all criminal investigations. The Office of Internal Affairs is a subordinate office within OCI which conducts administrative and criminal investigations of alleged employee misconduct.

We would note at this point that the Office of Government Ethics (OGE) Form 450 Executive Branch Confidential Financial Disclosure Reports is being provided to the Committee in response to its request as the appropriate Congressional Committee having jurisdiction over the activities of this Agency. This limited release to the Committee does not constitute public release of these OGE Form 450 reports. These reports are confidential pursuant to section 107(a) of the Ethics in Government Act, Title 5, United States Code (U.S.C.) appendix, and section[s] 201(d) [and 502(b)] of Executive Order 12674, as modified; see also Title 5, *Code Federal Regulations* §§2634.604 and 2634.901(d) of the OGE regulations there under. In addition to the Freedom of Information Act (FOIA) exemption providing for nondisclosure of such information, which is specifically exempted from disclosure by statute, this Agency also deems these reports to be excluded from required public disclosure under the FOIA pursuant

to the exemptions for sensitive commercial and financial information as well as for personal privacy-protected information. See 5 U.S.C. §552(b)(3), (b)(4) and (b)(6). Furthermore, the reports are subject to appropriate protections under the Privacy Act, 5 U.S.C. §552a, as they constitute personal information and are contained in the OGE/GOVT-2 system of records. Therefore, we respectfully request that you and your staff use these reports for internal Committee purposes only and not release them to the public. Any requests for access by the public can be referred to this Agency. We would be glad to discuss with the Committee staff the protected status of any specific information.

1. **Provide all records and communications related to the conflict of interest referral by Wyeth Pharmaceuticals regarding Dr. Victoria Hampshire, V.M.D., including, but not limited to, emails and handwritten notes. State the date Wyeth first contacted FDA with concerns related to Dr. Hampshire and the date Wyeth officially referred its allegations regarding a conflict of interest.**

Wyeth contacted FDA on November 19, 2004, with concerns related to Dr. Hampshire.

Documents responsive to this request are located under Tab A

2. **Provide a list date of all meetings, teleconferences, and/or telephone calls between any FDA official/employee and Wyeth Pharmaceuticals regarding Dr. Victoria Hampshire. Please sort the list by date and provide the names of all participants at each event and a detailed description of the subject matter discussed. Provide a copy of all records and communications related to all meetings, teleconferences and/or telephone calls. Identify all participants with their full name, title, and office, including, but not limited to, the Office of the Commissioner, the Office of the Chief Counsel, the Center for Veterinary Medicine (CVM), the Office of Regulatory Affairs, the Office of Criminal Investigations, and the Office of Internal Affairs.**

Documents responsive to this request are located under Tab B.

3. **Provide all records and communications, including, but not limited to, emails and handwritten notes or other records of communications between Mr. Clint "C.T." Newsum, Vice President and General Counsel at Wyeth pharmaceuticals and FDA Office of Criminal Investigations.**

Documents responsive to this request are located under Tab C.

4. **Provide all records and communications related to a response from FDA to Wyeth Pharmaceuticals concerning a letter received by Dr. David Sundlof, Director of the Center for Veterinary Medicine (CVM) from [redacted] a veterinarian from [redacted] This request should include, but not be limited to, any response generated by CVM, the Office of Legal Counsel, and/or the Office of the Commissioner.**

FDA did not identify any responsive documents.

5. **Provide all records and communications between Wyeth Pharmaceuticals and Dr. David Sundlof, Director, CVM related to ProHeart 6 or Dr. Victoria Hampshire, V.M.D.**

Documents responsive to this request are located under Tab D.

6. **Provide all records and communications between any representative of Wyeth Pharmaceuticals, including but not limited to Mr. Robert Essner, and Commissioner Lester Crawford related to ProHeart 6 and/or Dr. Victoria Hampshire, V.M.D. This request should include, but is not limited to, any letters, emails, notes or other communication.**

Documents responsive to this request are located under Tab E.

7. **Provide all records and communications related to any investigation or inquiry regarding [redacted] This request should include, but not be limited to, the investigative file of [redacted]**

Per discussion with Committee staff by phone, FDA did not identify any responsive documents.

8. **Provide a list of all internal ethics investigations by FDA's Office of Internal Affairs, of any FDA employee based upon an ethics complaint originating from outside the FDA for the period of January 1996 through present. Additionally, provide a list of all internal ethics investigations by FDA Office of Internal Affairs of any FDA employee as a result of an ethics complaint originating from within FDA for the period of January 1996 through the present.**

Documents responsive to this request are located under Tab F.

Thank you again for your letter. If you have further questions or concerns, please let us know.

Sincerely,

Michelle Mital for

David Boyer
Assistant Commissioner
for Legislation

Enclosures

ATTACHMENT 40

TAB C 9/7/06

INDEX

(1) Email correspondence dated December 9, 2004 with subject line, "Contact Information." (1 page)
(2) Facsimile dated January 11, 2005 from C.T. Newsum of Fort Dodge Animal Health to Mark McCormack of FDA. (2 pages including the cover page)
(3) OIA notes from telephone interview with C.T. Newsum dated December 16, 2004 (2 pages)

McCormack, Mark

From: C.T. Newsum [ctnewsum@fdah.com]
Sent: Thursday, December 09, 2004 11:59 AM
To: mark.mccormack@fda.gov
Cc: Geoffrey Levitt
Subject: Contact Information

Mark:

Geoff requested I provide you with my contact information.

C.T. Newsum
Vice President and Division Counsel
Fort Dodge Animal Health
9225 Indian Creek Parkway, Suite 400
Overland Park, KS 66210
Telephone: 913-664-7004
Fax: 913-664-7086
E-mail: ctnewsum@fdah.com

Please feel free to contact me at your convenience.

CTN

Fort Dodge Animal Health
Division of Wyeth
9225 Indian Creek Pkwy.,
Building 32, Suite 400
Overland Park, KS 66210

FORT DODGE

FACSIMILE

Date: January 11, 2005

Number of pages (including cover): 2

To: Mark McCormack
FDA
Telephone: 301-827-0273
Fax: 301-827-0266
cc:

From: C.T. Newsum
Senior Vice President and Chief Counsel
Department: Law Department
Telephone: (913) 664-7004
Fax: (913) 664-7086

☐ Urgent ☒ For your review ☐ Please reply asap ☐ Please comment

Mark

Per our discussion, please see attached. Thank you for your attention to this matter.

Regards,

C.T. Newsum

Attachment

Tel Interview w/CT Newsum 12/16/04

Looking into INTERNET ACTIVISTS AGAINST PRO HEART 6. SAW NAME OF DR Hampshire pop-up.

CT - When was PH6 pulled?

Advanced Vetrinary Applications — Hampshire worked there prior to ~~Hampshi~~ FDA.
Hampshire's web site.

---

* Has she written scrips for heart worm products?

PH-6 - introduced to mkt April 2001
pulled 9/3/04. Voluntarily by Ft Dodge Health.
How much 8 million does sold.

---

* Stock price decline? I doubt it.

Total Sales - $850 million FDAH

Who went into sec Crawford & Troy -
Geoff Levit, CEO Wyeth
Robert Essner
DR Fischer

Why they started looking into her to begin with?

Financial connection bet Vet Centric and her?

Postings made by her prior to PRO HEART 6 being pulled - as opposed to hearsay "No."

Vet Centric - For vets that don't want to inventory their own products.

Money is made by - Vet Centric fills the order bills the customer in the name of the veterinarian. Reconciliation done monthly

Vet sets price, gets margin.

Fax or call in a prescription
Transfer Recievable to Vet Centric

practice dispensing fee

ATTACHMENT 41

Memorandum of Understanding

Between the Food and Drug Administration

and

Office of Inspector General

Department of Health and Human Services

PURPOSE:

Recognizing the statutory mandates of both components, and their important roles, and the necessity for maintaining a capable and trained internal investigational unit to conduct internal investigations, to provide a centralized investigative liaison between the Food and Drug Administration (FDA) and the Office of Inspector General (OIG), and to support the OIG's criminal investigations that involve FDA employees, the two components enter into this Memorandum of Understanding concerning the procedures they will observe in internal investigations involving FDA employees.

THE OFFICES

A. The Office of Inspector General

The Inspector General Act of 1978, Public Law 95-452, as amended by Public Law 100-504, 5 U.S.C. App., established the Office of Inspector General as an independent office within the Department of Health and Human Services (HHS). A major purpose of the OIG is to "conduct and supervise audits and investigations relating to the programs and operations of [HHS]." Section 2(1) of the Inspector General Act. The Act further provides that, "in carrying out the

duties and responsibilities established under this Act, each Inspector General shall report expeditiously to the Attorney General whenever the Inspector General has reasonable grounds to believe there has been a violation of Federal criminal law." Section 4(d).

B. The Office of Internal Affairs

The FDA, including its Office of Criminal Investigations (OCI), is a component of HHS and is responsible for implementing the Food, Drug, and Cosmetic Act, 21 U.S.C. § 321 et seq. and other statutes. The Office of Internal Affairs (OIA)[1] which is staffed by special agents detailed from OCI, was authorized and established by the Secretary of HHS, within the FDA, Office of Commissioner, to conduct internal investigations of employee misconduct. 60 Fed. Reg. 4417 (January 23, 1995). The OIA Statement of Organization states that OIA "provides a centralized investigative liaison between FDA and [OIG]" and shall serve "as an FDA investigative resource to conduct internal FDA investigations and to support OIG investigations." Id.

PROCEDURES

1. FDA will continue to ensure that its Office of Internal Affairs (OIA) is properly equipped and supported and staffed with trained and experienced criminal investigators (1811-series), and will continue to refresh the OIA staff by assigning agents from FDA's Office of Criminal Investigations to the OIA for duty tours on a rotating basis.

2. The OIG will continue to staff its FDA investigations with trained and experienced criminal investigators (1811-series) and will endeavor to provide adequate resources for investigations so as to enable OIA to investigate promptly after allegations are made.

3. OIG and FDA's OIA shall have prompt access to all files and documents within the FDA relevant to their investigations, and the resulting open investigative files and documents of these investigative entities shall be disclosed outside the Department only to prosecutors and other law enforcement entities, consistent with applicable law and regulation and as necessary to accomplish the respective missions of the OIG and OIA.

4. When OIA receives an allegation of criminal misconduct or violation of the HHS standards of conduct by an HHS employee, OIA shall immediately notify the OIG in writing or by electronic mail. Similarly, when OIG receives an allegation of criminal misconduct or violation of the HHS standards of conduct by an FDA employee it shall, as appropriate with its role under the Inspector General Act, immediately notify OIA in writing or by electronic mail. This notification by the OIG should occur unless the OIG determines that the notification is inconsistent with its role under the Inspector General Act.

5. If, at any point during an investigation, OIA determines that a criminal violation has likely been committed by an FDA employee, OIA shall immediately notify the OIG in writing or by electronic mail. If at any point during an OIG investigation, OIG determines that a criminal violation by an FDA employee has likely occurred, but the OIG determines it will not investigate that violation, it will, as appropriate with OIG's role under the Inspector General Act, immediately notify the OIA in writing or by electronic mail.

6. In recognition of the availability and performance of the FDA OIA, as an existing, trained, equipped and supported investigative unit engaged in investigations of allegations of violative or illegal conduct by FDA employees, and to avoid the duplication of resources and effort that would result from dual focus on any particular investigation, both components anticipate that such investigations will be conducted expeditiously by FDA's OIA, subject to OIG's reservation

of the right in all cases to pursue a case jointly with OIA, or, after consultation with OIA, to replace OIA as the primary agency assigned to an investigation of an FDA employee. OIA will maintain an open file until it receives a final summary and disposition from the OIG on such cases. Any referral of an investigation by the OIG to the OIA will be made expeditiously, enabling OIA to begin any necessary investigation on current information. If OIA believes that its development of an investigation requires issuance of a subpoena duces tecum, it may request that the OIG pursue the case jointly with the OIA.

7. A headquarters OIG/OI supervisor will meet with the OIA Special Agent in Charge on a monthly basis for the purpose of examining all open investigations or cases, preliminary investigations, and any other informal investigative matters which in the judgment of OIA would be of interest to OIG. OIA will provide OIG with a report of all open investigations or cases, preliminary investigations, and any other informal investigative matters which in the judgment of OIA would be of interest to OIG. The outcome of all cases and investigations concluded during the course of the previous month will also be discussed at this meeting.

8. The OIA will provide reasonable notice to the OIG prior to any presentation to the Department of Justice of an investigation in order to allow OIG to participate in the presentation if OIG chooses.

This Memorandum of Understanding is entered into voluntarily by both OIG and FDA. It may be modified at any time by agreement of the parties and may be terminated upon thirty days prior written notice by either agency.

This Memorandum of Understanding shall become effective upon the date of signing by both parties and shall continue until it is modified or terminated.

Signed this 30th day of July, 1998

Michael A. Friedman, M.D.
Lead Deputy Commissioner
Food and Drug Administration

Jorge Gibbs Brown
Inspector General

ATTACHMENT 42

TAB A - 6/7/06 letter

INDEX

CVM # 515-05

IRT 11/5/04

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

REQUEST FOR APPROVAL OF OUTSIDE ACTIVITY

(Ref.: HHS/FDA Standards of Ethical Conduct Regulations 5 CFR 5501)

☐ Initial Request
☐ Revised Request
☒ Renewal

1. NAME *(Last, First, Initial)*
Last: Hampshire
First: Victoria
Initial: A

2. ORGANIZATIONAL LOCATION
DHHS/FDA/CVM/OSC/DS

3. TITLE OF POSITION
Adverse Drug Events Coordinator

4.a. GRADE AND SALARY *(Federal)*
Pay Plan - Series: CDR-05 PHS
Salary: $70,120.00

4.b. FINANCIAL DISCLOSURE FILING STATUS
☐ Public ☐ None
☒ Confidential

5. *NAME, ADDRESS AND BUSINESS OF PERSON OR ORGANIZATION FOR WHOM OUTSIDE SERVICES WILL BE PERFORMED
Name of Business: The Metropolitan Emergency Animal Clin
Street: 12106 Nebel Street
City: Rockville State: MD Zip: 20894

6. LOCATION WHERE SERVICES WILL BE PERFORMED
Name of Location: The Metropolitan Emergency Animal Clin
Street: 12106 Nebel Street
City: Rockville State: MD Zip: 20817

7. NATURE OF ACTIVITY *(Indicate type of activity, e.g., teaching, consultative services, and give full description of specific duties or services to be performed. Specify, when possible, the scheduled days of week and hours of day proposed activity will be performed. ALSO, answer (a.), (b.), and (c.) below.)*
Clinical Care

Only published and publicly available information and data may be discussed. For consulting, DHHS/FDA rules regarding consulting will be observed.
Employee: *(a.)* ☐ is ☒ is not *(check one)* a project officer;
(b.) ☐ has ☒ has no *(check one)* CRADA or MTA-CRADA responsibilities; and
(c.) Center/Office ☒ has ☐ has no *(check one)* grants or contracts with this organization.

8. ESTIMATED TIME INVOLVED
a. PERIOD COVERED *(May not exceed one year)*
From: 11/01/2004 *(DD/MM/YYYY)* To: 11/01/2005 *(DD/MM/YYYY)*

If the start date above precedes the date of employee signature (Item 13.b., Page 2), then provide justification:

b. ESTIMATED TOTAL TIME DEVOTED TO ACTIVITY *(e.g., 4 hours per day, 2 days per week)*
Hours per day: 10 AND Days per week: 1

c. WILL WORK BE PERFORMED ENTIRELY OUTSIDE USUAL WORKING HOURS?
☒ Yes ☐ No If "No," indicate type of leave and estimated number of hours or days of absence from work: _____ *(Type of Leave)* and _____ *(Hours)* or _____ *(Days)*

9. DO YOUR OFFICIAL DUTIES RELATE IN ANY WAY TO THE PROPOSED ACTIVITY?
☒ No ☐ Yes *(Describe in sufficient detail for reviewing official to understand the relationship.)*

10. *IF PROVIDING CONSULTATIVE OR PROFESSIONAL SERVICES, ARE YOUR WOULD-BE ASSOCIATES RECEIVING, OR WILL THEY SEEK, A GRANT OR CONTRACT FROM A FEDERAL AGENCY? *(Services provided will not knowingly involve, directly or indirectly, preparation of material which could relate to any financial dealings between the outside organization and FDA.)*
☒ No ☐ Yes *(Describe)*

11. TYPE AND AMOUNT OF COMPENSATION
☐ Fee ☐ Honorarium ☐ Per Diem ☐ Per Annum ☐ None
☐ Royalty ☐ Expenses ☒ Other *(Specify)* See Itemized List
$ 550.00 Amount of Compensation $ 0.00 Expenses

12. WILL COMPENSATION BE DERIVED FROM A HHS GRANT OR CONTRACT? *(No compensation or expenses may be derived from HHS funds.)*
☒ No ☐ Yes

*See Page 2 of form (ACKNOWLEDGEMENT, ACTION TAKEN, COMMENTS AND INSTRUCTIONS ARE ON PAGE 2 OF FORM)

PSC Media Arts (301) 443-1090 EF

13. EMPLOYEE ACKNOWLEDGEMENT

This request is made with full knowledge of department and operating division policy and procedures on outside activities. I attest that I have read and understand the "Notice to Applicants for Prior Approval of Outside Activities" (pages 3 and 4), and that the statements I have made are true, complete and correct to the best of my knowledge and belief. I understand that I am disqualified from all official duty activities relating to this organization, effective immediately and for twelve months beyond the conclusion of this activity (5 CFR 2635.502) unless I seek authorization from FDA'S Deputy Ethics Counselor to participate in such activities.

a. SIGNATURE OF EMPLOYEE	b. DATE	c. *ADDITIONAL INFORMATION ATTACHED
Victoria Hollowell	11/1/04	☐ Yes ☒ No

14. ACTION RECOMMENDED BY REVIEWING OFFICIAL

a.	b. SIGNATURE / Printed Name:	c. TITLE	d. DATE
☑ APPROVAL ☐ DISAPPROVAL	[signature]	Director, OSC	11/8/04

e. COMMENTS OF RECOMMENDING OFFICIAL *(Comments required if activity is recommended for disapproval.)*

L.L. Callahan 11-16-04

15. ACTION TAKEN

a.	b. SIGNATURE / Printed Name:	c. TITLE	d. DATE
☐ APPROVAL ☐ DISAPPROVAL	[signature]	Director, CVM	11/24/04

e. COMMENTS OF APPROVING OFFICIAL *(Comments required if activity is disapproved.)*

INSTRUCTIONS

Item 5 - **Self-Employment:** If applicable, indicate self-employment, the type of service (as medical, legal, etc.), whether alone or with partners, giving their names, and, if providing professional services to a large number of clients or patients, estimate the total number rather than listing them separately.

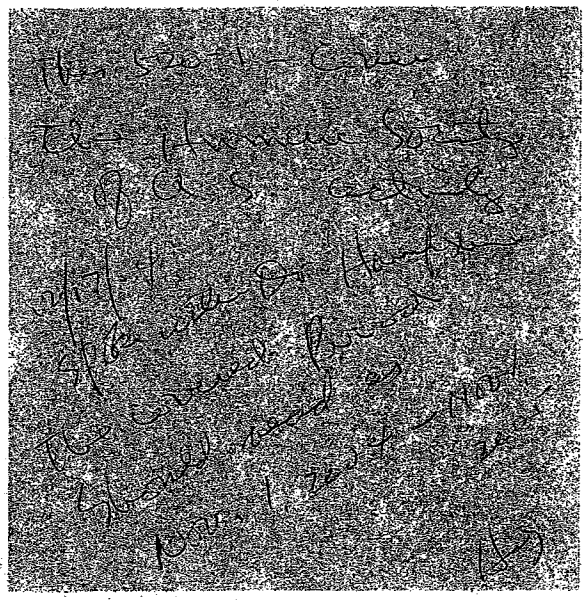
Item 10 - **Federal Grants or Contracts Involved:** Describe the Federal grants or contracts (type, granting or contracting department, etc.). Full details must be provided on any aspect of professional and consultative services which involves, directly or indirectly, the preparation of grant applications, contract proposals, program reports, and other material which are designed to become the subject of dealings between institutions and government units and the Federal Government.

Item 13.c. - **Attachments:** Be sure to sign copies of all attachments submitted.

INFORMATION TO EMPLOYEE: The collection of the information requested on this form is authorized by Executive Order 12731 and the regulations issued thereunder. The information you disclose will be used to determine whether a conflict of interest would exist between the outside activity and your official duties. The information will be held in confidence and made available only to persons specifically authorized by the head of the principal operating component or designee. The information may be used: a) by a Federal, State or local agency when there is an indication of a violation or potential violation of law; b) by a Federal agency in deciding on the hiring or retention of an employee or other benefit; c) for statistical information excluding personal identification of individuals; and d) for other routine uses published in accordance with 5 USC 552a. Your failure to provide the information requested will preclude your engaging in the outside activity for which approval is required.

11. TYPE AND AMOUNT OF COMPENSATION (CONTINUATION PAGE)			
TYPE OF COMPENSATION	AMOUNT OF COMPENSATION	EXPENSES	COMMENTS
Fee	$550.00		Clinical work
TOTALS:	$550.00		

ENTER ADDITIONAL COMMENTS BELOW



OGE Form 450, 5 CFR Part 2634, Subpart I
U.S. Office of Government Ethics (9/02)
(Replaces 4/99 edition)

Form Approved:
OMB No. 3209-0006

Executive Branch CONFIDENTIAL FINANCIAL DISCLOSURE REPORT

Page Number 1 of 3

Employee's Name *(Last, first, middle initial)*	Position/Title	Grade	Reporting Status:
Hampshire, Victoria A.	Adverse Drug Events coordinator	CDR 05	☐ New entrant ☒ Annual
Agency	**Branch/Unit and Address**	**Work Phone**	**If New Entrant, Date of Appointment**
DHHS/FDA/CVM/OSC/DS	7519 Standish Pl Room 2426 Rockville, MD	(301) 927-7822	

Check box if special Government employee (SGE) ☐ | If an SGE, Home Address *(Number, Street, City, State and ZIP Code)*

I certify that the statements I have made on this form and all attached statements are true, complete, and correct to the best of my knowledge. | Signature of Employee [redacted] | Date 11/3/04

Date Received by Agency	*On the basis of information contained in this report, I conclude that the filer is in compliance with applicable laws and regulations (except as noted in "comments" box below).*	Signature and Title of Supervisor/Other Intermediate Reviewer *(If agency requires)*	Date
		[redacted]	12/6/04

Signature of Agency's Final Reviewing Official and Title [redacted] | Date 12/7/04 | Comments of Reviewing Officials 520-1

(Check box if continued on reverse) ☐

Part I Help

Part I: Assets and Income

None ☐

Identify for you, your spouse, and dependent children: 1) assets with a fair market value greater than $1,000 at the close of the reporting period or producing income over $200; and 2) sources of earned income such as salaries, fees, honoraria (other than U.S. Government salary or retirement benefits, such as the Thrift Savings Plan) which generated over $200 in income during the reporting period. Earned income sources of your spouse must be reported if greater than $1,000 (greater than $200 for honoraria). No earned income needs to be reported for dependent children.

Assets include (but are not limited to): stocks, bonds, tax shelters, real estate, mutual funds, pensions, annuities, IRAs, trusts, commodity futures, trades and businesses, and partnership interests.

Exclude your personal residence, unless you rent it out, and deposit accounts in financial institutions. See instructions for additional exclusions.

	Assets and Income Sources *(Identify specific employer, business, stock, bond, mutual fund, type/location of real estate, etc.)*	(X) if no longer held	Nature of Income over $200 *(Rent, interest, dividends, capital gains, salary, etc.)*	Date *(Only for honoraria)*
Examples	Rental Condo, Anchorage, Alaska		Rent	
	Dee, Jones & Smith, Hometown, USA	X	Salary	
	(S) Alexandria Medical Clinic, Alexandria, VA		Salary	
	Franklin Equity Mutual Fund		Dividends/Capital Gains	
1	[redacted] Rental Income.		[redacted]	
2	Income outside activity 1. Metropolitan		$5,550.00/yr	520-1
3	Emergency Animal Clinic			
4	Income outside activity 2.		$4,000.00/yr.	520-1
5	The Humane Society of The			
6	United States			
7	[redacted]			
8	100 shares Air Tran Airways			
9	100 shares American Pacific Bank			
10	1500 shares Nokia.			

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OGE Form 450, 5 CFR Part 2634, Subpart I
U.S. Office of Government Ethics (9/02)
(Replaces 4/99 edition)

Executive Branch CONFIDENTIAL FINANCIAL DISCLOSURE REPORT

Employee's Name *(Last, first, middle initial)*
Hampshire, Victoria A.

Part I: Assets and Income

Part I Help

Assets and Income Sources *(Identify specific employer, business, stock, bond, mutual fund, type/location of real estate, etc.)*	(x) if no longer held	Nature of Income over $200 *(Rent, interest, dividends, capital gains, salary, etc.)*	Date *(Only for honoraria)*
11			
12			
13			
14			
15			
16			
17			
18			
19			
20			
21			
22			
23			
24			
25			
26			
27			

Employee's Name *(Last, first, middle initial)*	Work Phone
Hampshire, Victoria A.	(301) 927-7822

Part II Help

Part II: Liabilities

None ☐

Report for you, your spouse, and dependent children, liabilities over $10,000 owed at any time during the reporting period (over $10,000 at the end of the period if revolving charge accounts). Exclude a mortgage on your personal residence unless it is rented out; loans for autos, household furniture or appliances; and liabilities owed to certain family members (see instructions).

	Creditors *(Name and address)*	Type of Liability *(Mortgage, promissory note, etc.)*
Example	First Alaska Bank, Anchorage, Alaska	Mortgage on rental property in Anchorage, AK
1	Wells Fargo Mortgage; Rental Property	Mortgage
2	American Educatinal Services (formerly Student Loan Servicing Center	School Loan
3		

Part III Help

Part III: Outside Positions

None ☐

Report any positions, whether or not compensated, which you held outside the U.S. Government during the reporting period. Positions include (but are not limited to) an employee, officer, director, trustee, general partner, proprietor, representative, executor, or consultant for a business, nonprofit or labor organization, or educational institution. Exclude positions with religious, social, fraternal, or political entities or those solely of an honorary nature. You need not report any positions of your spouse or dependent children.

	Organization *(Name and address)*	Type of Organization	Position	(X) If no longer held
Example	Dee, Jones & Smith, Hometown, USA	Law Firm	Associate	X
1	Director Advanced Veterinary Applications for income from the Humane Society of the United States	Clinical Care and consulting	Director; Sole Proprietor	
2	Employee Metropolitan Emergency Animal Clinic	Clinical Care	Associate	
3				
4				

Part IV Help

Part IV: Agreements or Arrangements

None ☐

Report your agreements or arrangements for current or future employment, leaves of absence, continuation of payment by a former employer (including severance payments), or continuing participation in an employee benefit plan. You need not report agreements or arrangements of your spouse or dependent children.

	Terms of Any Agreement or Arrangement	Parties	Date
Example	Will receive retained pension benefits (independently managed, fully funded, defined contribution plan)	Dee, Jones & Smith, Hometown, USA	2/99
1			
2			
3			

Part V Help

Part V: Gifts and Travel Reimbursements

Do not complete this part if you are a new entrant or special Government employee.

None ☐

Report for you, your spouse, and dependent children, gifts or travel reimbursements you have received from one source totaling more than $285. Exclude anything valued at $114 or less; anything received by your spouse or dependent child totally independent of their relationship to you; anything from a relative or from the U.S. Government; anything given to your agency in connection with your official travel; and food, lodging, or entertainment received as personal hospitality at the donor's residence or premises.

	Source	Description *(For travel-related items, include itinerary)*	Date
Example	Dee, Jones & Smith, Hometown, USA	Leather briefcase as a departing gift	2/99
1			
2			
3			
4			

MEMORANDUM

DATE: December 1, 2004

TO: Victoria Hampshire
CVM

FROM: Hedy Tam, Program Integrity Officer (HFA-320)
Ethics and Integrity Staff
Office of Management Programs
Office of Management

SUBJECT: Request for Form HHS 520-1 "Request for Approval of Outside Activity"

On your "Confidential Financial Disclosure Report" (OGE 450) dated November 3, 2004, you reported what appears to be an outside activity with ***Employee Metropolitan Emergency Animal Clinic and Humane Society of the United States***, for which "Request for Approval of Outside Activity" **(HHS 520-1)** are required. In order to complete the review and certify your OGE 450, we need to receive an approved HHS 520-1. The request for Approval of Outside Activity form **(HHS-520)** is no longer permitted for FDA employees, and will not be accepted.

FDA has instituted a new process for completing and filing Form HHS 520-1. Please follow the instructions below:

You must obtain and complete Form HHS 520-1 using FDA's automated process accessible through the FDA Administrative Portal. NOTE: Before attempting to access the system, you must have Adobe Reader version 5.1 or later on your computer. If you have any difficulties downloading Adobe Reader, contact the Employee Resource & Information Center at 301.827.3742 or 1.866.807.3742 and select "1" for computer services.

You must also have your EASE user ID and password to access the FDA Administrative Portal at http://adminportal.fda.gov/pls. If you do not have your EASE user ID and password, you should contact your EASE Center Representative or ADP Coordinator. A listing of these contacts is provided at http://intranet.fda.gov/ocio/Applications/ease/poclist1.htm. You may also contact the EASE Help Desk at 301.998.6777 for additional assistance.

From the FDA Administrative Portal, you should type in your EASE User ID and password at the prompt and then click on "Login". To access the HHS 520-1 form, select the "E-forms" link located under the "Single Sign-on Applications" section of the portal. You will be directed to enter your EASE User ID and password again.

A "Help" button is available to provide instructions on how to use the system. When you click on form HHS 520-1 from the list, the form will be displayed in the browser. Fill in the information desired. When you are finished, select an option from the drop-down list box at the top of the form.

- **Exit Without Saving** - closes the form without saving any data. Returns you back to the list of forms.
- **Save**- saves the form with the data as a "Draft". The filled-in form can be found by clicking on the Draft link when you decide to finish filling in the data, and would like to submit the form.
- **Complete** - marks the form as complete. The form cannot be modified after it is completed. The form can be found by clicking on the Completed link.

Once you have selected "Complete", you may print the form by going to File/Print or click on the print button in the PDF frame. Sign and date Form HHS 520-1 and submit it through the normal approval process. **FOR FDA TRACKING PURPOSES, EMPLOYEES MUST SELECT "COMPLETE" BEFORE PRINTING AND SUBMITTING FORM HHS-520-1 FOR APPROVAL.** Forward your completed form to your immediate supervisor for review and recommended action in Block 14. Once your immediate supervisor signs Form HHS 520-1, the supervisor must forward the form through the Ethics Coordinator (Linda Callahan HFV-15) to the approving official for your operating component for approval/disapproval in Block 15.

If you have any questions regarding this notice, or would like to discuss this matter further, please feel free to contact me at (301) 827-5516.

Tam, Hedy S

From: Callahan, Linda J
Sent: Wednesday, December 01, 2004 12:36 PM
To: Hampshire, Victoria; Tam, Hedy S
Cc: Post, Lynn O
Subject: FW: 520-1 CVM (outside activity)and additional information on OGE 450

Tori and Hedy:

I signed off on the HHS-520 on 11/16/04. It goes through David Wardrop, Executive Officer, next before submission to Dr. Sundlof for approval. Joan Urban, OD, tracks it for Dr. Sundlof's signature and sends it back to the appropriate Management Officer/Assistant for xeroxing copies for the employee, their personnel file, and sends the original to Ethics in a sealed envelope.

I'll send a note to Joan and Gwen to determine where it is and cc you both.

Thanks,

Linda

-----Original Message-----
From: Hampshire, Victoria
Sent: Wednesday, December 01, 2004 12:21 PM
To: Tam, Hedy S
Cc: Post, Lynn O; Callahan, Linda J
Subject: RE: 520-1 CVM (outside activity)and additional information on OGE 450

HI Hedy;

It's nice to hear from you again.

I think I followed the instructions below and I printed the form 520-1 and forwarded it. I saved a copy of it above. Is it just that maybe it has not found your desk yet?

Tory

Victoria Hampshire, VMD
Adverse Drug Events Coordinator
Office Surveillance/Compliance
Center for Veterinary Medicine
Room 2624
7500 Standish Place
Rockville, MD 20855
301-827-7822

-----Original Message-----
From: Tam, Hedy S
Sent: Wednesday, December 01, 2004 10:44 AM
To: Hampshire, Victoria
Subject: 520-1 CVM (outside activity)and additional information on OGE 450
Importance: High

Slaughter, Jenny S

From: Hampshire, Victoria
Sent: Tuesday, February 08, 2005 1:23 PM
To: Slaughter, Jenny S
Subject: RE: Request for Form HHS 520-1

Thanks Jenny! I'm tied up in meetings most of the day. Don't need to waste your time. Just wanted to be sure that my approach was ok. Seems like to be on the safe side, just fill out one on the Advan. Vet. App. I'll explain in the comments and/or cover letter that it is presently inactive and when that actually became inactive. Feel free to call me when you get it and if you want to discuss further.

Tory

-----Original Message-----
From: Slaughter, Jenny S
Sent: Tuesday, February 08, 2005 1:20 PM
To: Hampshire, Victoria
Subject: RE: Request for Form HHS 520-1

Receipt of income does not determine whether you need an approved outside activity request. If you do sporatic work at the Metropolitan Emergency Animal Clinic then you are deemed to have an outside activity. The Metropolitan Emergency Animal Clinic is not what I am questioning at this time. The one I'm concerned about is the Advanced Veterinary Applications, I do not have an approved HHS520-1 for this particular activity. Your OGE 450 "Confidential Financial Disclosure Report" did not indicate that the outside activity with AVA had ended, and I need to make sure that I have an approved form on file before closing our your 2004 annual financial disclosure report.

FYI - I did get your telephone message. If you still want to talk about this, give me a call at the number below. Thanks!

Jenny Slaughter
Director, Ethics and Integrity Staff
Office of Management Programs (OMP)...*A Diverse Portfolio of Essential Services*
Office of Management, FDA
Parklawn Bldg., Room 4-72
301-827-5518
301-480-0404 (fax)

-----Original Message-----
From: Hampshire, Victoria
Sent: Tuesday, February 08, 2005 11:40 AM
To: Slaughter, Jenny S
Subject: RE: Request for Form HHS 520-1

HI. I'm not receiving income from either at the present time. I sporadically work at the Metropolitan Emergency Animal Clinic and listed the most I would work there on the outside activity form..

As for Advanced Veterinary Applications. I keep it open but inactive at the time. So I did not think I needed an outside activity for an inactive consulting business but I did think I needed to report it on my Confidential

Disclosure because it appears in the tax record.

I will fill out a new 520-1 that states the reduced activity of the AVA business.

Tory

-----Original Message-----
From: Slaughter, Jenny S
Sent: Tuesday, February 08, 2005 11:27 AM
To: Hampshire, Victoria
Cc: Tam, Hedy S; Killian, Mary Ann
Subject: Request for Form HHS 520-1
Importance: High

Dr. Hampshire,

While conducting a review of your conflict of interest file, I noted that on your Form OGE 450 "Confidential Financial Disclosure Statement" dated 11/3/04, you reported an outside activity as 1) Director, Sole Proprietor of "Advanced Veterinary Applications for income from the Humane Society of the United States" and 2) Associate "Employee Metropolitan Emergency Animal Clinic".

On December 14, 2004, we received an updated form HHS 520-1 "Request for Approval of Outside Activity" for your outside activity with the The Metropolitan Emergency Animal Clinic covering the period 11/1/2004 until 11/1/2005. According to a note in the file, Ms. Hedy Tam, Ethics and Integrity Staff, contacted you and made an inquiry on the status of your Form HHS 520-1 for your outside activity as Director, Sole Proprietor of Advanced Veterinary Applications. Ms. Tam was told that your approved HHS 520-1 for The Metropolitan Emergency Animal Clinic also covered the activity of Advanced Veterinary Applications. (In the past, you combined your outside activities into one request, however, on your current HHS 520-1, it only covers the Employee Metropolitan Emergency Animal Clinic).

Because the two outside activities are for two completely different organizations, you will be required to complete and receive approval on Form HHS 520-1 for your involvement as Director, Sole Proprietor of Advanced Veterinary Applications. The current HHS 520-1 for Metropolitan Emergency Animal Clinic makes no mention of your Sole Proprietor of Advanced Veterinary Applications. When completing Form HHS 520-1, please make sure under Item #7 "Nature of Activity", that you give a full description of the specific duties or services to be performed. Until my office receives the approved HHS 520-1 for Advanced Veterinary Applications, we will keep your case open.

Please let me know if you have any questions.

Jenny Slaughter
Director, Ethics and Integrity Staff
Office of Management Programs (OMP)...*A Diverse Portfolio of Essential Services*
Office of Management, FDA
Parklawn Bldg., Room 4-72
301-827-5518
301-480-0404 (fax)

Slaughter, Jenny S

From: McCormack, Mark
Sent: Friday, February 11, 2005 2:25 PM
To: Slaughter, Jenny S
Subject: FW: Outside Activity Request - Advanced Veterinary Applications

-----Original Message-----
From: Wardrop, David
Sent: Friday, February 11, 2005 2:14 PM
To: McCormack, Mark
Subject: FW: Outside Activity Request - Advanced Veterinary Applications

Interesting. David

-----Original Message-----
From: Hampshire, Victoria
Sent: Friday, February 11, 2005 2:09 PM
To: Callahan, Linda J
Cc: McChesney, Daniel G; Wardrop, David
Subject: RE: Outside Activity Request - Advanced Veterinary Applications

Dan, David: I took care of this with Linda. I let Linda Know that the above company has been dormant between the last filing and now I had even considered closing it except that it's more expensive to close than keep open for any opportunities that come up and for friends and family who want veterinary care items. I do have to file a corporate return every year which details income/expenses if you have any questions. I am going to be asking the Metropolitan Emergency Clinic and the Humane Society of the United States into this one and ask for 1099s.

Because I collect so little income through any outside activity at this point, my account has advised to roll everything into this particular outside activity as the parent activity. My return is due March 15th. I have a teleconference with my accountant next week and will revise all of it by March 15th.

-----Original Message-----
From: Callahan, Linda J
Sent: Friday, February 11, 2005 11:04 AM
To: Hampshire, Victoria
Cc: McChesney, Daniel G; Wardrop, David
Subject: Outside Activity Request - Advanced Veterinary Applications
Importance: High

Hi Tory:

I've reviewed you Outside Activity Request for Advanced Veterinary Applications. There are some corrections that need to be made to the form. I can make the changes on the form for you, or you may stop by my office to correct, but your guidance and concurrence is required.

1. **#4b. You checked "Public" filer, but those filers are SES and Title 42. You are considered a "Confidential" filer. The correct box "Confidential" must be marked**

and the "Public" box should be white-out and initialed.

2. **#7 Nature of Activity, under a., b. and c. You marked that you "are not" a project officer. You must also check one of the boxes for b. whether you "has" or "has no" CRADA or MTA-CRADA responsibilities; and c. whether Center/Office "has" or "has no" grants or contracts with this organization?**

3. **#11 Type and Amount of Compensation must also include the approximate total yearly amount. Per Jeff Weber's memo dated 2/13/04. You state that you expect to have limited requests over the next year at $50 per hour. Can you provide an estimate for a total yearly amount, even if it is less than $xxxx or approximately $xxxx?**

The compensation information must be provided in order for the activity to be evaluated for approval. Department Ethics Officials offer the following guidance regarding the level of detail. "*While the income may not be known in the exact amount in advance, it should be stated as specifically as possible under the circumstances. So, if the person knows he will be getting $5,000 for teaching a course, the form should be annotated with that amount. If the person knows she will be getting $200 for every book chapter she edits, but doesn't know how many chapters she will be editing, the form could say something like, "$200 per chapter, employee thinks approx. 5-7 chapters." If the person will be paid at an hourly rate of $30 per hour but it is an ongoing employment situation with no fixed termination date, the form could say that. In short, each situation will be different, but the form should include whatever is* ***the most specific information under the circumstances***."

Thanks for your prompt attention so I can move this request forward to Dr. Sundlof for final approval.

Linda

Tam, Hedy S

From: Hampshire, Victoria
Sent: Friday, February 11, 2005 2:15 PM
To: Tam, Hedy S
Cc: McChesney, Daniel G
Subject: Advanced Veterinary Applications

Hedy.

I got this going yesterday. I had a meeting with my account recently because the return is due March 15 even though it's pretty inactive.

He advises me to keep it open and to roll the other two outside activities into one . So this one on this entity should suffice for now but I will create a revised one so that everything from HSUS and the Metropolitan Emergency Clinic, friends/family buying veterinary services from me, etc.. is detailed on one form. Can we do this since each entity can write a check to Advanced Veterinary Applications? It would be easier from an accounting perspective and I can always provide corporate returns with detailed payments as attachments.

Tory Hampshire

Victoria Hampshire

Per Telephone conversation w/ Mark McCormack, held off on getting back to her until he gets back w/ me.

2/11/05

Slaughter, Jenny S

From: McCormack, Mark
Sent: Friday, February 11, 2005 2:38 PM
To: Slaughter, Jenny S
Subject: FW: Outside Activity Request - Advanced Veterinary Applications
Importance: High

1

-----Original Message-----
From: Wardrop, David
Sent: Friday, February 11, 2005 1:03 PM
To: McCormack, Mark
Subject: FW: Outside Activity Request - Advanced Veterinary Applications
Importance: High

FYI

-----Original Message-----
From: Callahan, Linda J
Sent: Friday, February 11, 2005 11:04 AM
To: Hampshire, Victoria
Cc: McChesney, Daniel G; Wardrop, David
Subject: Outside Activity Request - Advanced Veterinary Applications
Importance: High

Hi Tory:

I've reviewed you Outside Activity Request for Advanced Veterinary Applications. There are some corrections that need to be made to the form. I can make the changes on the form for you, or you may stop by my office to correct, but your guidance and concurrence is required.

1. **#4b. You checked "Public" filer, but those filers are SES and Title 42. You are considered a "Confidential" filer. The correct box "Confidential" must be marked and the "Public" box should be white-out and initialed.**

2. **#7 Nature of Activity, under a., b. and c. You marked that you "are not" a project officer. You must also check one of the boxes for b. whether you "has" or "has no" CRADA or MTA-CRADA responsibilities; and c. whether Center/Office "has" or "has no" grants or contracts with this organization?**

3. **#11 Type and Amount of Compensation must also include the approximate total yearly amount. Per Jeff Weber's memo dated 2/13/04. You state that you expect to have limited requests over the next year at $50 per hour. Can you provide an estimate for a total yearly amount, even if it is less than $xxxx or approximately $xxxx?**

The compensation information must be provided in order for the activity to be evaluated for approval.

Department Ethics Officials offer the following guidance regarding the level of detail. "*While the income may not be known in the exact amount in advance, it should be stated as specifically as possible under the circumstances. So, if the person knows he will be getting $5,000 for teaching a course, the form should be annotated with that amount. If the person knows she will be getting $200 for every book chapter she edits, but doesn't know how many chapters she will be editing, the form could say something like, "$200 per chapter, employee thinks approx. 5-7 chapters." If the person will be paid at an hourly rate of $30 per hour but it is an ongoing employment situation with no fixed termination date, the form could say that. In short, each situation will be different, but the form should include whatever is* ***the most specific information under the circumstances***."

Thanks for your prompt attention so I can move this request forward to Dr. Sundlof for final approval.

Linda

Dapolito, George
From: Killian, Mary Ann
Sent: Monday, November 21, 2005 11:13 AM
To: Dapolito, George
Subject: FW: outside activity to speak on the matter of my outside activity

George,

Please be on the look out for this form, she is on a detail to CDRH.

MaryAnn Killian
Program Integrity Advisor
Ethics and Integrity Staff
Office of Management Programs
Office of Management, FDA
Room 4-72 Parklawn, Bldg
301.827.5512

-----Original Message-----
From: Hampshire, Victoria
Sent: Monday, November 21, 2005 11:11 AM
To: Lochner, Donna R.
Cc: Killian, Mary Ann
Subject: outside activity to speak on the matter of my outside activity

HI Donna;

Jenny Slaughter is not in this week but Mary Ann is on the lookout for this outside activity. I asked Mary Ann what I should write and I think what I wrote is basically what I will end up saying

Let know if you have any questions when you see it Mary Ann and let me know when it is signed.

My only agenda here is to clarify the outside acitivity. I will not be commenting on the investigation or agency personnel until the matter is clarified by senate finance.

Tory

Dapolito, George

From: Killian, Mary Ann
Sent: Tuesday, November 22, 2005 12:41 PM
To: Dapolito, George
Subject: FW: Outside Activity

FYI
MaryAnn Killian
Program Integrity Advisor
Ethics and Integrity Staff
Office of Management Programs
Office of Management, FDA
Room 4-72 Parklawn, Bldg
301.827.5512

-----Original Message-----
From: Hampshire, Victoria
Sent: Tuesday, November 22, 2005 12:35 PM
To: Colleli, Karen M
Cc: Frampton, David W; Killian, Mary Ann; 'MarkC@whistleblower.org'
Subject: RE: Outside Activity

Thanks, I am talking to David now. He was very helpful. I need to emphasize that Mark is holding back reporters. It is important to me to clear the air and if possible and this can be expedited, please do so. If it cannot be expedited, please call Mark Cohen at his office 202-408-0034.

Tory

-----Original Message-----
From: Colleli, Karen M
Sent: Tuesday, November 22, 2005 12:22 PM
To: Hampshire, Victoria
Cc: Frampton, David W
Subject: RE: Outside Activity

Victoria,

Your Outside Activity has already been sent to Dave Frampton. I will copy him in hopes of expediting it.

Karen Colleli
FDA/CDRH/ODE/PMO
Corp Rm 110T, HFZ-405
301-594-3055 x130
301-443-8004 (Fax)
karen.colleli@fda.hhs.gov

-----Original Message-----
From: Hampshire, Victoria
Sent: Tuesday, November 22, 2005 11:43 AM
To: Ramdat, Deborah A.; Colleli, Karen M
Cc: Dapolito, George; 'MarkC@whistleblower.org'; Killian, Mary Ann
Subject: RE: Outside Activity

Thanks very much guys. I'm trying hard to comply and I'd like to speak on this issue as soon as possible to "clear the record". Karen, I came by your office and you were at lunch but if I may be of help in hand carrying this through George or Mary Ann, please let me know.

-----Original Message-----
From: Ramdat, Deborah A.
Sent: Monday, November 21, 2005 3:58 PM
To: Colleli, Karen M
Cc: Hampshire, Victoria
Subject: Outside Activity

Hi Karen,

Please expedite the processing of this for Tori. Thanks.

Deborah A. Ramdat
(301) 443-8320 x 140
dar@cdrh.fda.gov

From: Hampshire, Victoria '

Sent: Wednesday, November 23, 2005 9:55 AM

To:

Subject: The mailings on Friday clarifying to FDA Press that I did not know I was being investigated, their response and my response thanking them.

Zawisza, Julie"

To:

Subject: Re: Press statement on Victoria Hampshiire
Date: Sun, 20 Nov 2005 09:29:03 -0500

Top of Form 1

Bottom of Form 1

Done and my pleasure.

Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: victoria hampshire
To: Zawisza, Julie 'Mark Cohen'

CC:
Sent: Sat Nov 19 21:44:12 2005
Subject: RE: Press statement on Victoria Hampshiire

Dear Julie and Mark:

Thank you very much for working on this. My husband and I have been rushed
in a previous engagement traveling to We were either in flight or
driving through rather remote parts of and have only just returned to
the hotel where the internet is very slow.

Julie: I very much appreciate FDA's kind words and willingness to correct
the statement on such short notice.

Tory

"Zawisza, Julie" wrote:

I am happy to correct this and thanks for letting me know.

Julie Zawisza

cell:

-----Original Message-----
From: Mark Cohen

Sent: Friday, November 18, 2005 3:09 PM
To: julie
Cc:
Subject: Press statement on Victoria Hampshiire

Dear Ms. Zawisza:

I write on behalf of Victoria Hampshire, who we represent at the Government Accountability Project. Ms. Hampshire is concerned that the press statement that FDA plans to release tonight is inaccurate in one regard: It uses the language that the FDA investigation of her was conducted "With your knowledge..." In fact, Dr. Hampshire was not aware at the time that she was being investigated. We'd ask that you correct this in the press release.

Sincerely,

Mark P. Cohen, Esq.
Government Accountability Project
Food and Drug Safety Director

Dapolito, George

From: Killian, Mary Ann
Sent: Monday, November 28, 2005 6:44 AM
To: Slaughter, Jenny S; Dapolito, George
Subject: FW: Outside Activity

The latest email from Victoria Hampshire.

MaryAnn Killian
Program Integrity Advisor
Ethics and Integrity Staff
Office of Management Programs
Office of Management, FDA
Room 4-72 Parklawn, Bldg
301.827.5512

-----Original Message-----
From: Hampshire, Victoria
Sent: Wednesday, November 23, 2005 8:47 AM
To: Frampton, David W; Killian, Mary Ann; 'MarkC@whistleblower.org'
Subject: RE: Outside Activity

Mark; I received your call this morning and left you a voice mail. David, can you give Mark a call and a timeframe if it is not possible to expedite this request. Additionally, if it is not necessary to have an outside activity in order to clear the facts, or Mark can discuss with you and/or the FDA press office specific requests from the media and specific talking points that I have shared with him, then I would suggest that as another alternative. The goal here is to be up front with CDRH and FDA and to clarify the facts as mispresented by Wyeth.

Mark, David's number is 240-276-0450 x107

> -----Original Message-----
> **From:** Hampshire, Victoria
> **Sent:** Tuesday, November 22, 2005 12:35 PM
> **To:** Colleli, Karen M
> **Cc:** Frampton, David W; Killian, Mary Ann; 'MarkC@whistleblower.org'
> **Subject:** RE: Outside Activity
>
> Thanks, I am talking to David now. He was very helpful. I need to emphasize that Mark is holding back reporters. It is important to me to clear the air and if possible and this can be expedited, please do so. If it cannot be expedited, please call Mark Cohen at his office 202-408-0034.
>
> Tory
>
> > -----Original Message-----
> > **From:** Colleli, Karen M
> > **Sent:** Tuesday, November 22, 2005 12:22 PM
> > **To:** Hampshire, Victoria
> > **Cc:** Frampton, David W
> > **Subject:** RE: Outside Activity

Victoria,

Your Outside Activity has already been sent to Dave Frampton. I will copy him in hopes of expediting it.

Karen Colleli
FDA/CDRH/ODE/PMO
Corp Rm 110T, HFZ-405
301-594-3055 x130
301-443-8004 (Fax)
karen.colleli@fda.hhs.gov

-----Original Message-----
From: Hampshire, Victoria
Sent: Tuesday, November 22, 2005 11:43 AM
To: Ramdat, Deborah A.; Colleli, Karen M
Cc: Dapolito, George; 'MarkC@whistleblower.org'; Killian, Mary Ann
Subject: RE: Outside Activity

Thanks very much guys. I'm trying hard to comply and I'd like to speak on this issue as soon as possible to "clear the record". Karen, I came by your office and you were at lunch but if I may be of help in hand carrying this through George or Mary Ann, please let me know.

-----Original Message-----
From: Ramdat, Deborah A.
Sent: Monday, November 21, 2005 3:58 PM
To: Colleli, Karen M
Cc: Hampshire, Victoria
Subject: Outside Activity

Hi Karen,

Please expedite the processing of this for Tori. Thanks.

Deborah A. Ramdat
(301) 443-8320 x 140
dar@cdrh.fda.gov

Gorenstein, Linda G

From: Heuer, Kathleen - FDA
Sent: Friday, December 02, 2005 4:08 PM
To: Unger, Sue; Slaughter, Jenny S; Diehl, Irene; Holden, Kimberly
Cc: Gorenstein, Linda G; Dapolito, George
Subject: Re: URGENT Approval needed for Outside Activity Request

PRIORITY

I approve.

Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Unger, Sue <SUnger1@OC.FDA.GOV>
To: Slaughter, Jenny S <JSLAUGHT@OC.FDA.GOV>; Diehl, Irene <Irene.Diehl@FDA.GOV>; Heuer, Kathleen - FDA <Kathleen.Heuer@FDA.GOV>; Holden, Kimberly <Kimberly.Holden@FDA.GOV>
CC: Gorenstein, Linda G <LGORENST@OC.FDA.GOV>; Dapolito, George <GDapolito@OC.FDA.GOV>
Sent: Fri Dec 02 15:36:13 2005
Subject: RE: URGENT Approval needed for Outside Activity Request

Neither Kathy nor Kim are in the office. Kathy at a doctor's appt and Kim on leave. Both are probably reading BBerry's.

-----Original Message-----
From: Slaughter, Jenny S.
Sent: Friday, December 02, 2005 3:27 PM
To: Diehl, Irene; Heuer, Kathleen - FDA; Holden, Kimberly
Cc: Gorenstein, Linda G; Unger, Sue; Dapolito, George
Subject: URGENT Approval needed for Outside Activity Request
Importance: High

We are currently processing a Form HHS-520 for Victoria Hampshire which will permit her to speak to various media outlets (e.g., NBC, CBS; Boston Globe, Washington Post etc.) on matters relating to a recent senate finance investigation. This case is very similar to Dr. David Graham, CDER employee. Both Dr. Hampshire and Dr. Graham are represented by Mark Cohen, Esq. from the Government Accountability Project.

We have discussed and received approval from Andy Caplan, HHS GC/Ethics Division for Dr. Hampshire to group all related speaking matters on one HHS 520. George has received numerous telephone calls from Dr. Hampshire's attorney inquiring on the status of approval. If possible, I would like to hand carry this HHS-520 through the process so we can resolve this matter before cob today.

After I concur with the HHS 520, George will be hand carrying the document for signature. If this poses a problem, please let me know.

Jenny Slaughter
Director, Ethics and Integrity Staff
Office of Management Programs (OMP)
Office of Management, FDA
Parklawn Bldg., Room 4-72
301-827-5518
301-480-0404 - FAX

Slaughter, Jenny S

From: Hampshire, Victoria (CDRH)
Sent: Monday, December 05, 2005 11:05 AM
To: Slaughter, Jenny S
Cc: 'Mark Cohen'
Subject: RE: Outside Activity Form

Thanks so much Jenny. I hope you have a good holiday.

Tory

-----Original Message-----
From: Slaughter, Jenny S
Sent: Monday, December 05, 2005 10:36 AM
To: Hampshire, Victoria (CDRH)
Cc: Dapolito, George
Subject: RE: Outside Activity Form

We received final approval on your Outside Activity request. George is in the process of sending you a PDF, thanks for your patience.

Questions, please let us know.

Jenny Slaughter
Director, Ethics and Integrity Staff
Office of Management Programs (OMP)
Office of Management, FDA
Parklawn Bldg., Room 4-72
301-827-5518
301-480-0404 - FAX

-----Original Message-----
From: Hampshire, Victoria (CDRH)
Sent: Monday, December 05, 2005 9:35 AM
To: Slaughter, Jenny S
Subject: RE: Outside Activity Form

OK, when it's through, the adobe scan is great if you can do it.

Tory

ATTACHMENT 42 A

Food and Drug Administration
Office of Internal Affairs

REPORT OF INVESTIGATION

****

TITLE: Victoria A. Hampshire
Senior Regulatory Staff
CVM

CASE NO: 05-OIA-966-007

TYPE OF CASE: Conflict of Interest

INVESTIGATION MADE AT: Office of Internal Affairs

PERIOD COVERED: 1/29/05 – 03/07/05

INVESTIGATION MADE BY: SA Mark McCormack and SA Mike Redmond

REPORTING AGENT: SA Mark McCormack

STATUS OF CASE: ( ) CONTINUING INVESTIGATION
( ) SIGNIFICANT DEVELOPMENT
(X) PENDING ADMINISTRATIVE ACTION
( ) PENDING JUDICIAL ACTION
( ) REFERRAL TO ANOTHER AGENCY
( ) CLOSED

Mark S. McCormack / 3/2/05
Mark S. McCormack
Special Agent

Horace L. Coleman / 3-7-05
Horace L. Coleman
Special Agent in Charge

****

RESTRICTED INFORMATION

This report is furnished on an official need-to-know basis and must be protected from dissemination which might compromise the best interests of the Food and Drug Administration, Office of Internal Affairs. This report shall not be released in response to a Freedom of Information Act or Privacy Act request or disseminated to other parties without prior consultation with the FDA Office of Internal Affairs. UNAUTHORIZED RELEASE MAY RESULT IN CRIMINAL PROSECUTION.

DISTRIBUTION: Dr. Stephen Sundlof – Director – CVM – HFV-1
Captain Russell Green - OMS/DRS, HF-35

1. INTRODUCTION:

Reference is made to the Case Initiation and Fact Sheet, dated 11/24/04.

2. SYNOPSIS:

A review of subpoenaed documents from Vet Centric, a third party prescription fulfillment house, has been completed. Based upon our review of the records it appeared that this account was set up to accommodate animal prescription needs for family and friends; not a for profit concern.

Investigation revealed that the subject's most recent HHS-520-1, dated 2/8/05, was submitted for approval and three supervisors in the chain of command had already signed off on it. While it was awaiting approval from the Center Director the subject asked his administrative assistant for the document back and made a substantive change. As such the HHS 520-1 would never have been approved.

In a personal interview the subject admitted she inappropriately received information concerning OIA's Official Investigation from a fellow employee at CVM; an Obstruction of an Official Criminal Investigation; potentially a federal felony charge(s).

The subject claims she, in a panic she asked for the forms back from the Center Director's assistant and made the substitution; claiming not with intent to deceive, but to clarify her activities with AVA.

The investigating agent provided a Letter of Prosecution to Mr. Steven M. Dunne, Assistant United States Attorney (AUSA), U.S. Courthouse, Greenbelt, MD. AUSA Dunne declined prosecution in this case. An Office of Government Ethics form OGE 202 will be submitted.

Subject was interviewed on 2/24/05. When we explained what had occurred, and our subsequent corroboration, she immediately understood why Fort Dodge Animal Health had raised concerns about a conflict of interest and her recusal by CVM officials from the AER and Public Advisory Meeting Processes.

Case continued pending administrative review/action.

3. DETAILS OF INVESTIGATION:

A review of subpoenaed documents revealed that the same few names appear as clients (friends and family). Between the subject's EOD of 10/21/02, and the present, she has only received approximately $774.55 from Vet Centric for orders filled; of which $472.57 was paid to her in November of 2004, from the second order placed by an agent for Fort Dodge Animal Health to cement their Conflict of Interest allegation. In other words, without the FDAH order, in three years the subject only would have made approximately $300.00.

On all of her previous Requests for Approval of Outside Activity (HHS-520-1) the subject had listed AVA as consulting. I asked the Office of Ethics to request an update from the subject's outside activity request for AVA and to request the subject to be specific in the details. I asked David Wardrop to fax it to me as soon as it was submitted. On the evening of Friday, 2/11/05, I received the fax from CVM. In the additional comments page I read that the subject wrote in part "also the deposit fo [sic] any income received for veterinary services to friends and family from my home business pharmacy".

I immediately telephoned Dave Wardrop, reaching him on his Blackberry. I asked him why four members in the chain of command at CVM would sign off on that document. Mr. Wardrop advised that was not what he reviewed and signed off on.

At 6AM on Monday, 2/14/05, Dave Wardrop called and advised he had retrieved the original copy from his safe and what he had did not match what I had received. We quickly determined that somewhere in the signature process the document had been altered; with the original additional comments page being removed and a completely different additional comments page substituted.

I asked him to secure the documents in his safe. On 2/17/05, I retrieved both originals; which are marked for identification: DEW 2/17/05 and MSM 2/17/05 (Attachments #1 and #2).

On 2/24/05, I received a declination of prosecution from an AUSA in Greenbelt, MD.

On the same date SA Redmond and I interviewed the subject at the Office of Internal Affairs.

When we explained the entire set of facts as to how the case originated and why what actions were taken the subject stated, "Now I understand what all this is about". The subject stated that Vet Centric was a vehicle to provide prescription service for her mom and dad who never made more than $30,000 per year (dad now deceased) and a few other friends and family members. The subject stated it was never set up as a vehicle to make money, and she never intended to deceive the FDA.

The subject stated that she repeatedly attempted to meet with supervisors in her chain of command to find out what was going on and was "shut out" at every turn.

The subject stated that she never had a bias against Fort Dodge Animal Health or Pro Heart 6; but rather did her job in a professional manner and maintained that an independent review of her work product would verify that.

Regarding the Congressional inquiry in this case the subject admitted having a casual relationship with Member of Congress Chris Van Hollen by way of a children's soccer team. The subject admitted telling the congressman about her recusal from the Pro Heart 6 issue; thus the Congressional Inquiry received by the FDA. The subject also admitted to seeking counsel from Tom Devine (David Graham's attorney).

We explained to the subject that now the issue was one of trust and integrity; regarding the switching out of the Additional Comments page of her HHS-520-1. The subject admitted to having lunch with fellow FDA employee [redacted] and telling her about her sleepless nights and wondering why she was removed from the project. [redacted] "hinted" at what the problem might be.

Upon further questioning the subject admitted that [redacted] told her she was told by [redacted]

The subject stated that she panicked, gone down to Joan (LNU) and attached a new comment sheet. The subject claimed that she put a pink stick-on note to clarify the change. The subject claims Dr. Sundlof had not signed off on the document.

The subject stated that after learning the reason for her appearance of a Conflict of Interest she again had occasion to see Congressman Van Hollen. The subject stated she explained to him exactly what had happened and she could now understand why the FDA took the action it did (recusal). The subject stated that the congressman thanked her for explaining the issue.

It should be noted that during the interview the subject advised there were other DVM's at CVM; including some with full practices that utilized Vet Centric and other fulfillment houses. The subject also stated that some of them were dead set against Pro Heart 6 being removed from the market as it was very profitable.

The subject provided a signed/sworn statement (Attachment# 3).

Case continued pending administrative review/action.

4. OTHER INVESTIGATION:

None

5. JUDICIAL/ADMINISTRATIVE ACTION:

The investigating agent provided a Letter of Prosecution to Mr. Steven M. Dunne, Assistant United States Attorney (AUSA), U.S. Courthouse, Greenbelt, MD. AUSA Dunne declined prosecution in this case. An Office of Government Ethics form OGE 202 will be submitted.

6. DISPOSITION OF EVIDENCE, CONTRABAND, AND PERSONAL PROPERTY:

N/A

7. DISPOSITION STATUS:

Case continued pending administrative review/action.

8. INFORMATION TO BE INDEXED:

Subject indexed on previous ROI.

9. ATTACHMENTS:

1. Copy of original HHS-520-1, marked for identification DEW 2/17/05, and MSM2/17/05.
2. Copy of altered HHS-520-1, marked for identification DEW 2/17/05, and MSM 2/17/05.
3. Copy of subject's signed/sworn statement.

Attachment 1

DCW 2/11/05 MSM 2/17/05

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

REQUEST FOR APPROVAL OF OUTSIDE ACTIVITY

(Ref.: HHS/FDA Standards of Ethical Conduct Regulations 5 CFR 5501)

☐ Initial Request
☐ Revised Request
☒ Renewal

1. NAME *(Last, First, Initial)*
Last: Hampshire
First: Victoria
Initial: A

2. ORGANIZATIONAL LOCATION
DHHS/FDA/CVM/OSC

3. TITLE OF POSITION
Senior Regulatory Officer

4.a. GRADE AND SALARY *(Federal)*
Pay Plan - Series: PHS 05
Salary: $76,800.00

4.b. FINANCIAL DISCLOSURE FILING STATUS
☐ Public ☐ None
☒ Confidential

5. *NAME, ADDRESS AND BUSINESS OF PERSON OR ORGANIZATION FOR WHOM OUTSIDE SERVICES WILL BE PERFORMED
Name of Business: Advanced Veterinary Applications
Street: ?
City: ? State: MD Zip:

6. LOCATION WHERE SERVICES WILL BE PERFORMED
☒ Location address and business address are the same
Name of Location: Advanced Veterinary Applications
Street:
City: ? State: MD Zip:

7. NATURE OF ACTIVITY *(Indicate type of activity, e.g., teaching, consultative services, and give full description of specific duties or services to be performed. Specify, when possible, the scheduled days of week and hours of day proposed activity will be performed. ALSO, answer (a.), (b.), and (c.) below.)*

Writing or consulting on laboratory animal care matters related to pain and distress, emergency and critical care and handheld digital equipment for large transgenic rodent programs.

Only published and publicly available information and data may be discussed. For consulting, DHHS/FDA rules regarding consulting will be observed.
Employee: *(a.)* ☐ is ☒ is not *(check one)* a project officer;
(b.) ☐ has ☒ has no *(check one)* CRADA or MTA-CRADA responsibilities; and
(c.) Center/Office ☐ has ☒ has no *(check one)* grants or contracts with this organization.

8. ESTIMATED TIME INVOLVED

a. PERIOD COVERED *(May not exceed one year)*
From: 04/11/2004 *(DD/MM/YYYY)* To: 04/11/2005 *(DD/MM/YYYY)*

If the start date above precedes the date of employee signature (Item 13.b., Page 2), then provide justification:

I was not aware that I should file an outside activity for an inactive business. On 2/8/05 Hedy Tam from The Office of Management Programs suggested that I best file one because the business appears on my financial disclosure form.

b. ESTIMATED TOTAL TIME DEVOTED TO ACTIVITY *(e.g., 4 hours per day, 2 days per week)*
Hours per day: _____ AND Days per week: _____ Other: 12 hours per year

c. WILL WORK BE PERFORMED ENTIRELY OUTSIDE USUAL WORKING HOURS?
☒ Yes ☐ No If "No," indicate type of leave and estimated number of hours or days of absence from work: _____ *(Type of Leave)* and _____ *(Hours)* or _____ *(Days)*

9. DO YOUR OFFICIAL DUTIES RELATE IN ANY WAY TO THE PROPOSED ACTIVITY?
☒ No ☐ Yes *(Describe in sufficient detail for reviewing official to understand the relationship.)*

10. *IF PROVIDING CONSULTATIVE OR PROFESSIONAL SERVICES, ARE YOUR WOULD-BE ASSOCIATES RECEIVING, OR WILL THEY SEEK, A GRANT OR CONTRACT FROM A FEDERAL AGENCY? *(Services provided will not knowingly involve, directly or indirectly, preparation of material which could relate to any financial dealings between the outside organization and FDA.)*
☒ No ☐ Yes *(Describe)*

11. TYPE AND AMOUNT OF COMPENSATION
☒ Fee ☐ Honorarium ☐ Per Diem ☐ Per Annum ☐ None
☐ Royalty ☐ Expenses ☐ Other *(Specify)* _____
Hourly Rate? $ 100/hr ≈ $500.00 yr. Amount of Compensation $ 50/hr Expenses

12. WILL COMPENSATION BE DERIVED FROM A HHS GRANT OR CONTRACT? *(No compensation or expenses may be derived from HHS funds.)*
☒ No ☐ Yes

*See Page 2 of form (ACKNOWLEDGEMENT, ACTION TAKEN, COMMENTS AND INSTRUCTIONS ARE ON PAGE 2 OF FORM)

PSC Media Arts (301) 443-1090 EF

ENTER ADDITIONAL COMMENTS BELOW

This is a consulting company for the development of humane scoring paradigms (pain and distress) and hand held device software for tracking laboratory and critical animal care in decentralized facilities. I developed it prior to employment at CVM. It is mostly inactive except for sporadic requests which have been run through CVM leadership when they occur to make sure there is no conflict. Examples include a request from the NAS to participate in a panel evaluating animal care at the National Zoo, consulting for the Humane Society on Research Animal Issues, and writing a solicited article for Laboratory Animal Medicine or ILAR.

The Office of Ethics noted that I listed the company as an asset on my financial disclosure and asked that I submit an HHS-520-1 to cover it, even when it was inactive.

I expect to have limited requests for similar kinds of activity or requests through this company over the next year.

ATTACHMENT 2

DVW 2/17/05 MSM 2/17/05

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

REQUEST FOR APPROVAL OF OUTSIDE ACTIVITY

(Ref.: HHS/FDA Standards of Ethical Conduct Regulations 5 CFR 5501)

☐ Initial Request
☐ Revised Request
☒ Renewal

1. NAME *(Last, First, Initial)*
Last: Hampshire
First: Victoria
Initial: A

2. ORGANIZATIONAL LOCATION
DHHS/FDA/CVM/OSC

3. TITLE OF POSITION
Senior Regulatory Officer

4.a. GRADE AND SALARY *(Federal)*
Pay Plan - Series: PHS 05
Salary: $76,800.00

4.b. FINANCIAL DISCLOSURE FILING STATUS
☐ Public ☐ None
☒ Confidential

5. *NAME, ADDRESS AND BUSINESS OF PERSON OR ORGANIZATION FOR WHOM OUTSIDE SERVICES WILL BE PERFORMED
Name of Business: Advanced Veterinary Applications
Street:
City: State: MD Zip:

6. LOCATION WHERE SERVICES WILL BE PERFORMED
☒ Location address and business address are the same
Name of Location: Advanced Veterinary Applications
Street:
City: State: MD Zip:

7. NATURE OF ACTIVITY *(Indicate type of activity, e.g., teaching, consultative services, and give full description of specific duties or services to be performed. Specify, when possible, the scheduled days of week and hours of day proposed activity will be performed. ALSO, answer (a.), (b.), and (c.) below.)*

Writing or consulting on laboratory animal care matters related to pain and distress, emergency and critical care and handheld digital equipment for large transgenic rodent programs.

Only published and publicly available information and data may be discussed. For consulting, DHHS/FDA rules regarding consulting will be observed.
Employee: *(a.)* ☐ is ☒ is not *(check one)* a project officer;
(b.) ☐ has ☒ has no *(check one)* CRADA or MTA-CRADA responsibilities; and
(c.) Center/Office ☐ has ☒ has no *(check one)* grants or contracts with this organization.

8. ESTIMATED TIME INVOLVED

a. PERIOD COVERED *(May not exceed one year)*
From: 04/11/2004 *(DD/MM/YYYY)* To: 04/11/2005 *(DD/MM/YYYY)*

If the start date above precedes the date of employee signature (Item 13.b., Page 2), then provide justification:

I was not aware that I should file an outside activity for an inactive business. On 2/8/05 Hedy Tam from The Office of Management Programs suggested that I best file one because the business appears on my financial disclosure form.

b. ESTIMATED TOTAL TIME DEVOTED TO ACTIVITY *(e.g., 4 hours per day, 2 days per week)*
Hours per day: _____ AND Days per week: _____ Other: 12 hours per year

c. WILL WORK BE PERFORMED ENTIRELY OUTSIDE USUAL WORKING HOURS?
☒ Yes ☐ No If "No," indicate type of leave and estimated number of hours or days of absence from work: _____ *(Type of Leave)* and _____ *(Hours)* or _____ *(Days)*

9. DO YOUR OFFICIAL DUTIES RELATE IN ANY WAY TO THE PROPOSED ACTIVITY?
☒ No ☐ Yes *(Describe in sufficient detail for reviewing official to understand the relationship.)*

10. *IF PROVIDING CONSULTATIVE OR PROFESSIONAL SERVICES, ARE YOUR WOULD-BE ASSOCIATES RECEIVING, OR WILL THEY SEEK, A GRANT OR CONTRACT FROM A FEDERAL AGENCY? *(Services provided will not knowingly involve, directly or indirectly, preparation of material which could relate to any financial dealings between the outside organization and FDA.)*
☒ No ☐ Yes *(Describe)*

11. TYPE AND AMOUNT OF COMPENSATION
☒ Fee ☐ Honorarium ☐ Per Diem ☐ Per Annum ☐ None
☐ Royalty ☐ Expenses ☐ Other *(Specify)* _____
$100/hr ≈ $500.00 yr. Amount of Compensation $ 50/hr Expenses

12. WILL COMPENSATION BE DERIVED FROM A HHS GRANT OR CONTRACT? *(No compensation or expenses may be derived from HHS funds.)*
☒ No ☐ Yes

*See Page 2 of form (ACKNOWLEDGEMENT, ACTION TAKEN, COMMENTS AND INSTRUCTIONS ARE ON PAGE 2 OF FORM)

DRW 2/1 — MSM 2/17/0

13. EMPLOYEE ACKNOWLEDGEMENT

This request is made with full knowledge of department and operating division policy and procedures on outside activities. I attest that I have read and understand the "Notice to Applicants for Prior Approval of Outside Activities" (pages 3 and 4), and that the statements I have made are true, complete and correct to the best of my knowledge and belief. I understand that I am disqualified from all official duty activities relating to this organization, effective immediately and for twelve months beyond the conclusion of this activity (5 CFR 2635.502) unless I seek authorization from FDA'S Deputy Ethics Counselor to participate in such activities.

a. SIGNATURE OF EMPLOYEE	b. DATE	c. *ADDITIONAL INFORMATION ATTACHED
Victoria Hydrue	2/8/05	☐ Yes ☒ No

14. ACTION RECOMMENDED BY REVIEWING OFFICIAL

a.	b. SIGNATURE / Printed Name	c. TITLE	d. DATE
☒ APPROVAL ☐ DISAPPROVAL	Daniel G McChesney	Director, HFV-200	2/9/05

e. COMMENTS OF RECOMMENDING OFFICIAL *(Comments required if activity is recommended for disapproval.)*

B Callahan 2-11-05 — 15. ACTION TAKEN — 2/11/05

a.	b. SIGNATURE / Printed Name	c. TITLE	d. DATE
☒ APPROVAL ☐ DISAPPROVAL	Stephen F. Sundlof, DVM, PhD	Director, Center for Veterinary Med.	2/11/05

e. COMMENTS OF APPROVING OFFICIAL *(Comments required if activity is disapproved.)*

INSTRUCTIONS

Item 5 - **Self-Employment:** If applicable, indicate self-employment, the type of service (as medical, legal, etc.), whether alone or with partners, giving their names, and, if providing professional services to a large number of clients or patients, estimate the total number rather than listing them separately.

Item 10 - **Federal Grants or Contracts Involved:** Describe the Federal grants or contracts (type, granting or contracting department, etc.). Full details must be provided on any aspect of professional and consultative services which involves, directly or indirectly, the preparation of grant applications, contract proposals, program reports, and other material which are designed to become the subject of dealings between institutions and government units and the Federal Government.

Item 13.c. - **Attachments:** Be sure to sign copies of all attachments submitted.

INFORMATION TO EMPLOYEE: The collection of the information requested on this form is authorized by Executive Order 12731 and the regulations issued thereunder. The information you disclose will be used to determine whether a conflict of interest would exist between the outside activity and your official duties. The information will be held in confidence and made available only to persons specifically authorized by the head of the principal operating component or designee. The information may be used: a) by a Federal, State or local agency when there is an indication of a violation or potential violation of law; b) by a Federal agency in deciding on the hiring or retention of an employee or other benefit; c) for statistical information excluding personal identification of individuals; and d) for other routine uses published in accordance with 5 USC 552a. Your failure to provide the information requested will preclude your engaging in the outside activity for which approval is required.

DCW 2/7/05 NSM 2/17/05

ENTER ADDITIONAL COMMENTS BELOW

The Office of Ethics noted that I listed the company as an asset on my financial disclosure and asked that I submit an HHS-520-1 to cover it, even when it was inactive. When I filed in November 2004, I was not doing anything in this company and expected it to be dormant. I offered to print a corporate return but it was declined. I am specifying what exactly I did do and hope to do in the future:

This is a consulting company for the development of humane scoring paradigms (pain and distress) and hand held device software for tracking laboratory and critical animal care in decentralized facilities. I developed it prior to employment at CVM.

It is mostly inactive except for sporadic requests which have been run through CVM leadership when they occur to make sure there is no conflict. Examples include a request from the NAS to participate in a panel evaluating animal care at the National Zoo, consulting for the Humane Society on Research Animal Issues, and writing a solicited article for Laboratory Animal Medicine or ILAR, special consulting for the Metropolitan Emergency Animal Clinic and also the deposit fo any income received for veterinary services to friends and family from my home business pharmacy. I do not actively solicit business in it at this time.

Because it costs me money to keep this business as a corporation and In order to keep future outside activities more simple, I have asked the Metropolitan Emergency Animal Clinic, the Humane Society of the United States, friends and family who wish to order veterinary supplies through my veterinary accounts such as Webster Veterinary, Vetcentric, Butler, Buck to make their checks out to the company name so that I may minimize outside activity requests. I have worked with my accountant to try to make future outside activities into one request.

The most I hope to earn in consulting in 2004-2005 is $1000.00 (approximately)

The most I will probably earn in other veterinary-related activities/supplies resold to family at cost is $60.00 for pharmacy activity.

The most I will probably earn in any clinical consulting is $5,000.00

DEW 2/17/05 MSM 2/17/05

11. TYPE AND AMOUNT OF COMPENSATION (CONTINUATION PAGE)			
TYPE OF COMPENSATION	AMOUNT OF COMPENSATION	EXPENSES	COMMENTS
TOTALS:			

DSW 2.11.05 NSOM 2/17/05

NOTICE TO APPLICANTS FOR PRIOR APPROVAL OF OUTSIDE ACTIVITIES

APPROVAL OF AN HHS FORM 520-1 DOES NOT RELEASE YOU FROM A CONTINUING LEGAL OBLIGATION TO DISQUALIFY YOURSELF FROM OFFICIAL ASSIGNMENTS AFFECTING YOUR OUTSIDE EMPLOYER. WHILE PERFORMING AN APPROVED OUTSIDE ACTIVITY, ANY ACTIONS TAKEN IN CONFLICT WITH APPLICABLE ETHICS LAWS MAY SUBJECT YOU TO CRIMINAL PROSECUTION AND/OR DISCIPLINARY PROCEEDINGS.

Caution. When you work for a company, organization, or other employer outside your government job, your relationship with that outside employer has certain legal and ethical consequences. The approval of an outside activity does not mean that you are free of conflicts of interest. You must still follow all substantive ethics requirements after approval is granted. Consult the ethics regulations at 5 C.F.R. §§ 2635.802 and 5501.106(d)(4) which are reprinted on the reverse side of this notice.

Conflicts Resolution. An approved HHS Form 520-1 does not signify that you need not be concerned about conflicts of interest. Under the law, conflicts of interest arising out of outside employment can be resolved in advance in only three ways: (1) you can inform your supervisor and disqualify yourself from participating in a conflicting government matter (often called a recusal); (2) you can ask for and receive, if certain legal requirements are satisfied, a separate legal document from your appointing official or designee that specifically permits you to work on the government matter (known as a waiver, an exemption, or an authorization); or (3) you can resign from either your government or outside job.

Effect of Prior Approval. The outside activities prior approval process has very limited purposes. When a supervisor or other reviewer approves an HHS Form 520-1 for your outside activity, only two assessments are being made, which are discussed below. You reasonably may rely on these specific determinations only if you provided all relevant information on the form and the circumstances under review do not thereafter change. You remain responsible for the legal consequences of any change in personal or business affairs.

First, based on the information which you provide, the reviewer determines whether your proposed activity is plainly prohibited by applicable statutes or regulations. For example, if you want to lobby federal agencies on behalf of a non-profit organization that employs you, prior approval will be denied because a criminal statute prohibits such representational activities.

Second, assuming your proposed activity is not specifically prohibited, the reviewer determines whether, under the circumstances, approval should be denied for other reasons specified under the law. For example, the reviewer may deny approval if the facts show that you used your government position to obtain an outside compensated business opportunity. Another common reason for denying approval is that the outside activity may prevent you from handling work that is expected of you. Because the outside activity may cause you to have to disqualify yourself from a broad range of job assignments, or even a few crucial projects, that will affect your outside employer, it may be impossible for you to discharge fully your government duties. If, however, your outside activity is approved, the reviewer has determined that the matters in which you will not be allowed to participate are not "so central or critical to the performance of [your] official duties" that your ability to perform the duties of your position would be materially impaired. In other words, you cannot work on a government matter affecting your outside employer, but the reviewer expects that you will be able to stay away from these assignments and still do your job.

Recusal Obligation. When performing your federal duties, you must avoid participating in any government matter that will affect your own self-interest in continuing your outside job. For example, you would have to disqualify yourself from participating in any official matter that might put your outside employer out of business or seriously affect its finances, either positively or negatively, so that the odds of your remaining employed are also affected. Also, when you work for an outside employer, the financial interests of that company or organization are considered to be your own. This means that you cannot participate in government matters that will affect that company or organization. You cannot work on a government matter that involves your outside employer as a specific party, such as a contract, grant, audit, or investigation. The law also requires you to stay away from government matters that are larger in scope, such as deliberations and decisions on developing, implementing, or enforcing statutes, regulations, policies, studies, or proposals, that will have an effect on a large class of employers like the one for which you work on the outside. For example, if you have an outside position as an employee of a hospital, a drug company, or a nonprofit organization, you cannot participate personally in any significant way in a policy decision that affects the financial interests of the industry or organizational sector in which these employers operate. A waiver often can be granted for such "particular matters of general applicability," if you notify your appointing official in advance and receive a written determination.

Scope of Recusal. Although many employees understand the need to disqualify themselves from participating in an official matter that affects their outside employer, they often believe erroneously that they can pick and choose among the various aspects of a particular matter and stay away only from the important decisions. Such incomplete recusals will not protect you from a criminal conflict of interest violation. Unless a waiver, approved in advance, identifies specific permitted activities, you must refrain entirely and absolutely from participating personally and substantially in a government matter that affects your own financial interest or that of an outside employer. When you are involved significantly in proposing, planning, advising, deciding, or implementing some official action, and you do so individually or by actively directing subordinates, your participation is personal and substantial.

Drw - 1 of MSM 2/1/05

EXCERPTS FROM THE STANDARDS OF ETHICAL CONDUCT FOR EMPLOYEES OF THE EXECUTIVE BRANCH AND THE DEPARTMENT OF HEALTH AND HUMAN SERVICES SUPPLEMENTAL AGENCY ETHICS REGULATIONS:

TITLE 5 CODE OF FEDERAL REGULATIONS

§ 2635.802 Conflicting outside employment and activities.

An employee shall not engage in outside employment or any other outside activity that conflicts with his official duties. An activity conflicts with an employee's official duties:

(a) If it is prohibited by statute or by an agency supplemental regulation; or

(b) If, under the standards set forth in §§2635.402 and 2635.502, it would require the employee's disqualification from matters so central or critical to the performance of his official duties that the employee's ability to perform the duties of his position would be materially impaired.

Employees are cautioned that even though an outside activity may not be prohibited under this section, it may violate other principles or standards set forth in this part or require the employee to disqualify himself from participation in certain particular matters under either subpart D or subpart E of this part.

Example 1: *An employee of the Environmental Protection Agency has just been promoted. His principal duty in his new position is to write regulations relating to the disposal of hazardous waste. The employee may not continue to serve as president of a nonprofit environmental organization that routinely submits comments on such regulations. His service as an officer would require his disqualification from duties critical to the performance of his official duties on a basis so frequent as to materially impair his ability to perform the duties of his position.*

Example 2: *An employee of the Occupational Safety and Health Administration who was and is expected again to be instrumental in formulating new OSHA safety standards applicable to manufacturers that use chemical solvents has been offered a consulting contract to provide advice to an affected company in restructuring its manufacturing operations to comply with the OSHA standards. The employee should not enter into the consulting arrangement even though he is not currently working on OSHA standards affecting this industry and his consulting contract can be expected to be completed before he again works on such standards. Even though the consulting arrangement would not be a conflicting activity within the meaning of §2635.802, it would create an appearance that the employee had used his official position to obtain the compensated outside business opportunity and it would create the further appearance of using his public office for the private gain of the manufacturer.*

§ 5501.106(d)(4) Standard for approval.

Approval shall be granted unless it is determined that the outside employment or other outside activity is expected to involve conduct prohibited by statute or Federal regulation, including 5 CFR part 2635 and this part.

Note: The granting of approval for an outside activity does not relieve the employee of the obligation to abide by all applicable laws governing employee conduct nor does approval constitute a sanction of any violation. Approval involves an assessment that the general activity as described on the submission does not appear likely to violate any criminal statutes or other ethics rules. Employees are reminded that during the course of an otherwise approvable activity, situations may arise, or actions may be contemplated, that, nevertheless, pose ethical concerns.

Example 1: *A clerical employee with a degree in library science volunteers to work on the acquisitions committee at a local public library. Serving on a panel that renders advice to a non-Federal entity is subject to prior approval. Because recommending books for the library collection normally would not pose a conflict with the typing duties assigned the employee, the request would be approved.*

Example 2: *While serving on the library acquisitions committee, the clerical employee in the preceding example is asked to help the library business office locate a missing book order. Shipment of the order is delayed because the publisher has declared bankruptcy and its assets, including inventory in the warehouse, have been frozen to satisfy the claims of the Internal Revenue Service and other creditors. The employee may not contact the Federal bankruptcy trustee to seek, on behalf of the public library, the release of the books. Even though the employee's service on the acquisitions committee had been approved, a criminal statute, 18 U.S.C. 205, would preclude any representation by a Federal employee of an outside entity before a Federal court or agency with respect to a matter in which the United States is a party or has a direct and substantial interest.*

Attachment 3

WRITTEN STATEMENT

VHH 2/24/05

I, Victoria Hampshire, residing/employed at FDA/CVM.,
make the following statement freely and voluntarily:

I understand there are 2 issues surrounding my outside activities:

① The nature of the AVA business of which I am sole proprietor

② The change in detail regarding my outside activity which was completed approximately last week.

AVA is a Maryland corporation I started for humane care and use consulting, pain scoring and software design, and limited clinical care. It was started prior to my employment at FDA. I did not have a Vetcentric prescribing account at that time. After joining FDA in 2001 a colleague at FDA suggested it as a good way to prescribe on a limited basis without carrying pharmaceutical overhead. It was never something I intended to make money on and was mostly a mechanism to prescribe drugs for friends, family and old (former) clients.

I had not even logged on my vetcentric account for some time. When I called the firm (vetcentric) on or about February 10, I asked for a printout of all purchases and discovered that nearly $1,000 of supplies had been ordered by someone in New York and through my own investigative work discovered that the drug company probably tried to purchase heartworm products but when I declined ~~beer~~ to fill an Rx because I did not know them, they then purchased large amounts of OTC products. I then asked Vetcentric to close the account. →

Additionally, I had become completely paranoid and sleepless since being given a cold shoulder at work (on or about November 2004 and regarding any subject related to

ProHeart 6. This was made worse when my Deputy Center Director Dr Tollefson attempted to reassign me on Jan 7, 2005. I did not understand at that time what I could have done and did not make the connection with the outside activity. I continued to try to find out as much as I could about how the bites claim came to be. I became more suspicious when the ethics office asked for a renewed outside activity but still didn't think about veterinue because it was so small a part of anything I did. [redacted] and I had lunch and she hinted at what the problems might be. This was either the same day or the day after I had been asked to file a new outside activity. I panicked

and realized that I did not adequately detail who my outside services or all the vendors were. I went back to my office and called Joan Gottschalk to see if it was too late to attach a new comment explaining them. She said Dr. Sondlof had not gotten to it yet. I took a note down and stapled the new detailed one to the old one and also left a pink note on it detailing my plans for the company and to call me with any questions. I have tried to explain anything anybody wanted to know about this company. It has been next to impossible to get an answers from anybody regarding what needed to be clarified. I want to make it clear that I did not want to deceive anybody. I wanted to talk about it but was of the opinion I was shut out.

In summary -

① I did not intend to deceive

② I did not review ProHeart ADE's in a biased way

③ I did not make or plan to make profits by preserving huge quantities of ProHeart 6 competitors

④ I have been sleepless, insecure and panicked as requests to stay out of key meetings were made.

⑤ I allowed panick, insecurity and sleeplessness to overcome sensible routing of revised information in my outside activity. I apologize for the impression that I left (leaves)

⑥ I did not see my superiors as accessible or forthcoming on the details of this investigation or what eventually became known as a probable investigation.

(7) I realize now that my superiors may not have been able to be forthcoming or open in this matter.

(8) Thank you for permitting me to explain what the outside activity is about.

Q: Who did [redacted] say she received her knowledge of the incident from?
A: [redacted]
Q: Do you have anything to add?
A: Yes, I would like to apologize for any appearance of a conflict of interest ~~and for any inconvenience I caused.~~ I now understand why I was removed from the project.

I have read/have had read to me the above statement consisting of 6 pages, and the statement made by me is true and accurate to the best of my knowledge and belief.

No threats or promises have been made to me and no pressure or coercion of any kind has been used against me.

Signature

Signed and sworn to before me this 24th day of Feb, 2005.

Mark L. McLamb 2/24/05
Special Agent/Date
FDA, Office of Internal Affairs

Authority to administer oaths:
Title 5, U.S. Code, Section 303

[illegible] 2/24/05
Witness/Date

ATTACHMENT 42 B

Food and Drug Administration
Office of Internal Affairs

REPORT OF INVESTIGATION

****

TITLE: Victoria A. Hampshire
Senior Regulatory Staff
CVM

CASE NO: 05-OIA-966-007

TYPE OF CASE: Conflict of Interest

INVESTIGATION MADE AT: Office of Internal Affairs

PERIOD COVERED: 11/22/04 – 01/29/05

INVESTIGATION MADE BY: SA Mark McCormack and SA Mike Redmond

REPORTING AGENT: SA Mark McCormack

STATUS OF CASE: (X) CONTINUING INVESTIGATION
( ) SIGNIFICANT DEVELOPMENT
( ) PENDING ADMINISTRATIVE ACTION
( ) PENDING JUDICIAL ACTION
( ) REFERRAL TO ANOTHER AGENCY
( ) CLOSED

Mark S. McCormack 1/29/05
Mark S. McCormack
Special Agent

Horace L. Coleman 01-31-05
Horace L. Coleman
Special Agent in Charge

****

RESTRICTED INFORMATION

This report is furnished on an official need-to-know basis and must be protected from dissemination which might compromise the best interests of the Food and Drug Administration, Office of Internal Affairs. This report shall not be released in response to a Freedom of Information Act or Privacy Act request or disseminated to other parties without prior consultation with the FDA Office of Internal Affairs. UNAUTHORIZED RELEASE MAY RESULT IN CRIMINAL PROSECUTION.

DISTRIBUTION:

1. INTRODUCTION:

Reference is made to the Case Initiation and Fact Sheet, dated 11/24/04.

2. SYNOPSIS:

Officials from Wyeth Pharmaceuticals presented information to Dr. Lester Crawford, Acting Commissioner, FDA, which appeared to indicate Victoria Hampshire, DVM, Senior Regulatory Staff, CVM, (the subject in this case) was operating an internet animal pharmacy; a conflict of interest. Subject is also quoted by animal activists on the web as being against Pro Heart 6.

Agents McCormack and Redmond, Office of Criminal Investigations/Office of Internal Affairs (OCI/OIA) immediately responded to CVM and interviewed Dr. Stephen Sundlof, Director, CVM.

HHS/OIG has joined in this investigation.

As one of her duties Dr. Hampshire was compiling Adverse Event Reports (AERS) for Pro Heart 6, a reportedly very profitable canine medication for heartworm prevention, which is administered by injection by Veterinarians.

Pro Heart 6 is manufactured by Fort Dodge Animal Health, which is wholly owned division of Wyeth Pharmaceuticals.

By September 2004, Dr. Hampshire had complied in excess of 5,000 AERS, including reports of 500 canine deaths, both involving Pro Heart 6. Officials from CVM met with representatives from Fort Dodge Animal Health, who voluntarily agreed to remove Pro Heart 6 from the market.

Fort Dodge Animal Health has taken the position that the subject has a conflict of interest.

Fort Dodge Animal Health has since taken the position that Pro Heart 6 is both a safe and effective product and has subsequently requested a Public Advisory Meeting, which is scheduled to take place on 1/31/05.

Additional investigation revealed subject was the listed owner of a Web site called Advanced Veterinary Applications.

On 1/6/05, SA McCormack verbally presented an overview of the investigative facts to date to officials at CVM. On 1/7/05, CVM officials advised SA McCormack that Dr. Hampshire was being immediately re-assigned and recused her from any involvement in the Pro Heart 6 issue.

Case continued pending additional investigation.

3. DETAILS OF INVESTIGATION:

On 11/22/04, Mark S. McCormack, Special Agent in Charge (Acting), Office of Internal Affairs, was contacted by Dr. Stephen Sundlof, Director CVM, regarding a possible conflict of interest involving Dr. Victoria Hampshire, a Public Health Service (PHS) employee.

Agents McCormack and Redmond, (OCI/OIA), immediately responded to CVM and interviewed Dr. Stephen Sundlof, Director CVM.

Dr. Sundlof advised that officials from Wyeth Pharmaceuticals presented information to Dr. Lester Crawford, Acting Commissioner, FDA, information which appeared to indicate Victoria Hampshire, DVM, Senior Regulatory Staff, CVM, was operating an internet animal pharmacy, a conflict of interest.

On 11/22/04, I emailed Ms. Jenny Slaughter, Director, Office of Ethics, inquiring as to what outside activities had been approved for the subject. On 11/23/04, Ms. Slaughter advised that the subject had not sought, nor was approval granted for operating an Internet Pharmacy. Ms. Slaughter stated she would send me a copy of the subject's ethics file.

Reviews of the records reveal the subject received a letter dated February 10, 2003, from Ms. Slaughter. In the letter the subject is notified that the Ethics Branch was notified by CVM that she had been promoted to the CC-05 level and now occupied a position designated as a confidential filing position. On her OGE 450 dated 3/10/03, the subject lists The Metropolitan Emergency Animal Clinic. In the Type of Organization column the subject wrote Animal Hospital. The subject also lists an organization as Director AVA Consulting and lists an income of $600.00 per year. At this time it is unknown if AVA is the Advanced Veterinary Applications web site.

In her position at CVM, Dr. Hampshire was compiling Adverse Event Reports (AERS) for Pro Heart 6, a reportedly very profitable canine medication for heartworm prevention which is administered by injection by veterinarians. Pro Heart 6 is manufactured by Fort Dodge Animal Health; which is wholly owned division of Wyeth Pharmaceuticals.

By September 2004, Dr. Hampshire had complied in excess of 5,000 AERS, including reports of 500 canine deaths, both involving Pro Heart 6. Officials from CVM met with representatives from Fort Dodge Animal Health, who voluntarily agreed to remove Pro Heart 6 from the market.

Mr. CT Newsum, Senior Vice President and Chief Counsel for Fort Dodge Animal Health, has spoken with SA McCormack on numerous occasions over the course of this investigation. Speaking on behalf of Fort Dodge Animal Health, Mr. Newsom has steadfastly maintained that the appearance of a conflict of interest on the part of the subject should be ample reason to recuse her from any participation in the review of AERS or participation in the Public Health Advisory Meeting involving Pro Heart 6.

Fort Dodge Animal Health has since taken the position that Pro Heart 6 is both a safe and effective product and has subsequently requested a Public Advisory Meeting, which is scheduled to take place on 1/31/05.

SA Redmond requested a download of emails and internet activity from the FDA email sever from Dr. Hampshire's FDA computer from ISSO Kevin Stine. SA Redmond determined there was no inappropriate use of Dr. Hampshire's FDA issued computer.

Based on the materials provided by Wyeth to Dr. Crawford (who passed them to Dr. Sundlof) SA Redmond determined Dr. Hampshire was in fact the registered owner of an internet website called Advanced Veterinary Applications. Additional investigation by SA Redmond determined that an order or prescription sent to Advanced Veterinary Applications is actually fulfilled by a firm called Vet Centric, based in Annapolis, MD. SA Redmond tasked Senior Intelligence Research Specialist Jared Johnson, OCI/HQ, with determining if Dr. Hampshire had *any* Nexus with Vet Centric Corporation, (ownership interest or seat on the Board of Directors). Johnson determined she had none (other than being a customer).

SA Nunzio Orlando, HHS/OIG, joined in the investigation and served a subpoena on Vet Centric for records pertaining to Advanced Veterinary Applications (the subject's web site). Copies have been received and will be reviewed.

On 1/6/05, SA McCormack verbally presented an overview of the investigative facts to date to officials at CVM. On 1/7/05, CVM officials advised SA McCormack that Dr. Hampshire was being immediately re-assigned and recused her from any involvement in the Pro Heart 6 issue.

Case continued pending additional investigation.

4. OTHER INVESTIGATION:

None

5. JUDICIAL/ADMINISTRATIVE ACTION:

None

6. DISPOSITION OF EVIDENCE, CONTRABAND, AND PERSONAL PROPERTY:

N/A

7. DISPOSITION STATUS:

Case continued.

8. INFORMATION TO BE INDEXED:
Victoria A. Hampshire
SSN:
DOB:

9. ATTACHMENTS:

None.

ATTACHMENT 42 C

Food and Drug Administration
Office of Internal Affairs

REPORT OF INVESTIGATION

****

TITLE: Victoria A. Hampshire
Senior Regulatory Staff
CVM

CASE NO: 05-OIA-966-007

TYPE OF CASE: Conflict of Interest

INVESTIGATION MADE AT: Office of Internal Affairs

PERIOD COVERED: 03/07/05 – 68/05

INVESTIGATION MADE BY: SA Mark McCormack and SA Mike Redmond

REPORTING AGENT: SA Mark McCormack

STATUS OF CASE: ( ) CONTINUING INVESTIGATION
( ) SIGNIFICANT DEVELOPMENT
(X) PENDING ADMINISTRATIVE ACTION
( ) PENDING JUDICIAL ACTION
( ) REFERRAL TO ANOTHER AGENCY
( ) CLOSED

Mark S. McCormack 6/8/05
Mark S. McCormack
Special Agent

Horace L. Coleman 6-8-05
Horace L. Coleman
Special Agent in Charge

****

RESTRICTED INFORMATION

This report is furnished on an official need-to-know basis and must be protected from dissemination which might compromise the best interests of the Food and Drug Administration, Office of Internal Affairs. This report shall not be released in response to a Freedom of Information Act or Privacy Act request or disseminated to other parties without prior consultation with the FDA Office of Internal Affairs. UNAUTHORIZED RELEASE MAY RESULT IN CRIMINAL PROSECUTION.

DISTRIBUTION:

1. INTRODUCTION:

Reference is made to the Case Initiation and Fact Sheet, dated 11/24/04.

2. SYNOPSIS:

A review of subpoenaed documents from Vet Centric, a third party prescription fulfillment house, has been completed. Based upon our review of the records it appeared that this account was set up to accommodate animal prescription needs for family and friends; not a for profit concern.

Investigation revealed that the subject's most recent HHS-520-1, dated 2/8/05, was submitted for approval and three supervisors in the chain of command had already signed off on it. While it was awaiting approval from the Center Director the subject asked his administrative assistant for the document back and made a substantive change. As such the HHS 520-1 would never have been approved.

In a personal interview the subject admitted she inappropriately received information concerning OIA's Official Investigation from a fellow employee at CVM; an Obstruction of an Official Criminal Investigation; potentially a federal felony charge(s).

The subject claims she, in a panic she asked for the forms back from the Center Director's assistant and made the substitution; claiming not with intent to deceive, but to clarify her activities with AVA.

The investigating agent provided a Letter of Prosecution to Mr. Steven M. Dunne, Assistant United States Attorney (AUSA), U.S. Courthouse, Greenbelt, MD. AUSA Dunne declined prosecution in this case. An Office of Government Ethics form OGE 202 will be submitted.

Subject was interviewed on 2/24/05. When we explained what had occurred, and our subsequent corroboration, she immediately understood why Fort Dodge Animal Health had raised concerns about a conflict of interest and her recusal by CVM officials from the AER and Public Advisory Meeting Processes.

Dave Wardrop, Executive Officer, CVM, stated he would meet with Dr. Sundlof next week and report what was done with this case.

Case continued.

3. DETAILS OF INVESTIGATION:

On 6/7/05, I sent an email to David Wardrop, Executive Officer, CVM, to determine what action was taken in this case. He emailed back on the same date advising he would get back to me by early next week.

Case continued pending administrative review/action.

4. OTHER INVESTIGATION:

None

5. JUDICIAL/ADMINISTRATIVE ACTION:

The investigating agent provided a Letter of Prosecution to Mr. Steven M. Dunne, Assistant United States Attorney (AUSA), U.S. Courthouse, Greenbelt, MD. AUSA Dunne declined prosecution in this case. An Office of Government Ethics form OGE 202 will be submitted.

6. DISPOSITION OF EVIDENCE, CONTRABAND, AND PERSONAL PROPERTY:

N/A

7. DISPOSITION STATUS:

Case continued pending administrative review/action.

8. INFORMATION TO BE INDEXED:

Subject indexed on previous ROI.

9. ATTACHMENTS:

None.

ATTACHMENT 42 D

Food and Drug Administration
Office of Internal Affairs

REPORT OF INVESTIGATION

****

TITLE: Victoria A. Hampshire
Senior Regulatory Staff
CVM

CASE NO: 05-OIA-966-007

TYPE OF CASE: Conflict of Interest

INVESTIGATION MADE AT: Office of Internal Affairs

PERIOD COVERED: 6/8/05 – 9/23/05

INVESTIGATION MADE BY: SA Mark McCormack and SA Mike Redmond

REPORTING AGENT: SA Mark McCormack

STATUS OF CASE: ( ) CONTINUING INVESTIGATION
( ) SIGNIFICANT DEVELOPMENT
( ) PENDING ADMINISTRATIVE ACTION
( ) PENDING JUDICIAL ACTION
( ) REFERRAL TO ANOTHER AGENCY
(X) CLOSED

Mark S. McCormack 9/23/05
Mark S. McCormack
Special Agent

Horace L. Coleman 9/23/05
Horace L. Coleman
Special Agent in Charge

****

RESTRICTED INFORMATION

This report is furnished on an official need-to-know basis and must be protected from dissemination which might compromise the best interests of the Food and Drug Administration, Office of Internal Affairs. This report shall not be released in response to a Freedom of Information Act or Privacy Act request or disseminated to other parties without prior consultation with the FDA Office of Internal Affairs. UNAUTHORIZED RELEASE MAY RESULT IN CRIMINAL PROSECUTION.

DISTRIBUTION:

1. INTRODUCTION:

Reference is made to the Case Initiation and Fact Sheet, dated 11/24/04.

2. SYNOPSIS:

Victoria Hampshire (the subject in this case) and [redacted] another CVM employee, were provided a verbal reprimand and counseling by their supervisors and a memo documenting these actions was completed and retained by their respective supervisors.

In [redacted] of 2005, a licensed veterinarian from [redacted] wrote the Center Director of CVM. In her letter the veterinarian stated that a sales representative from Fort Dodge Animal Health disparaged the subject in this case and CVM's handling of the Pro Heart 6 drug issue. The sales representative continued stating that Pro Heart 6 would soon be back on the market.

A representative from CVM called and apprised the investigating agent of this situation, provided a copy of the letter via email, and asked for advice. After reviewing the material and determining there were egregious claims it was (is) OIA position that the matter would be best handled with a formal response to Fort Dodge Animal Health by FDA legal counsel.

Case closed at the Office of Internal Affairs.

3. DETAILS OF INVESTIGATION:

On 6/24/05, I Cathy Beck called me and advised that CVM had received a letter from [redacted] a D.V.M., in [redacted] Cathy Beck, CVM, forwarded a copy of [redacted] letter to me. Ms. Beck also asked for advice and asked for permission to release OIA's Report of Investigation. On the same date I responded to Ms. Beck via email. I advised Ms. Beck that no one had permission to release or reproduce the Office of Internal Affairs Report of Investigation. I also advised that given the egregious nature of the complaint OIA felt it would be best addressed by FDA legal counsel, to protect CVM and Dr. Hampshire's integrity.

Case closed at OIA.

4. OTHER INVESTIGATION:

None

5. JUDICIAL/ADMINISTRATIVE ACTION:

On 7/19/05, Mr. David Wardrop, Executive Officer – CVM, sent me an email which advised that Victoria Hampshire (the subject in this case) and [redacted] another CVM employee, were provided a verbal reprimand and counseling by their supervisors and a memo documenting these actions was completed and retained by their respective supervisors.

An Office of Government Ethics form OGE 202 was previously submitted in this case.

6. DISPOSITION OF EVIDENCE, CONTRABAND, AND PERSONAL PROPERTY:

N/A

7. DISPOSITION STATUS:

Case closed.

8. INFORMATION TO BE INDEXED:

Subject indexed on previous ROI.

9. ATTACHMENTS:

None.

ATTACHMENT 42 E

Case Initiation and Fact Sheet

Case Number: 05-OIA-966-007 Case Title: Victoria A. Hampshire

Case Assignment: SA McCormack

COMPLAINT:

Date and Time Received: 11:30 AM 11/22/04 Person Receiving Allegation: SA McCormack

Complaint received by: Telephone: X Letter: Other:

Name of Complainant: Dr. Stephan F. Sundloff
Address: 7519 Standish Place, Rockville, MD
Telephone Number: 301-827-2950

Allegation and/or Issues: Subject is alleged to be operating an Internet Pharmacy. When Dr. Sundloff became aware of this allegation he immediately called OIA.

SUBJECT(S): Victoria A. Hampshire
Grade: CC 05
Title: Senior Regulatory Staff
Component: CVM
Region: Rockville, MD
Telephone Number:

Other Agency Involvement:

OIG Notification: Telephone: Memorandum: Fax: ✓
Date Notified: 11-24-04
Person Notified: ~~Doyle~~/Wilson OIC COAR

COMMENTS: Mark L. McCormack - for

SAIC=s Signature Horace L. Coleman - SAIC Date: 11/24/04

ATTACHMENT 43

U.S. Department of Justice

United States Attorney
District of Maryland
Southern Division

Allen F. Loucks
United States Attorney

Steven M. Dunne
Assistant United States Attorney

400 United States Courthouse
6500 Cherrywood Lane
Greenbelt, MD 20770-1249

301-344-4433

301-344-4126
FAX 301-344-4516
Steven.Dunne@usdoj.gov

February 24, 2005

BY FACSIMILE

Mark S. McCormack
Senior Special Agent
FDA/Office of Internal Affairs
One Church Street, Suite 700
Rockville, MD 20850

Nunzio Orlando
Special Agent
HHS/Office of Inspector General
12420 Parklawn Drive, Room 1-30
Rockville, MD 20857

Re: FDA employee Victoria Hampshire

Dear Senior Special Agent McCormack and Special Agent Orlando:

Thank you for the letter dated February 23, 2005, from Senior Special Agent McCormack summarizing the investigation to date relating to FDA employee Victoria Hampshire. For the reasons we have discussed, this Office has declined criminal prosecution of this matter at this time. Please let me know if you have any questions or concerns.

Very truly yours,

Allen F. Loucks
United States Attorney

By: Steven M. Dunne
Steven M. Dunne
Assistant United States Attorney

ATTACHMENT 44

Dr. Hampshire's Side of the Story

Victoria Hampshire, VMD

CDR, USPHS Veterinary Category

November 6, 2006

The following slide presentation includes a preface including important facts to be aware of in each of the slides presented by Wyeth CEO Robert Essner to former US Food and Drug Administration (FDA) Commissioner Lester Crawford and Chief Legal Counsel Dan Troy on November 19th, 2004. Each of the Wyeth slides are followed by counterpoints that include:

- Aspects of Dr. Hampshire's job that were matters of public record or otherwise should were known to FDA officials and/or members of Wyeth or its subsidiary Fort Dodge Animal Health (FDAH).

- Factual errors that were known to Wyeth/FDAH at the time of the presentation

    - Supporting documentation indicating why Wyeth or the FDA knew these were factual errors

Definitions and Acronyms in this presentation:

FDA= US Food and Drug Administration

Vetcentric= Vetcentric Veterinary Pharmacy

AVA= Advanced Veterinary Applications; the disclosed outside activity maintained until April 2005 by Dr. Hampshire

FDAH= Fort Dodge Animal Health; a subsidiary of Wyeth Pharmaceuticals.

AHA= American Heartworm Association

AVMA= American Veterinary Medical Association

PH6= ProHeart 6

Where appropriate, Dr. Hampshire discusses the rebuttal in first tense.

•EXECUTIVE SUMMARY:

Wyeth/FDAH's talk to then Acting Commissioner Crawford indicates that Dr. Hampshire's interpretation of the data was flawed and emotional. FDAH was well aware of the serious nature of the adverse events and the need for me to investigate these complaints because:

- Between launch, and the allegation Wyeth made about Dr. Hampshire they transmitted these reports to the FDA.
  - Under 21 CFR 514.80, Fort Dodge transmitted approximately 5000 of these veterinary reports of suspect adverse drug events to the agency.
  - This is a lot of reports and not simply a smattering of events illustrating my concern. I repeatedly expressed the basis for concern was a large number of frequent, severe, and similar types of reports with strong timing for drug association.
- Numerous frequent contacts between FDAH and with Dr. Hampshire in her official capacity illustrate that FDAH had details about the events and knew Dr. Hampshire had responsibility for following them. These numerous and frequent contacts are available in the electronic mail record. I have saved some of them.
- FDAH requested a meeting with Dr. Hampshire on July 13, 2004 to discuss some of the more concerning severe and infrequent but increasing events such as neoplasia, cardiac signs, and the potential for vaccine interaction. This meeting is on Hampshire's CVM outlook calendar and was attended by: FDAH members LaRosh, Palmeter, Connell and FDA members Sharar, Larkins, Batten, Hampshire.

Therefore: FDAH withheld important facts about their knowledge of the seriousness of the adverse events and their visit to Dr. Hampshire on July 13, 2004 in which the purpose of the visit was to discuss these more serious infrequent but escalating events.

EXECUTIVE SUMMARY....CONTINUED

II.WYETH/FDAH uses Dr. Hampshire's interpretation of heartworm ineffectiveness complaints as a rationale for bias. FDAH was well aware of my expertise in Adverse Events and in heartworm product ineffectiveness and conducted this meeting in secrecy above the level of the employees who would have had knowledge of these clearances to speak and publish. Dr. Crawford was not actively practicing and was generally uninformed about these matters. Wyeth/FDAH failed to inform Dr. Crawford or Mr. Troy yet had full knowledge of these facts because:

- FDAH sponsored the July 2004 National AHA meeting in which the AHA invited me as the expert on Heartworm product ineffectiveness.
- Sponsors of this meeting requested in writing that I attend, present a talk, and publish a paper on the matter.
- These events occurred in the summer of 2004, well in advance of this private meeting.

Therefore, Wyeth/FDA failed to point out to Dr. Crawford and Mr. Troy that I was a recognized expert. Since no members at the Center level were present at the November 19, 2006 meeting, Dr. Crawford would have had no immediate knowledge of this expertise because the talk and manuscript were cleared at the Center Level.

EXECUTIVE SUMMARY.....CONTINUED

III. Point 3: When Fort Dodge presented the allegations of conflict and bias to then Acting Commissioner Dr. Lester Crawford; the highest ranked employee of the US Food and Drug Administration, they were well aware that Dr. Hampshire's moonlighting activity Advanced Veterinary Applications was a Veterinary outside activity with a Vetcentric membership from which usual and ordinary veterinary medicine was being delivered at the standard of care because:

– The Maryland Record of Business which FDAH indicates they obtained does not list the business as a pharmacy and does indicate the original activities of the business which were not disclosed to Cr. Crawford.

–the US government agents documented that FDAH hired an agent to try to procure h eartworm competitors in order to try to bolster their allegation and he failed to do so.

–Upon failing to induce a buy of the products Wyeth alleges Dr. Hampshire had reason to sell, Wyeth's agent Mr. O'Hare then procured over the counter products that could be bought at any pet store.

–Wyeth's slide show and Vetcentric's shipping record indicate that Wyeth's agent received these products in Vetcentric packaging and had complete knowledge this was a Vetcentric prescribing relationship and not a pharmacy in which Dr. Hampshire was principal.

EXECUTIVE SUMMARY POINT 3 ....CONTINUED

- **Wyeth/FDAH was well aware of the usual and ordinary nature of this type of activity because:**

- **Fort Dodge Animal Health is a Vetcentric distributor.**
  - **The routine internet search as Wyeth claims in their presentation that they did indicates that numerous animal hospitals have links to Vetcentric in which Fort Dodge products such as Etogesic (for pain) and Ketofen (also for pain) appear as selections.**
  - **The record indicates that Dr. Hampshire had, at various times, prescribed Fort Dodge products to her own clients.**
  - **The business records that Wyeth states they received on AVA indicated that AVA was not a pharmacy, it was a veterinary consulting and relief business.**
  - **Being veterinary professionals, FDAH officials would know that Vetcentric prescribing accounts and sponsored web-links are routine and ordinary**

Therefore, Wyeth Pharmaceuticals, was well aware of the nature of Hampshire's Vetcentric prescribing activities, the usual and ordinary consumer contacts that reflect veterinary relationships with Vetcentric, and the serious effects that ProHeart 6 had on some dogs when they presented their slide show to Dr. Crawford.

Executive Summary, Continued

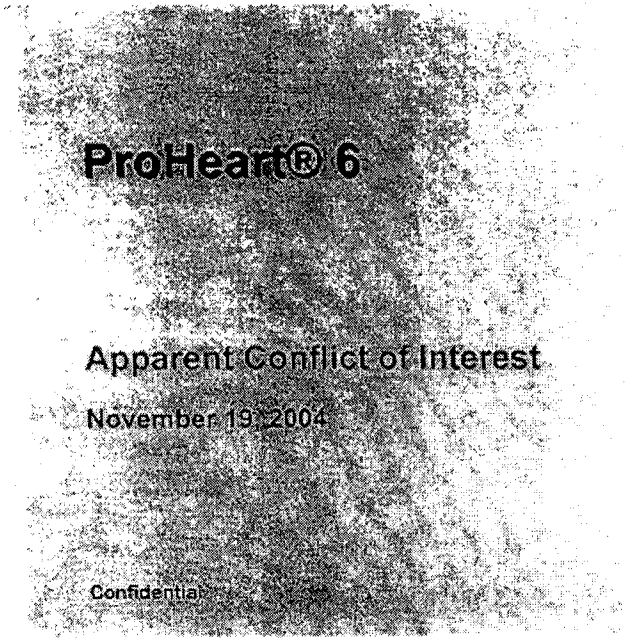
Thus, Robert Essner and representatives of Wyeth Pharmaceuticals and its subsidiary Fort Dodge Animal Health knowingly and actively failed to convey all facts that they were aware of to then acting FDA Commissioner Crawford and Chief Legal Counsel Mr. Troy on November 19, 2006. The failure to disclose these important facts resulted in severe harm to Dr. Hampshire's reputation when she was suddenly and arbitrarily reassigned on January 6, 2005 because:

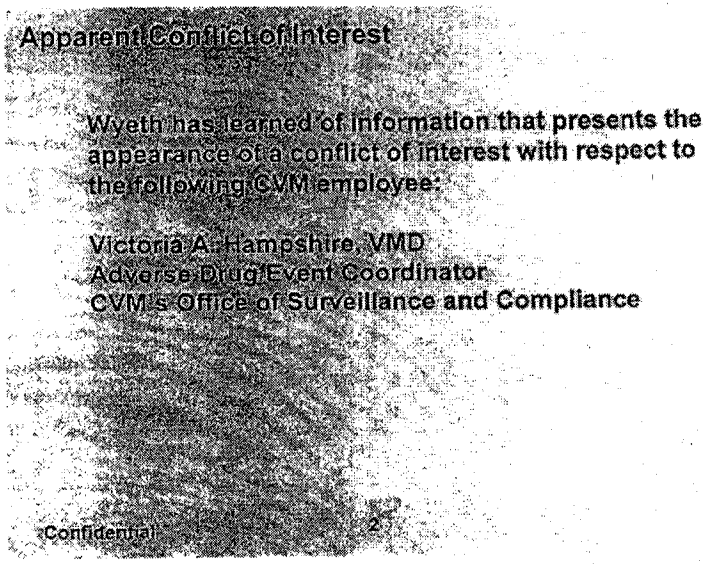
- The Veterinary Community is small, graduating only about 2500 professionals per year.
- Dr. Hampshire held a very visible position within CVM/FDA
- FDAH and its sales force sponsor or have exclusive business dealings with nearly every veterinary-associated organization and event including the American Heartworm Association, the American Veterinary Medical Association and Banfield, The Pet Hospital.

The 29 slides

- The following are each one of the slides reproduced from an Adobe version of the original confidential presentation to Dr. Crawford.
- Please read the adjoining rebuttal text; or in the event of a long rebuttal, slide(s) following the Wyeth/FDAH slide

Wyeth/FDAH Slide 1 and 2

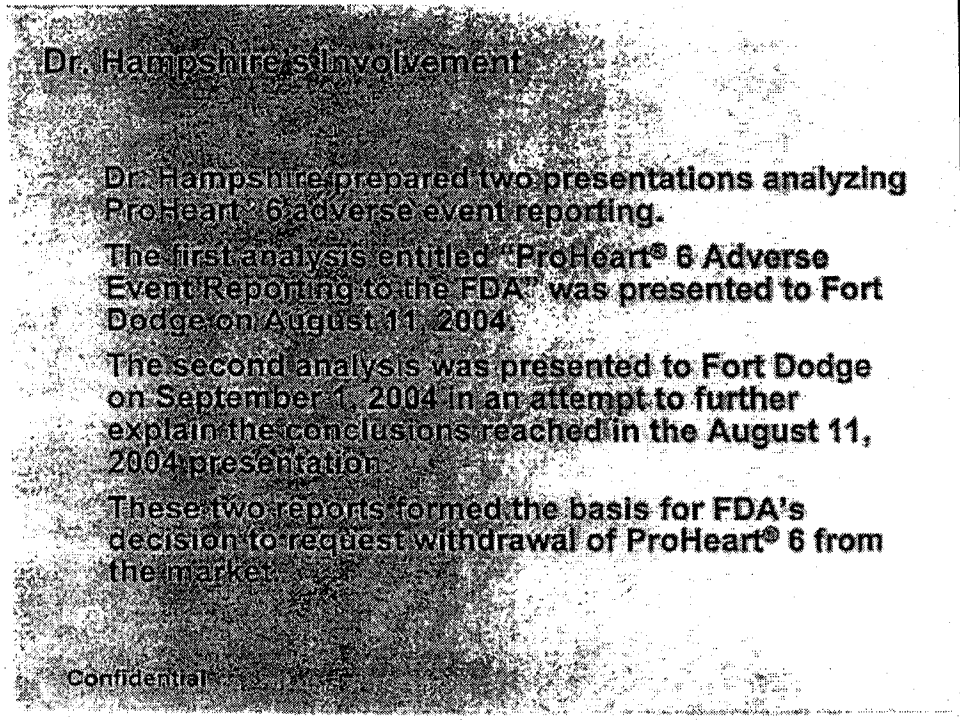




Rebuttal:

The confidential nature of this slide prohibited either Dr. Hampshire, or those who had clearance and supervisory authority for her work from attending the meeting and from presenting full facts about her disclosed approved outside activities, authorities, and responsibilities before Dr. Crawford reached a decision to have Dr. Hampshire reassigned and criminally investigated.

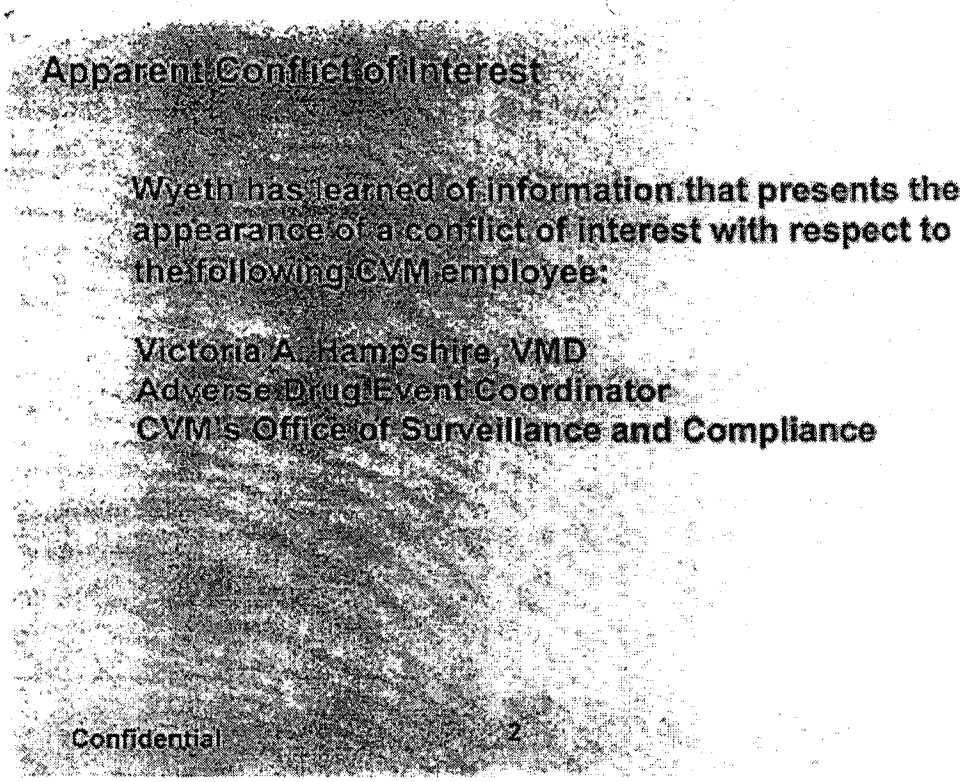
Wyeth/FDAH Slide 3:



REBUTTAL:

- The two presentations to which Wyeth refers were in draft form and represented confidential discussions pre-recall with the firm.
- CVM management shared the August 11 slides with FDAH officials without my input or knowledge as I was on vacation at the time. The August 11th meeting was was originally supposed to have taken place upon my return so that I could be present to discuss the view presented in the slides.
- The second analysis did explain the conclusions I drew.
- The slides do not form the basis for the recall. Rather, the 5000 reports about which the slides summarize form this basis.

Wyeth/FDAH Slide 4

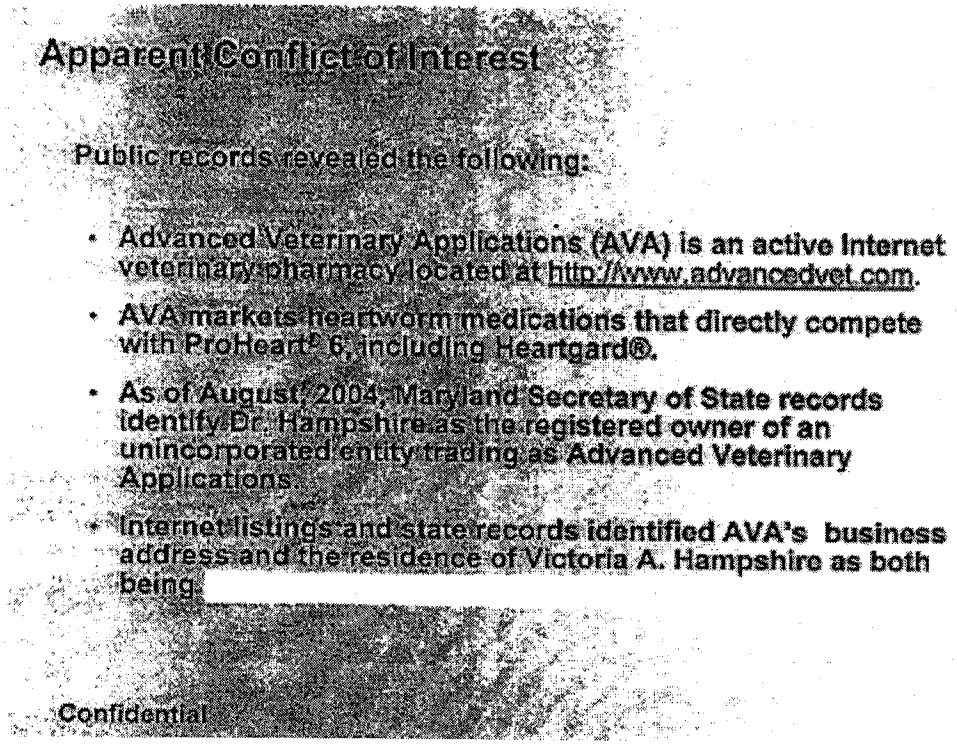


Rebuttal

Wyeth also learned of information refuting the appearance of conflict and failed to present this information in the way in which it occurred and/or the usual and ordinary nature of Vetcentric prescribing relationships about which they themselves benefit.

Therefore Wyeth/FDAH misled the FDA because Wyeth knowingly failed to reveal facts regarding the Vetcentric business about which they, along with all other veterinary sponsors were full participants through their product distribution agreements.

Wyeth/FDAH Slide 4



Public Records also revealed that AVA was principally a consulting and software entity. Outside activity filings also indicated some clinical relief work as the Government determined. The next slide is the original AVA filing with the State of Maryland.

STATE OF MARYLAND
ARTICLES OF INCORPORATION OF

Victoria Hampshire, VMd, P.A.

(A PROFESSIONAL SERVICE CORPORATION)

FIRST: The undersigned, Victoria Hampshire, VMd, whose address is 7307 Nevis Road, Bethesda, Maryland USA, being at least eighteen years of age, does hereby form a corporation under the laws of the State of Maryland.

SECOND: The name of the corporation is **Victoria Hampshire, VMd, P.A.**

THIRD: The purpose(s) for which the corporation is formed are as follows:

1. To engage in Consulting and Software, veterinary services
2. To do such acts and carry on such business as may be permitted by Title 5 Subtitle (1) of the Corporations and Associations Article of the Annotated Code of Maryland.

FOURTH: The post office address of the principal office of the corporation in Maryland is: **7307 Nevis Road, Bethesda, Maryland USA.**

FIFTH: The name and post office address of the resident agent of the corporation in Maryland is: **Victoria Hampshire, VMd, 7307 Nevis Road, Bethesda, Maryland USA.**

SIXTH: The corporation has authority to issue **1,500** shares with **$1.00** par value per share.

SEVENTH: The number of directors of the corporation shall be 1 which number may be increased or decreased pursuant to the bylaws of the corporation, and so long as there are less than three (3) stockholders, the number of directors may be less than three (3) but not less than the number of stockholders, and the name(s) of the director(s) who shall act until the first meeting or until their successors are duly chosen and qualified is/are:

Name	Address
Victoria Hampshire	**7307 Nevis Road** **Bethesda, Maryland USA**

ORIGINAL FILING
PLEASE KEEP FOR
YOUR RECORDS

EIGHT: The duration of the corporation shall be perpetual.

IN WITNESS WHEREOF, I have signed these Articles and acknowledge the same to be my act.

Victoria Hampshire, VMd, Incorporator

I hereby consent to my designation in this document as resident agent for this corporation.

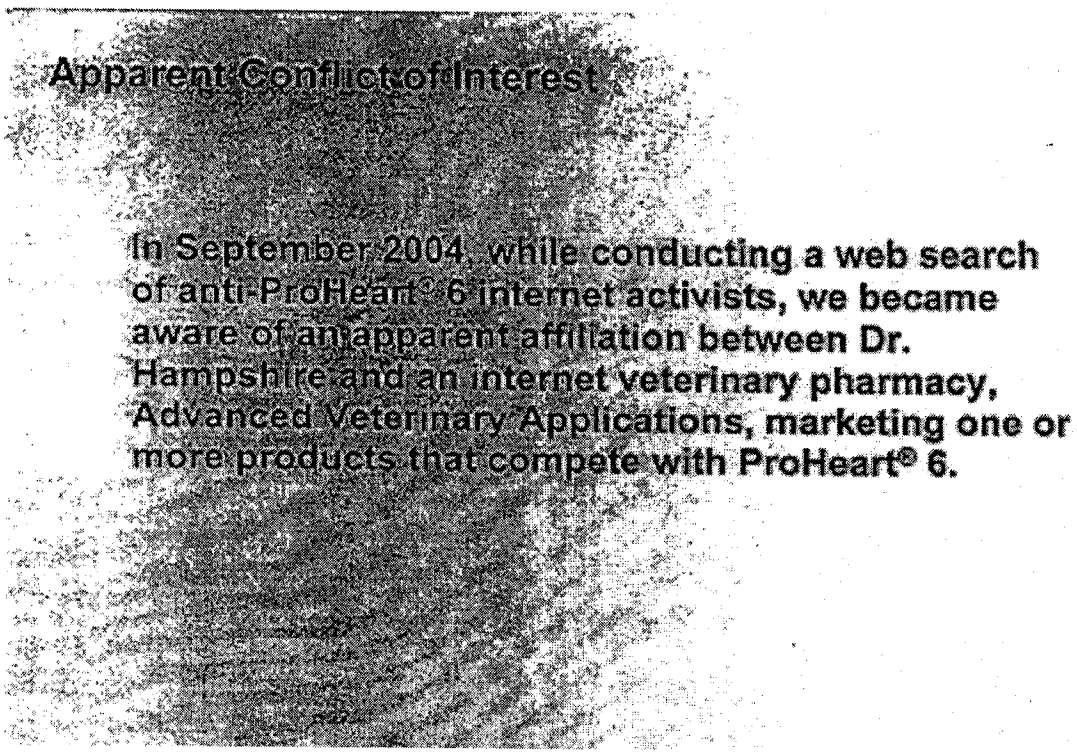
Victoria Hampshire, VMd, Resident Agent

RETURN TO:

Nellie R. Akalp
My Corporation Dot Com
30041 Agoura Rd Suite 205
Agoura Hills, CA 91301
Fax: 818-879-8005

ID # D06047849 ACK # 1000244074000000
LIBER: B00198 FOLIO: 0285 PAGES: 0002
VICTORIA HAMPSHIRE, VMD, P.A.

Wyeth FDAH Slide 5

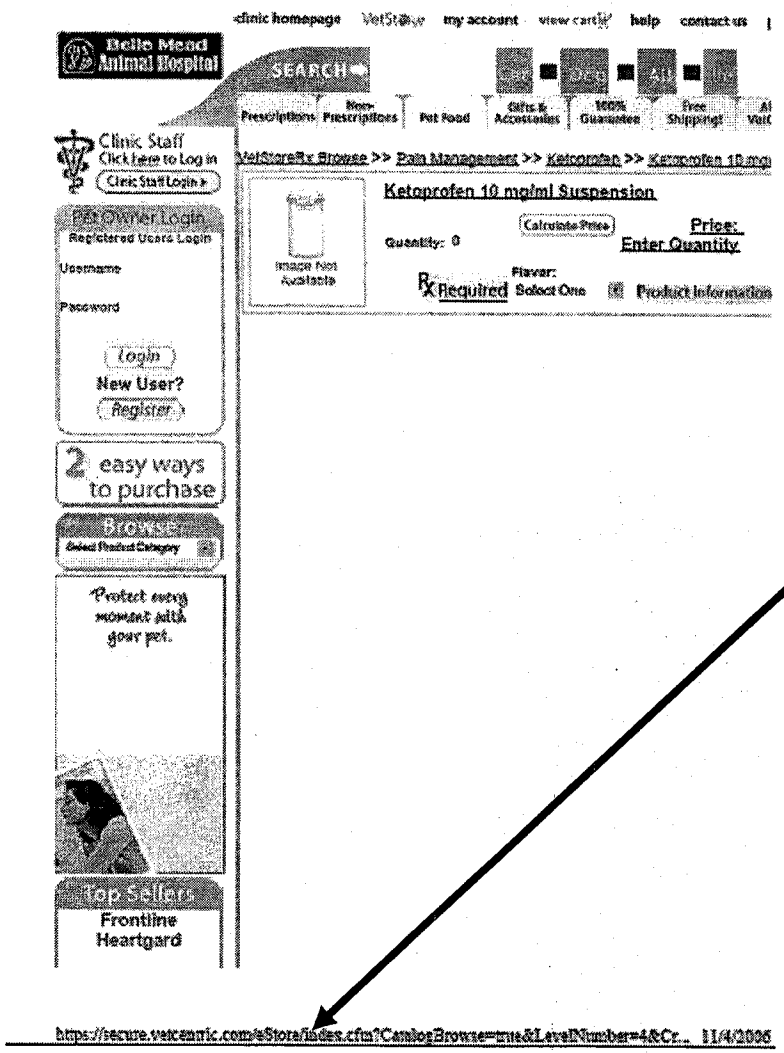


Rebuttal:

Wyeth/FDAH also indicate further in their presentation (slides 8 and 9) that they are fully aware that:

- **1. this is a Vetcentric arrangement**
- **2. They market their companion animal products through Vetcentric.**

Rebuttal to Slide 5 (continued)



- Here for example is a typical Vetcentric-hosted website for a one Bell Meade Animal Hospital where you might find for example Ketoprofen; a prescription FDAH product for pain relief.
- AVA's Vetcentric-hosted website has since been terminated however, on this example, note the web hosting address at the bottom of the page clearly indicating this is a Vetcentric-hosted site.
- Therefore, in Slide 5 of Wyeth/FDAH's November 19th presentation, Wyeth has failed to present facts that they obtained about AVA's business ,official state filing, or about the fact that FDAH itself market's its products through Vetcentric.
- Instead Wyeth/FDAH presented facts that painted Dr. Hampshire's as:
  - 1. Principal to a pharmacy rather than consulting/clinical, and software business
  - 2. A professional dedicated only to prescribing competitors to FDAH products.

Wyeth/FDAH Slide 6

Apparent Conflict of Interest

In September 2004, while conducting a web search of anti-ProHeart® 6 internet activists, we became aware of an apparent affiliation between Dr. Hampshire and an internet veterinary pharmacy, Advanced Veterinary Applications, marketing one or more products that compete with ProHeart® 6.

Rebuttal:

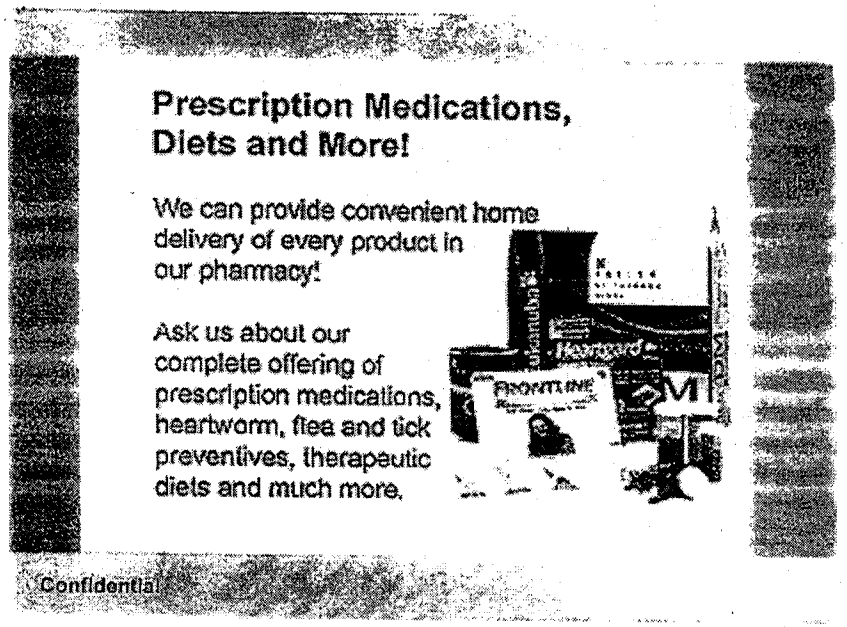
Using the most creative means of internet searching, there is no incidence of anti-PH6 activist chatter referencing AVA and further, Wyeth FDAH has not demonstrated any in this presentation.

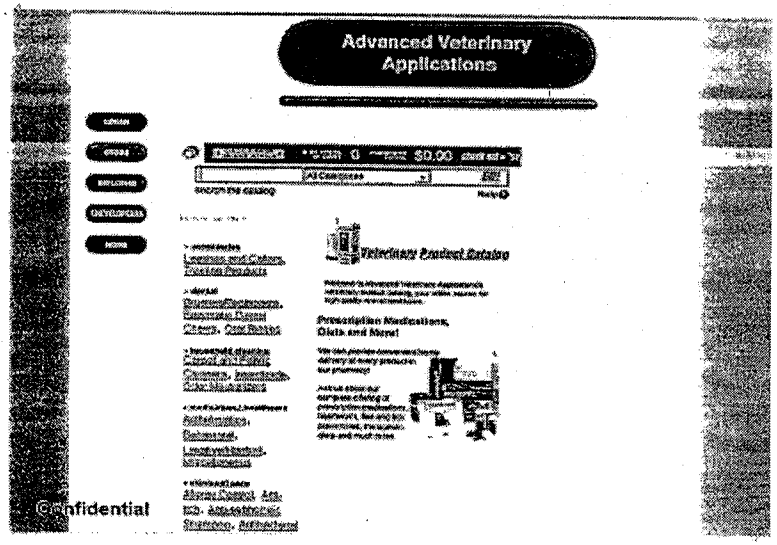
The most likely source of FDAH's knowledge of my association as principal of AVA would be a literature search or a web search of my name, not the internet activists. I had published and presented under this principal before employment at FDA and, in rare circumstances with approval and clearance while a part time safety reviewer at FDA

This slide is extremely misleading because it untruthfully paints a relationship between public and private duties and is not substantiated with any method or result of such a search.

Therefore: This slide is knowingly misleading and unsubstantiated.

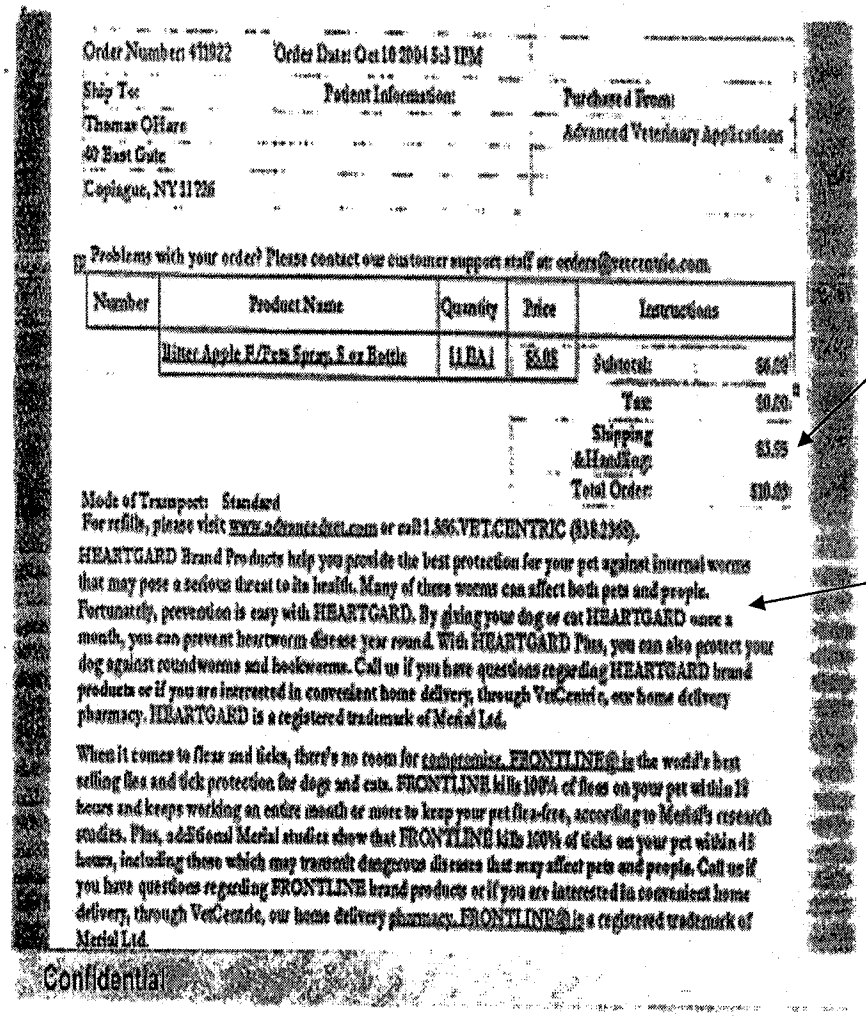
Wyeth/FDAH Slide 7 and 8





- Rebuttal:
- Again, these slides fail to include the Vetcentric web-hosting address at the page bottom and only portray competitor products to FDAH. It fails to mention or portray pictures of their own products featured in this pharmacy (see slide 5 of this presentation.

Wyeth/FDAH Slide 8



Order Number: 411922 Order Date: Oct 10 2004 5:3 11PM

Ship To:
Thomas O'Hare
40 East Gate
Copiague, NY 11726

Patient Information:

Purchased From:
Advanced Veterinary Applications

Problems with your order? Please contact our customer support staff at: orders@vetcentric.com.

Number	Product Name	Quantity	Price	Instructions
	Bitter Apple F/Pets Spray, 8 oz Bottle	1 EA	$6.05	

Subtotal: $6.05
Tax: $0.00
Shipping & Handling: $3.95
Total Order: $10.00

Mode of Transport: Standard

For refills, please visit www.vetcentric.com or call 1.866.VETCENTRIC (838.2368).

HEARTGARD Brand Products help you provide the best protection for your pet against internal worms that may pose a serious threat to its health. Many of these worms can affect both pets and people. Fortunately, prevention is easy with HEARTGARD. By giving your dog or cat HEARTGARD once a month, you can prevent heartworm disease year round. With HEARTGARD Plus, you can also protect your dog against roundworms and hookworms. Call us if you have questions regarding HEARTGARD brand products or if you are interested in convenient home delivery, through VetCentric, our home delivery pharmacy. HEARTGARD is a registered trademark of Merial Ltd.

When it comes to fleas and ticks, there's no room for compromise. FRONTLINE® is the world's best selling flea and tick protection for dogs and cats. FRONTLINE kills 100% of fleas on your pet within 18 hours and keeps working an entire month or more to keep your pet flea-free, according to Merial's research studies. Plus, additional Merial studies show that FRONTLINE kills 100% of ticks on your pet within 48 hours, including those which may transmit dangerous diseases that may affect pets and people. Call us if you have questions regarding FRONTLINE brand products or if you are interested in convenient home delivery, through VetCentric, our home delivery pharmacy. FRONTLINE® is a registered trademark of Merial Ltd.

Confidential

Rebuttal to Slide 8:

- This slide is misleading and speaks to the level of pretexting Mr. O'Hare engaged in for Wyeth/FDAH.
  - The slide is of a packing invoice for just over $10.00 when Mr. O'Hare purchased his first buy. Wyeth/FDAH does not present his second buy of over one-thousand dollars of over the counter items from Vetcentric while pretending to be a client of Dr. Hampshire's
  - The slide discusses the availability of flea/tick and heartworm preventatives that happen to be competitors to PH6 in such a way as to suggest that Dr. Hampshire was soliciting buys of this type of product.

Wyeth/FDAH Slide 9

Apparent Conflict of Interest

To confirm AVA was an active business, we placed two orders for product through the AVA website

Orders are sent to VetCentric (fulfillment house) for processing

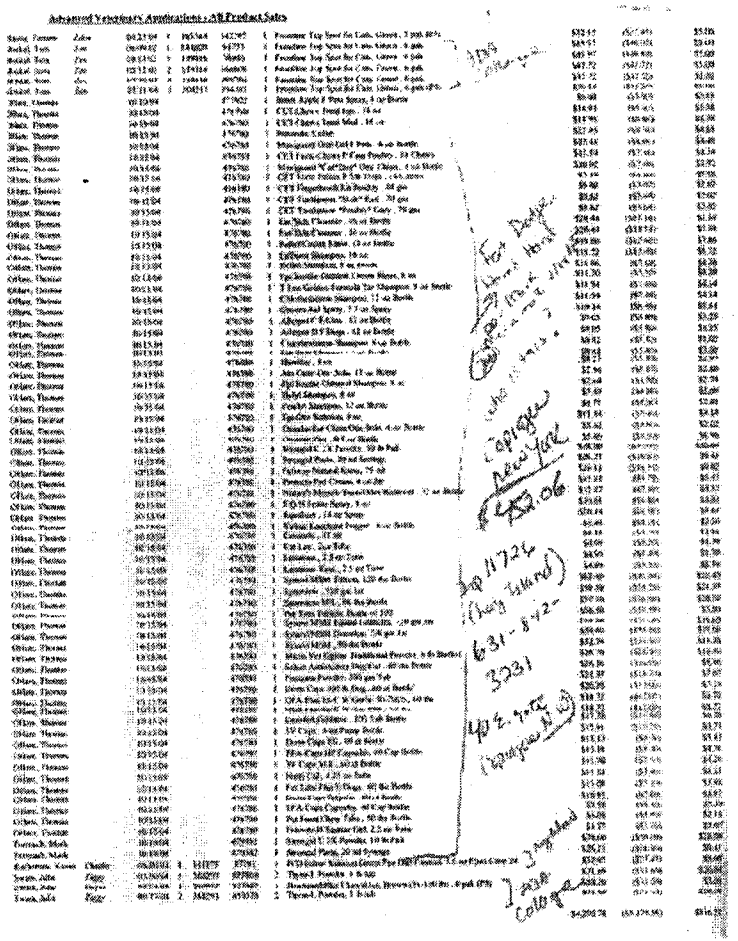
VetCentric ships product and invoices to customers

AVA receives the difference between the amount billed the customer and VetCentric's product cost

Rebuttal to Slides 8 and 9

- Wyeth/FDAH hired an agent (Mr. O'Hare) to procure two orders; one for just over ten dollars and one for over one thousand dollars; the extent of this second buy is not discussed in this presentation but it was completed on October 15, 2006 and received well in advance of this presentation in Vetcentric packaging.
- Both orders were for over the counter medications that can be purchased at PetSmart or (in the case of large animal drugs) at Southern States or in the waiting room of any practicing veterinarian.
- Wyeth/FDAHs speculates margin sales that I did not necessarily facilitate. In the two cases that their private agent procured over the counter sales, these margin sales were unknown to me and therefore, the margin check forced by Mr. O'Hare's purchase was thrown in the trash along with the entire end of month envelope which I assumed contained promotional items.

Rebuttal to Slides 8 and 9 of Wyeth/FDAH presentation, Continued



- This is the vetcentric sales record Dr. Hampshire received by request on February 14th , 2005 (or therabouts). She requested it after she learned of the allegation. Note the extensive purchasing that Mr. O'Hare performed, the notes she made to herself questioning who Mr. O'Hare was, and the relatively minute nature of two other purchases by known pet-owners who happened to have consulted me regarding their pet's needs.
- Because Mr. O'Hare was not known to Dr. Hampshire at the time she received this record, and because she was not expecting a margin check for unsolicited business of his kind, note also that the check Vetcentric sent to her address at the end of October was never cashed because she had no knowledge or expectation of income from Vetcentric. Her custom was to throw the promotionals usually containing the check in the trash unless she had deliberately charged a prescription fee.

Rebuttal to Slides 8 and 9 of Wyeth/FDAH presentation, Continued

Dr. Hampshire does recall getting a phone call from Vetcentric near the time of this purchase because she was driving home and had to pull off the road.

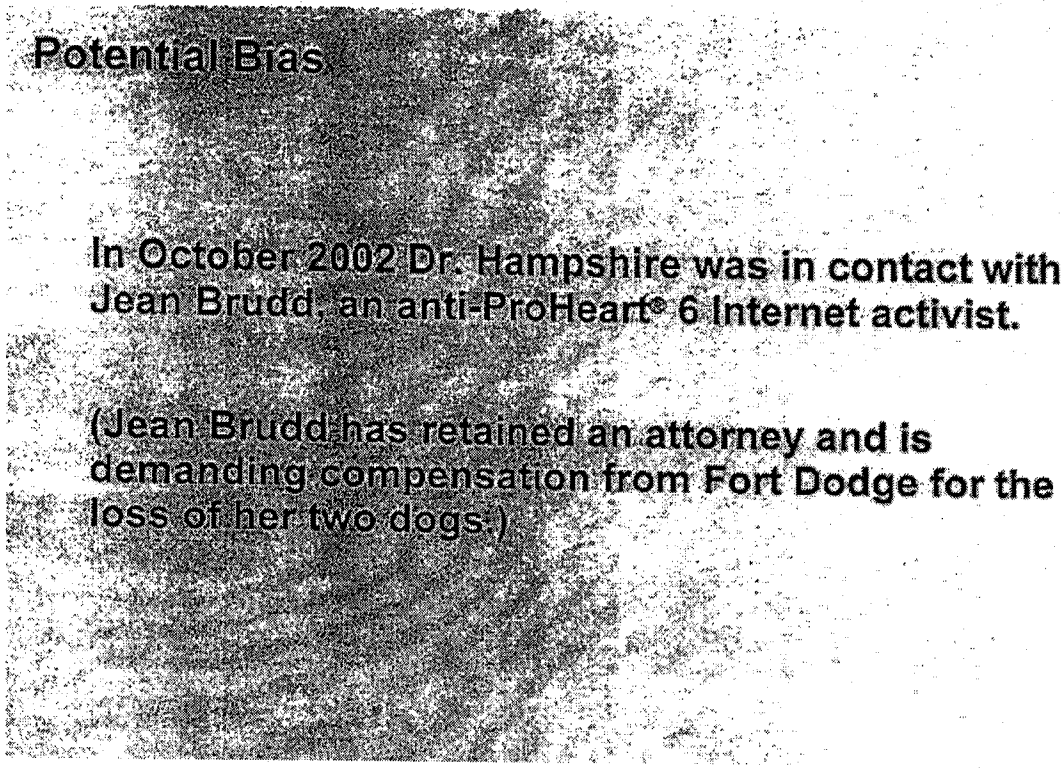
- **the purpose of the call was to inquire as to whether a gentleman whose name was not known to Dr. Hampshire, could have a prescription for Heartgard.**
- **At the time, Dr. Hampshire did not think anything of this call and told the Vetcentric pharmacist that the individual was not a client of hers and could not have Heartguard. It did not dawn on Dr. Hampshire that this could be an agent of Wyeth/FDAH pretending to be a client.**
- **Wyeth did not reveal to Dr. Crawford that they attempted to procure the products they allege Dr. Hampshire had an agenda to sell and that in this attempt they failed. At no time did Wyeth reveal this lack of success, or make the distinction between over the counter products and prescription products.**
- **On February 24, 2005, during Agent Redmond and t was later revealed to Dr. Hampshire her by Agents Redmond and McCormack, that this was an attempted induced buy by agents of Fort Dodge.**
- **The record shows that Mr. O'Hare, as agent of Wyeth/FDAH 1. Attempted to pretext as an AVA client and 2. Purchased a large quantity of product in order to create a margin sale that might convince inspectors of their alleged agenda to profit. And 3. Wyeth/FDAH concealed the magnitude of their pretexting to Dr. Crawford and Mr. Troy by simply showing the single Bitter Apple Spray in order to minimize any impression that they were aggressive, proactive, or engaged in pretexting to be a client of AVA.**

Rebuttal to Slides 8 and 9 of Wyeth/FDAH presentation, Continued

Therefore: Wyeth/FDAH engaged in the hire of an agent whose actions did not represent the character of my the business records that Wyeth/FDAH had already obtained. This part of the presentation is intentionally shocking and was deceptive through the manner and degree to which Wyeth went in order to facilitate an agenda Dr. Hampshire did not have and the record did not reflect.

Further, this nature of the small time activities of Dr. Hampshire was known to FDAH because David Hustead; agent of FDAH has a sister; Joanne Hustead and Husband Kevin Rackstraw, who are neighbors. Their cat was a patient of Dr. Hampshire. Dr. Hampshire prescribed ophthalmic ointment when Ms. Hustead later bought a new puppy. This interaction happened to have occurred at the time her brother, agent of FDAH visited her in Bethesda Maryland and while he was attending a VICH conference in October of 2003; one year before FDAH/Wyeth hired Mr. O'Hare to pretend to be a client of AVA. The ophthalmic ointment stocked by Dr. Hampshire was from a lot purchased from Webster Veterinary Supply; a different veterinary vendor.

Wyeth/FDAH Slide 10



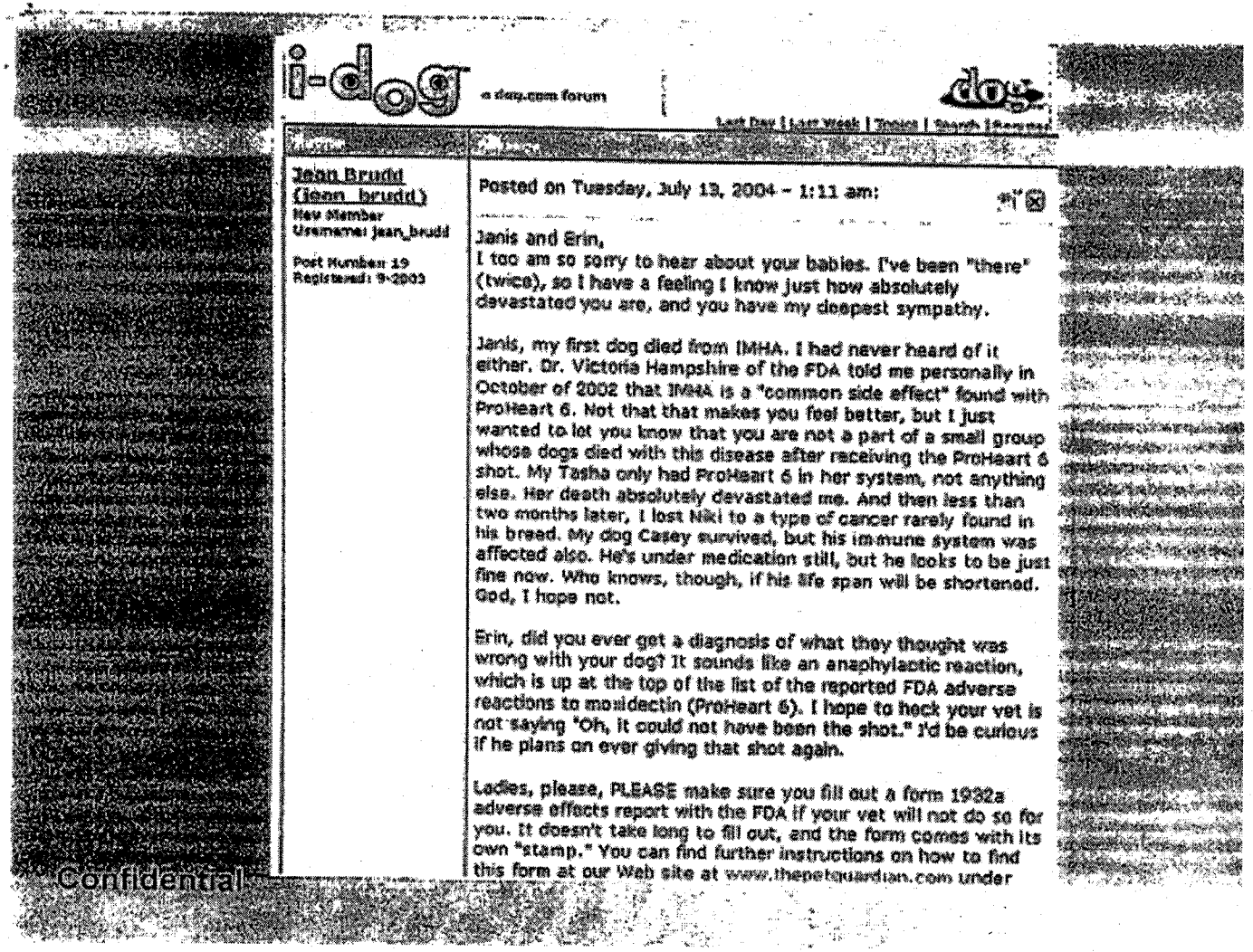
Rebuttal to Slide 10

- FDAH suggests that I elicited input from Jean Brudd.
- Mrs. Brudd was one of the first consumers to report an adverse reaction to FDA to me in her role as a part time safety officer in October 2002. I had many conversations with her and facilitated a legal route of communication between herself and the FDA.
- Mrs. Brudd reported her adverse events through Wyeth/FDAH and also directly through the FDA as confidential reports. She is fully entitled to do this and when she does, the FDA is compelled to keep any requests she has as confidential.
- However, I believe in her case, most of the dialogue was 3-way; that is both directly and indirectly through Wyeth/FDAH with the initial report coming through Wyeth/FDAH as an official form 1932A. All contact I had with Mrs. Brudd was through my role as consumer contact at FDA. I was in touch with her many times since October 2002. This contact was routine and ordinary business.

Rebuttal to Slide 10 (continued)

- The fact that Mrs. Brudd became an activist against PH6 is not relevant to my role at FDA or my interaction with her.
- The record of evidence is also that I ignored provocation by Mrs. Brudd to comment on matters not related to her case and the case of others when the complaint did not directly involve an adverse event of her own animal. She was in fact often referred to the CVM ombudsman Ms. Marcia Larkins. This can be proved by reading my electronic mail.
- Had Dr. Crawford included the CVM level leadership, this fact would likely have been revealed during the presentation and discussion following it.
- Wyeth failed to present the fact the fact that the first contact regarding Mrs. Brudd to the FDA was through a normal regulatory processes and that Wyeth FDA filed this case with the FDA. The failure to disclose this fact to Dr. Crawford resulted in a presentation indicating that I initiated contact and instigated Mrs. Brudd's activism.
- The fact that Mrs. Brudd is demanding compensation for the loss of her dogs is not related to her relationship with the FDA or myself.
- Mrs. Brudd is a free citizen and may blog whatever she chooses to blog on the internet.
- **Therefore,** Wyeth/FDAH withheld important facts about the timing, routing, and follow-up of Mrs. Brudd's case load to the FDA and presented a case to Dr. Crawford devoid of these important material facts which may have dampened the concern that I may have been acting

Wyeth/FDAH Slide 11



i-dog a dog.com forum

Last Day | Last Week | Topics | Search | Members

Jean Brudd (Jean_brudd)
New Member
Username: Jean_brudd

Post Number: 19
Registered: 9-2003

Posted on Tuesday, July 13, 2004 - 1:11 am:

Janis and Erin,
I too am so sorry to hear about your babies. I've been "there" (twice), so I have a feeling I know just how absolutely devastated you are, and you have my deepest sympathy.

Janis, my first dog died from IMHA. I had never heard of it either. Dr. Victoria Hampshire of the FDA told me personally in October of 2002 that IMHA is a "common side effect" found with ProHeart 6. Not that that makes you feel better, but I just wanted to let you know that you are not a part of a small group whose dogs died with this disease after receiving the ProHeart 6 shot. My Tasha only had ProHeart 6 in her system, not anything else. Her death absolutely devastated me. And then less than two months later, I lost Niki to a type of cancer rarely found in his breed. My dog Casey survived, but his immune system was affected also. He's under medication still, but he looks to be just fine now. Who knows, though, if his life span will be shortened. God, I hope not.

Erin, did you ever get a diagnosis of what they thought was wrong with your dog? It sounds like an anaphylactic reaction, which is up at the top of the list of the reported FDA adverse reactions to moxidectin (ProHeart 6). I hope to heck your vet is not saying "Oh, it could not have been the shot." I'd be curious if he plans on ever giving that shot again.

Ladies, please, PLEASE make sure you fill out a form 1932a adverse effects report with the FDA if your vet will not do so for you. It doesn't take long to fill out, and the form comes with its own "stamp." You can find further instructions on how to find this form at our Web site at www.thepetguardian.com under

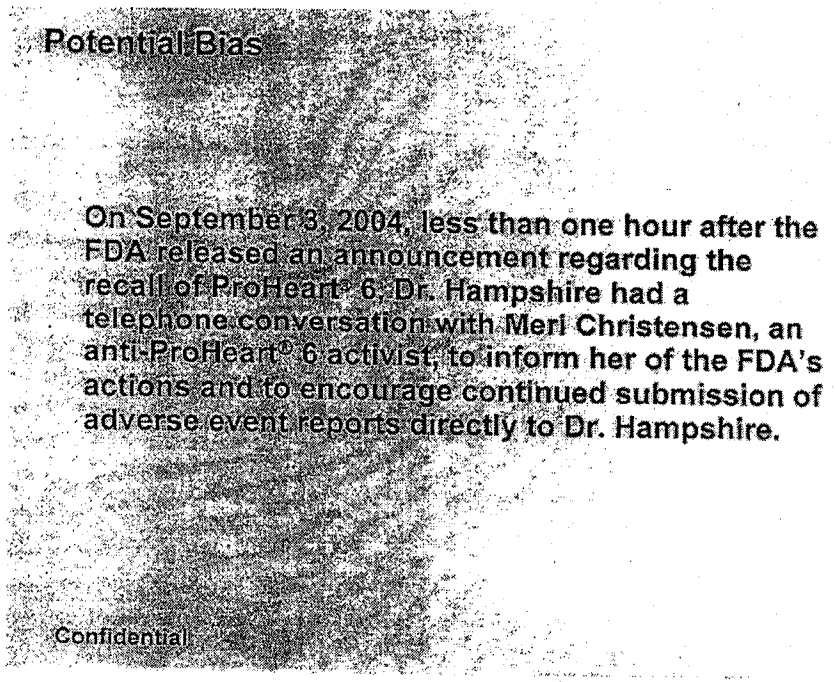
Rebuttal to Slide 11

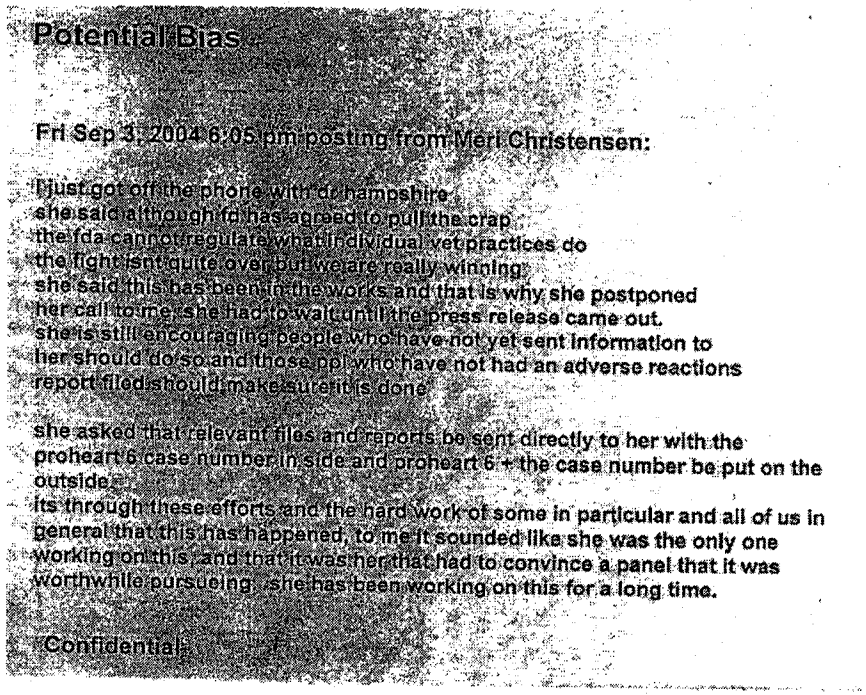
- Yes, I told Mrs. Brudd that immune-mediated hemolytic IMHA had been commonly reported to the FDA. I also showed her the publicly posted adverse events where she watched that sign grow in the database subsequent to her initial contact. It was well within my responsibilities as consumer contact to do that. I conducted routine and ordinary business in this respect.

- Mrs. Brudd had three dogs who presented with strong timing from PH6 reactions. Two died and the third is on longterm treatment. Her case is noteworthy because it sparked a discussion internally and with Wyeth/FDAH regarding whether or not there might be a lot release problem (three dogs; same batch). This concern was compounded by the lot recalls in 2004.
- This is further evidence that Wyeth/FDAH officials withheld information that they were well aware regarding Mrs. Brudd's contact with their corporation multiple times before this presentation. This withholding of facts presented the impression to Dr. Crawford that I instigated her input.

- I was not speaking to Mrs. Brudd without knowledge about IMHA. I was the technical expert in this matter and I knew what I was saying when I said it and acted well within the boundaries of my job to say it.
- Wyeth/FDAH knew I was a techncal expert because by the time they made their presentation, I had published my expertise.
- The blog by Mrs. Brudd indicates that she recognized me in my official capacity.

Wyeth/FDA Slides 12 and 13





Rebuttal to Slides 12 and 13

- The recall of ProHeart 6 caused my phone to ring off the hook. I had many conversations and e-mails from many consumers because that was my job. I have files and files of e-mails and phone records. I acted responsibly and accurately within the limits of my duties when I spoke to consumers before, during, and in the aftermath of the recall.

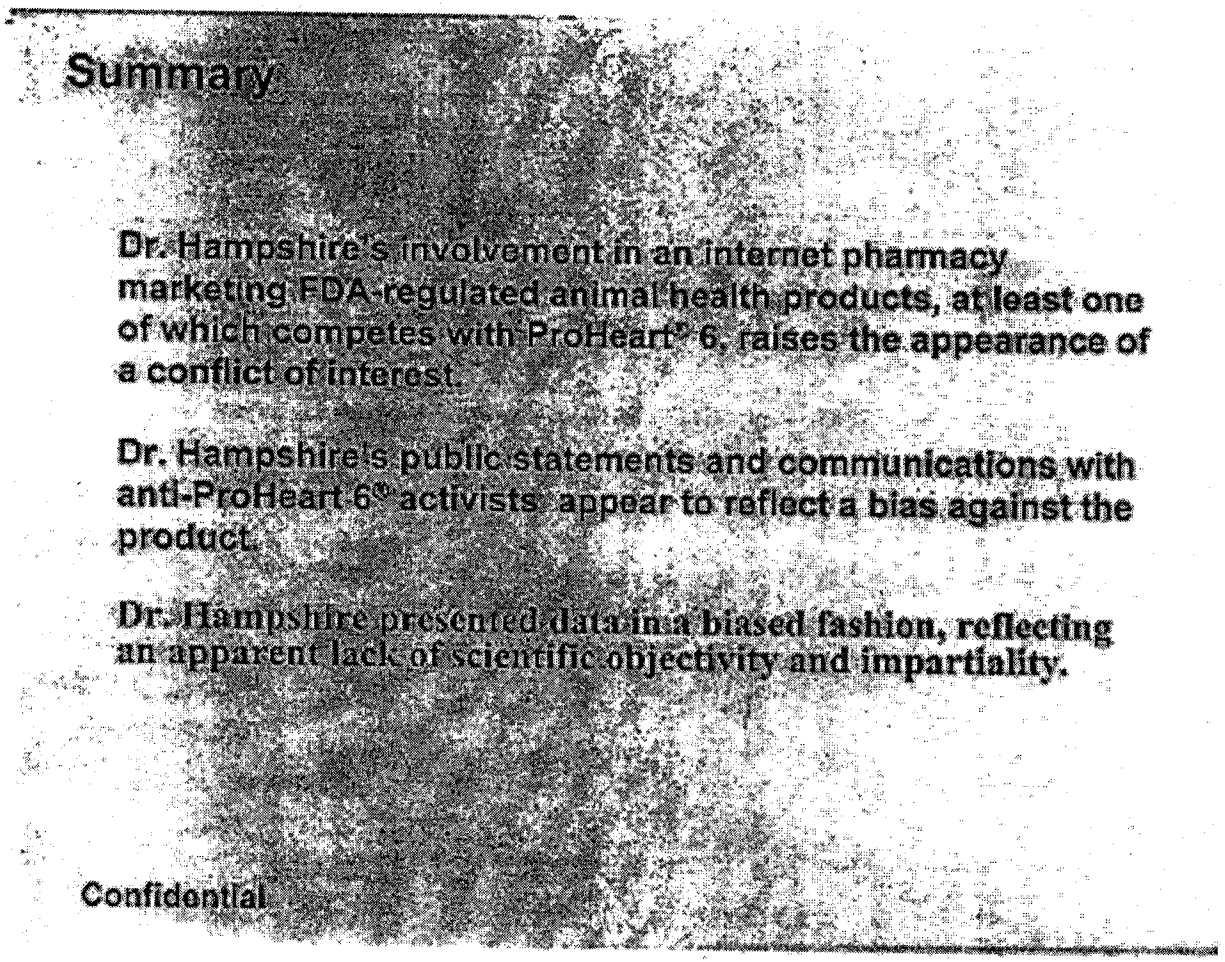
- Wyeth/FDAH suggests that this was outside the scope of my job. Wyeth withheld important facts about my oversight of hotline issues that were already published in the public domain well before this presentation (JAVMA, August 2004 by Hampshire et al.)

- Since Wyeth/FDAH had conducted numerous internet searches on me at this time, it would have been next to impossible that they were unaware of this routine and ordinary business responsibility, especially as it was published in a journal by an organization they subsequently published a partnership with. http://www.wyeth.com/news?nav=display&navTo=/wyeth_html/home/news/pressreleases/2006/1145471235419.html

Rebuttal to Slide 12 and 13 (continued)

- Therefore, it would have been virtually impossible that Wyeth/FDAH did not knowingly and deliberately withhold the fact that talking with consumers on the hotline was my business.
- Further, as for Dr. Crawford, the agency endorsed this approach because they asked me to help prepare press releases and talk to consumers. This is a matter of record on the Outlook Calendars.
- The FDA also endorsed this because they cleared the publication to which I refer and they included me in the agency-wide committee "Consumer Research Risk Working Group".
- Therefore, FDA and Wyeth/FDAH were fully aware of my responsibilities when collaborate made a decision to reassign me.

Wyeth Slide 28



Summary Rebuttal to Slide 28

- *My involvement as a prescribing partner to Vetcentric; a full veterinary pharmacy that sells Fort Dodge Animal Health products as well as all other products fell well within the practice of veterinary medicine and was disclosed at the same level as any other government veterinarian's prescribing activity.*
- My clinical competency and deployment readiness is a PHS requirement; one that has brought great credit to the PHS and the Agencies and one in fact that the Surgeon General's office is about to film for a documentary on the importance of readiness.
- *My review of ProHeart 6 was extensive, very thoughtful, unbiased, and at this time, substantiated.*

Rebuttal to Slide 28 continued; Summary

- *I made no public statements that were not endorsed by the agency or through the agency.*
- *The contact I had with consumers was part of my official responsibility and was always initiated through the illness of one of their pets and a report to the agency. I never had inappropriate contact with consumers nor did I belong to any internet groups. My electronic mail and phone records substantiated this.*
- *I never presented data in a biased manner. I presented data from over 5000 reports that were submitted to the agency by Fort Dodge. This data indicated that ProHeart 6 was an unsafe drug; a fact that was accepted by my superiors, their superiors, and eventually by a panel of experts.*
- *The data that I presented was solicited and published by experts in veterinary medicine well in advance of the November 19, 2004 closed-door meeting that Wyeth held with Dr. Crawford and Mr. Troy.*

ATTACHMENT 45

Case	Date Initiated	Manner Reported	Synopsis	Results of Inquiry
1	6/3/1996 (1996-OIA-966-089)	Pharmaceutical company reported information which led to the inquiry	OIA's review determined that an FDA employee had failed to recuse himself from an FDA Advisory Committee Meeting held on 30 April 1996 after a former colleague and friend had provided information to the committee against the position of the pharmaceutical company.	A review of the facts of the inquiry by HHS Office of Inspector General (OIG) it was determined there was insufficient evidence to support a criminal prosecution.
2	6/11/1996 (1996-OIA-974-094)	Anonymous HHS OIG Hotline complaint	The complaint that a Commissioned Corps Officer had received gifts from an FDA regulated corporation was unfounded. It was determined that the Division of Orphan Products (DOP), CDER, received a copy of a Physician's Desk Reference marked "for organizational library use" from a pharmaceutical company. This item was accepted by a Commissioned Corps Officer for DOP and placed within the DOP reference library.	The inquiry determined the allegations presented within the HHS OIG Hotline complaint were unsubstantiated and in that no violation of standards of conduct occurred.
3	6/10/1996 (1996-OIA-970-095)	Anonymous HHS OIG Hotline complaint	Investigation failed to substantiate the allegation that the FDA Employee had been engaging in placing sports bets using government telephones.	Complaint was unsubstantiated and no action was taken.
4	7/19/1996 (1996-OIA-970-110)	Anonymous Letter to HHS OIG resulted in inquiry	Investigation disclosed the allegation that an FDA employee had "received payments unrelated to any private business he is associated with" was unfounded. All information indicates that the letter had been authored by the subject of a criminal investigation that the FDA employee was to testify as a witness in.	Complaint was unsubstantiated and no action was taken.
5	8/14/1996 (1996-OIA-971-117)	Report from CBER resulted in inquiry	Allegation that FDA employee had worked on the development of a regulated product during the course of his FDA duties and then resigned to go to work for a commercial manufacturer of the product was determined to be unsubstantiated. Investigation did determine that the former FDA employee had called previous co-workers (other FDA employees) in an attempt to determine if a commercial product was going to be FDA approved.	Insufficient evidence to support criminal prosecution.

Case	Date Initiated	Manner Reported	Synopsis	Results of Inquiry
6	9/30/1996 (1996-OIA-966-126)	Inquiry initiated as a result of letter from Private Attorney	Former employee of contact lens manufacturer suing them for employee/labor issues requested FDA inspection of manufacturer anonymously. Consumer Safety Officer (CSO) who conducted inspection with no observations was hired by the manufacturer within six months of inspection. Inquiry failed to establish any connection between the two issues. The CSO routinely conducted inspections of the plant due to expertise in the area and sought employment with the manufacturer after the inspection as he was informed of a medical disqualification for career federal service.	No information developed to substantiate criminal prosecution.
7	10/15/1996 (1997-OIA-966-008)	Initiated as a result of Congressional complaint originating from Medical Device Manufacturer	Manufacturer of non-invasive glucose measuring instrument reported that four members of an FDA Advisory Council had conflicts of interest (COI) resulting in them voting not to recommend FDA approval of their product. The inquiry disclosed that there was nothing to substantiate a COI on the part of three of the individuals (FDA Employees). In regards to the fourth individual, he was an invited, non-voting member of the council who provided adverse opinions validated by his expertise in the field.	No information developed to substantiate criminal prosecution.
8	11/5/1996 (1997-OIA-966-010).	Initiated as a result of complaint from Medical Device Manufacturer	Investigation surrounded the post-employment of the former FDA Chief Counsel. The complaint was that the former FDA employee was in violation of 18 US Code, Section 207 when he accepted employment and provided legal guidance to a competitor of device manufacturer. An extensive review of the case facts by the US Attorney's Office, disclosed the facts did not meet the criminal elements for a prosecution under the above statute.	US Attorney declined prosecution.
9	12/3/1996 (1997-OIA-966-018)	Initiated as a result of a complaint from a Pharmaceutical company.	Pharmaceutical company reported a former FDA Product reviewer was involved in the solicitation of research work from a firm involving a product he had reviewed in an official capacity while employed by the FDA. The US Attorney's Office declined prosecution of 18 US Code, Section 208, as the timing of the solicitation was after he had concluded his employment with the FDA.	US Attorney declined prosecution

Case	Date Initiated	Manner Reported	Synopsis	Results of Inquiry
10	1/15/1997 (1997-OIA-966-034)	Initiated as a result of information received from CDER	An FDA Research Chemist conducting primary FDA reviews for generic drugs submitted by a pharmaceutical company terminated his employment with the FDA and was immediately employed by the pharmaceutical company producing the products he was previously conducting FDA research on. He then attempted to utilize his friendships and professional relationships within FDA to expedite a favorable review of the same generic drug he had completed research on while employed by the FDA. US Attorney agreed to prosecute under 18 US Code 207.	Pursuant to a settlement agreement between the former FDA employee and the US Attorney's Office, the former FDA employee was required to pay a civil fine of $15,000.00
11	11/20/1997 (1998-OIA-966-013)	Initiated as a result of information received from FDA Division of Science and Technology	Allegation that FDA employee of the FDA Division of Science and Technology violated 5 CFR 2635 (Standard of Conduct for Employees of Executive Branch) by seeking employment with a manufacturer of infant formula that conflicted with government duties. In addition, after termination of FDA employment, the former employee may have provided this manufacturer with information in violation of the FD&C Act.	Coordination was made with the Public Integrity Section, DOJ and the US Attorney's Office. The US Attorney's Office declined prosecution of the former employee.
12	12/29/1997 (1998-OIA-966-014)	Referral from FDA Office of Facilities, Acquisitions and Central Services	FDA employee was working on a National Cancer Institute (NCI) contract to set up an adverse reporting system similar to one utilized by FDA. Employee subsequently resigned and went to work for the contractor as the Director of Healthcare Systems for Commercial Applications. Allegations of Conflict of Interest or Standards of Conduct violations were unsubstantiated due to the employee's lack of involvement with contract negotiations.	Allegations were unsubstantiated.
13	5/22/1998 (1998-OIA-966-047)	Initiated based on information from CDRH	CDRH reported a potential violation of 18 US Code, Section 208 involving a voting member (FDA consultant) to an FDA Medical Devices Advisory Committee involved in the approval of a gas insufflator device (OB/GYN Endoscopy device). The FDA consultant failed to report financial holdings in a medical device manufacturer. The inquiry disclosed the company the consultant had invested in was not on the list of competing corporations.	Allegations were unsubstantiated.

Case	Date Initiated	Manner Reported	Synopsis	Results of Inquiry
14	9/22/1998 (1998-OIA-966-082)	This investigation originated in the Office of Internal Affairs (Confidential Source)	Information was developed during another OIA investigation which indicated that an FDA employee had business activities which were not approved as outside activity. Although this was determined to be true, the outside activity had no bearing on his FDA position. During the course of the inquiry it was determined that the FDA employee had also changed his rating of a company bidding on an FDA contract due to friendship.	The FDA employee was counseled by his supervisor. No additional action was taken.
15	12/1/1998 (1999-OIA-966-015)	Initiated based on information received from an FDA Compliance Officer	Allegation that the FDA Regional Food and Drug Director (RFDD) was planning to move an FDA District Office into a building which was owned by a personal friend. Investigation disclosed that while he had considered moving the District Office into a building that had been recommended by a friend who was also a federal employee, he did not know the owner of the building and was using the friend's recommendation due to space available, location and other factors. Allegation was unsubstantiated.	Allegations were unsubstantiated.
16	12/12/1998 (1999-OIA-966-020)	Initiated based on information received from FDA Division of Chemistry	Director, FDA Division of Chemistry reported a former FDA employee may have represented a Pharmaceutical company on a matter he was personally and substantially involved in while employed by FDA. Investigation disclosed the reporter was basing the complaint on the former FDA employee (while still with the FDA) having been present and providing guidance to an FDA official during a conference call regarding the company. Further inquires disclosed the questions were general in nature and the identity of the company involved was never disclosed during the call.	Allegations were unsubstantiated.

Case	Date Initiated	Manner Reported	Synopsis	Results of Inquiry
17	8/6/1999 (1999-OIA-966-096)	Initiated based on information received the FDA Cancer Diagnostic Program, National Cancer Institute (NCI)	FDA Employee involved in the approval of grants for NCI received letter on official letterhead from Commissioned Corps officer who was acting as Chief, FDA Division of Cell and Gene Therapies questioning an opinion rendered by the employee and questioning his decision not to approve a grant to an outside party. Investigation could not determine any relationship between the Commissioned Corps Officer and the grant requestor and the officer indicated it was his personal opinion that he should not have put on official letterhead.	As there were no indications the Commissioned Corps officer was engaged in this activity for personal benefit, no action was taken.
18	9/10/1999 (1999-OIA-966-0104)	Initiated based on Congressional inquiry	Allegation was that a FDA Special Government Employee (SGE) participating in a FDA medical device advisory panel had a conflict of interest with a device manufacturer as there was a patent dispute between the manufacturer and the SGE's primary employer (a university). Investigation disclosed that the SGE has exhaustively documented his financial relationship with his primary employer prior to being appointed to the advisory panel.	Allegations were unsubstantiated.
19	10/7/1999 (1999-OIA-966-107)	Initiated based on information received from the FDA Office of Public Affairs	A Philadelphia newspaper published an article indicating that while serving as an FDA official, a medical doctor assisted a business partner in the promotion of a weight-loss drug. The article further indicated that the medical doctor urged the Florida state medical board not to ban the drug after patient complaints. Investigation disclosed the medical doctor had no financial interest in the weight loss drug, but he admitted to providing some patients with referrals to the clinic marketing the drug after he had advised the patients of potential side effects.	As there were no indications the FDA employee engaged in this activity for personal benefit, no action was taken by FDA Management.
20	12/29/1999 (2000-OIA-966-024	This investigation originated in the Office of Internal Affairs (Confidential Source)	FDA Employee applied for employment with private industry, a Pharmaceutical company. During the time he applied for the job and was eventually rejected, he failed to recuse himself from matters between CDER and the Pharmaceutical company. Investigation disclosed the resume was submitted through a "headhunter" company and the FDA employee was never considered for the position by the company and notified his supervisors of this information.	Insufficient evidence to support action.

Case	Date Initiated	Manner Reported	Synopsis	Results of Inquiry
21	2/25/2000 (2000-OIA-966-040)	Initiated based on information from an FDA employee	FDA Special Government Employee (SGE) failed to list ownership of 100 shares of the company stock which is traded on the NYSE. The company, whose products are regulated by the FDA, was a leader in the development of Excimer Ophthalmic Refractive Surgical Systems (clear violation of FDA ethics regulations). The SGE was on an FDA Panel in which the company was at issue and would clearly be a conflict of interest. SGE claimed no knowledge of stock purchase, but that it had been made by her spouse	US Attorney declined prosecution. Subject's spouse sold stock at a net loss of $4,075.00.
22	4/17/2000 (2000-OIA-966-049)	Initiated based on information provided by President of a pharmaceutical company	President of pharmaceutical company reported that an FDA employee was a silent partner in a dietary supplement company. Subject had previously sought approval for such activity and it was denied as it is clearly a violation of FDA Ethics policy. Further, the FDA Employee appeared in a video which promoted a dietary supplement for the company.	Case was presented to the US Attorney's Office which declined prosecution. The FDA Employee subsequently received a verbal admonishment from his supervisor.
23	5/17/2000 (2000-OIA-966-059)	Initiated based on information received from CDER.	FDA Special Government Employee failed to disclose the fact that he was a consultant for a pharmaceutical company when he completed his conflict of interest form. The FDA employee provided explanatory answers for failing to disclose his association with the pharmaceutical company.	FDA management determined no administrative action would be taken against this employee.
24	1/18/2001 (2001-OIA-966-015	Initiated as a result of information received from FDA ORA Training Division.	FDA employee was allegedly approached, offered and accepted a position with a government contractor regarding a project the employee was involved with. Investigation disclosed that funds for the contract were allocated well before the FDA employee was offered the position with the government contractor. Further, the FDA Employee had performed very little work associated with the contract prior to accepting the position.	Complaint was unsubstantiated and no action was taken.

Case	Date Initiated	Manner Reported	Synopsis	Results of Inquiry
25	3/2/2001 (2001-OIA-966-033)	Initiated as a result information received from the Institute of Humane Gene Therapy (IHGT), University of PA	FDA Employee created a Conflict of Interest when he applied for a position at the University of PA (IHGT) while on the review team for a board making determination of federal grants. Investigation established the fact that the FDA Employee had applied for a position at IHGT while on the review team, but an extensive review of case facts by the US Attorney's Office disclosed the circumstances did not meet the criminal elements for prosecution	US Attorney declined prosecution. FDA Employee received a verbal reprimand from respective FDA Chain of Command.
26	2/8/2001 (2001-OIA-966-034)	Initiated as a result of information received from CDRH	FDA Employee created a Conflict of Interest by maintaining e-mail contact with a former employer, a medical device company in the Netherlands. Investigation verified the e-mail contact with device manufacturer; however, no critical or sensitive information was compromised or disclosed by the FDA Employee.	Insufficient evidence to support criminal prosecution. FDA Employee received verbal counseling regarding the appearance of a conflict of interest.
27	2/14/2001 (2001-OIA-966-038)	Initiated based on information received from the FDA Office of Ethics and Integrity Staff.	FDA employee in his annual financial disclosure form listed pharmaceutical company stock owned by his spouse, another FDA employee. A letter from the spouse to the FDA indicates her stock may pose a conflict of interest for her husband. Spouse also claims she did not inform her husband of ownership of stock to avoid a conflict of interest.	It was determined that a conflict of interest did not exist. However, both employees divested of the possible conflicting stock as a result of this investigation to avoid the appearance of a conflict.
28	6/26/2001 (2001-OIA-966-041)	Initiated based on a referral from the FDA Office of Ethics and Integrity Staff	A medical doctor who was a Special Government Employee (SGE) revealed that he privately was participating in co-operative trials of a cancer drug. This physician had previously sat on advisory panels at the FDA for the same drug, in violation of FDA Ethics Policy. Subject failed to report this fact on his annual FDA Ethics Questionnaire. Subject did not receive any monetary benefit from the study.	This was a scientific conflict and not a violation of 18 US Code, Section 208. Subject was verbally counseled by his supervisor.

Case	Date Initiated	Manner Reported	Synopsis	Results of Inquiry
29	8/27/2001 (2001-OIA-966-099)	Initiated based on information received from the FDA Office of Ethics and Integrity Staff.	FDA Special Government Employee failed to disclose a financial interest, consulting arrangement with a pharmaceutical company. Employee participated in two Obstetrics and Gynecology Devices Panel meetings in which subsidiaries of the pharmaceutical company were at issue. The nondisclosure of the financial interest and subsequent participation appeared to be in violation of the conflict of interest statute, 18 US. Code, Section 208. Investigation determined the failure to disclose the financial interest was inadvertent and, that had the employee revealed his financial interest, a waiver would have been granted due to the modest amount of the financial interest and the employee's expertise	As it appears the failure to disclose was inadvertent, no action was taken by FDA Management.
30	2/25/2002 (2002-OIA-966-048)	Initiated based on information from the FDA Ethics and Integrity Staff	FDA Employee was asking detailed questions about the process of proprietary name reviews for pharmaceuticals to include a specific drug name that was rejected. It was then revealed that the employee was retiring from the FDA and was to be employed by the company that had submitted the rejected name. Facts of the case were presented to the US Attorney's Office and prosecution was declined	No action was taken since prosecution was declined and the employee was retiring from the FDA.
31	11/07/2002 (2003-OIA-966-012)	Case Initiated as a result of complaint from FDA Employee	FDA Employee made allegations that a senior Commissioned Corps Officer (CCO) was incompetent, utilized government funds for personal ventures and misused the 348 Travel (travel in kind) program to the CCO's advantage. Investigation disclosed the FDA Employee making the complaint had made numerous unfounded allegations concerning this CCO and other FDA employees in the past. The allegations of incompetence, utilizing government funds for personal use and misusing the 348 travel program were also determined to be unsubstantiated.	Complaint was unsubstantiated and no action was taken.

Case	Date Initiated	Manner Reported	Synopsis	Results of Inquiry
32	8/4/2003 (2003-OIA-966-091)	Initiated as a result of information received from the an FDA District Office.	Subsequent to the FDA inspection of a medical clinic, the FDA District Office referred the matter as a possible conflict of interest. An FDA Employee reported that one of the Consumer Safety Officers (CSO) involved in the inspection of the clinic may have been involved in an inappropriate relationship with one of the employees at the clinic. The FDA employee stated that during the audit an employee from the clinic entered a file room and kissed the CSO.	The US Attorney opined there was insufficient evidence to support prosecution. The inappropriate relationship was referred to FDA leadership as a management issue.
33	9/1/2004 (2004-OIA-966-095)	Initiated as a result of a citizen complaint	The complainant alleged that the former FDA employee who retired from FDA in September 2004 had made pre and post employment intercessions for a pharmaceutical company. Investigation determined that the allegations presented by the complainant could not be substantiated.	Allegations could not be substantiated.
34	10/5/2004 (2005-OIA-966-002)	Initiated as a result of information received from FDA employee	The complainant alleged that the former FDA employee, currently working for a NY public relations company, requested his former office contact a pharmaceutical company concerning consumer advertising issues. The investigation determined that the allegations presented by the complainant could not be substantiated.	A US Attorney's Office and DOJ Public Integrity Section review determined there was insufficient evidence to support a violation.
35	11/24/2004 (2005-OIA-966-007)	Initiated based on information from the Center for Veterinary Medicine (CVM) based on a report from a pharmaceutical company	FDA Employee involved in review of safety and efficacy of a drug. Officials from the pharmaceutical company making the product presented materials to FDA officials that appeared to show the FDA employee was selling competitors drugs via a web based pharmacy, when in fact it was determined to be a "friends and family" type business. Subject did not have approval from FDA Ethics Branch to operate the web based business.	Case was presented to the US Attorney's Office and prosecution was declined. No action was taken against the FDA employee.
36	1/25/2005 (2005-OIA-966-020)	Case was initiated based on a request for assistance from HHS OIG	This case was an HHS-OIG investigation. FDA OIA assistance was requested because the subject was a current FDA employee. Case involved a former NIH employee who had accepted $5,000 from a company for the rights of first refusal for a patent she developed while working at NIH, in violation of Presidential Executive Order 10096.	Prosecution was declined by the U S Attorney's Office.

Case	Date Initiated	Manner Reported	Synopsis	Results of Inquiry
37	2/16/2006 (2006-OIA-966-045)	Initiated based on information received from the FDA Detroit District Office.	It was alleged that two FDA Employees from the Indianapolis Resident Post had a conflict of interest by participating in an inspection at a pharmaceutical plant while they were in active negotiations for employment with the same company. Investigation determined that one employee had accepted employment with the company, but the job solicitation occurred through a "headhunter" after the completion of the inspection. The second employee had not been offered a position with the company	An ethics review determined there was no violation of 18 US Code, Section 208 or ethics regulation.

** In addition to those cases listed above, there are three open investigation involving allegations of conflict of interest. Of these, two were internal referrals (one from an FDA District Office, one from the FDA Ethics Office) and the third was initiated as a result of a phone call from a private citizen.

ATTACHMENT 46

United States Senate

COMMITTEE ON FINANCE
WASHINGTON, DC 20510–6200

November 30, 2005

Via Electronic Transmission
Original via USPS Mail

Dr. Andrew C. von Eschenbach
Acting Commissioner
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Acting Commissioner von Eschenbach:

As a senior member of the United States Senate and as Chairman of the Committee on Finance (Committee), it is my duty under the Constitution to conduct oversight into the actions of executive branch agencies. As part of the Committee's ongoing review of the Food and Drug Administration (FDA) and events surrounding the investigation of Dr. Victoria Hampshire, V.M.D., I write today seeking a clarification from the FDA regarding facts FDA released to the press related to this matter.

It has come to my attention that on November 18, a spokesperson for the FDA provided information to a reporter from Reuters regarding the FDA's investigation of Dr. Victoria Hampshire that was factually inaccurate. Specifically, the article quoted the FDA spokesperson stating that "the [FDA] investigation was conducted with Dr. Hampshire's knowledge." Further, the FDA spokesperson went on to add that the FDA investigation of Dr. Hampshire was not a criminal investigation. Information that was obtained by Committee staff through a review of documents and interviews conducted with FDA personnel supports the position that these two statements made by the FDA spokesperson were factually inaccurate and portrayed in a light other than in the way they occurred.

Interviews conducted by Committee staff with Special Agents from the FDA's Office of Internal Affairs, of the Office of Criminal Investigation revealed, among other things, that the FDA internal investigation into Dr. Hampshire was in fact a criminal investigation and that Dr. Hampshire had no knowledge of the internal FDA criminal investigation until it was nearly completed. Documents and emails obtained by the Committee further support both of these facts, and show that the FDA was, at all times, aware of both of these facts. Further, Committee staff has obtained emails that show FDA officials were aware of factual inaccuracies in their November 18 press release.

For example, in an email dated November 18, 2005 Mr. Mark Cohen, the attorney for Dr. Hampshire, sent an email to the FDA Office of Communications stating:

"[T]he press release that the FDA plans to release tonight is inaccurate in one regard: It uses the language that the FDA investigation of her [Dr. Hampshire] was conducted 'With your knowledge…' In fact, Dr. Hampshire was not aware at the time that she was being investigated. We'd ask that you correct this in the press release."

The current inquiry into events surrounding the investigation of Dr. Hampshire remains open and the Committee is continuing to examine various aspects of this matter. While the recent information presented to the media by the FDA did not directly harm the ongoing inquiry, the potential damage that incorrect and misleading statements could cause remains a reality. I strongly encourage the FDA to examine the attached information and correct any factual irregularities that it presented to the media related to the November 18, 2005 article by Reuters. Please inform me immediately when this is done and in the event a decision is made not to correct these factual irregularities, please explain why FDA decided not to do so.

Thank you in advance for your cooperation on this matter. Should you or any of your staff have any questions regarding this matter or the documents in question, please contact Emilia DiSanto or Nick Podsiadly of my Committee staff at (202) 224-4515.

Sincerely,

Charles E. Grassley
United States Senator

Attachment

ATTACHMENT 47

Fort Dodge Animal Health
Division of Wyeth
9401 Indian Creek Parkway
Suite 1500
Overland Park, KS 66210

Steve Connell, DVM
Director
Professional Services
(800) 533-8536

July 22, 2002

Dear Doctor:

Thank you for purchasing *ProHeart 6* (moxidectin), Fort Dodge Animal Health's innovative product for six-month protection against heartworm infection in dogs. The purpose of this letter is to provide you with some new information regarding a recently approved label indication for *ProHeart 6,* as well as a review of the adverse events that have been reported for the product during its introduction into the marketplace. This update on the performance of *ProHeart 6* reflects our desire to share information that has been learned about the product after its first year on the market.

ProHeart 6 was launched in June 2001 with an indication to prevent canine heartworm disease caused by *Dirofilaria immitis* for six months, and to treat existing larval and adult stages of the canine hookworm, *Acylostoma caninum.* As a result of ongoing research on the product, the Center for Veterinary Medicine (CVM) recently approved an additional label indication for *ProHeart 6,* treatment of existing larval and adult stages of canine hookworm, *Uncinaria stenocephala.* The addition of *U. stenocephala* to the *ProHeart 6* label broadens the protection provided against canine hookworm infection, and results in a product that more closely meets the needs of practicing veterinarians.

Along with the new indication, a second label change will appear in the "Adverse Reactions" section of the product labeling, and is based on the reporting patterns received from the field. With over six million doses of *ProHeart 6* (moxidectin) sold during the first year, we have seen a number of reported reactions that were not seen in pre-approval clinical studies. This is typical in cases of a new product after introduction to a wide population base. Through our work with CVM, a new label statement has been approved for *ProHeart 6* describing our post-approval experience. The new statement being added is as follows:

Post-Approval Experience: although not all adverse reactions are reported, the following reactions are based on voluntary post-approval drug experience reporting: anaphylaxis/toid reactions, depression/lethargy, urticaria, and head/facial edema. As with anaphylaxis/toid reactions resulting from the use of other injectable products, standard therapeutic intervention should be initiated immediately.

Since introduction, we have received and tracked reports from practicing veterinarians regarding adverse events subsequent to the clinical use of *Proheart 6.* A review of these reports is presented below and includes events observed when *ProHeart 6* was administered alone, as well

as those observed when given with concurrent medications. The numbers presented are unfiltered, as reported to CVM, which include observations subsequently determined to be unrelated to product administration.

During the first twelve months of product use, 105 reports of site reactions post administration (.0016% of doses sold into veterinary clinics) have been received. These events are predominantly swelling, pain, and/or pruritos that are observed post administration. The vast majority are self-limiting in nature, though selected cases have been treated with anti-inflammatories, and in some cases, antibiotics.

A total of 946 reports of allergic responses post administration (.015%) have been received. As with vaccines, this category represents the most frequently reported event. Most of these reactions are mild and have responded to standard medical intervention. Some, however, have been more severe, including a small percentage of anaphylaxis cases. The most frequently reported effects have been vomiting and diarrhea, followed by angioedema and/or facial swelling, urticaria and gastrointestinal symptoms. Other less common events include ataxia, weakness, dyspnea, pale mucous membranes, lethargy and fever.

A total of 685 reports of illness post administration (.011%) have also been received. This category encompasses a wide variety of reports that are received in a broad timeframe (from one day to several months) post administration. There is overlap with the allergic events where both allergy and additional symptoms were recorded. The most frequently reported signs have been vomiting and diarrhea at variable time frames post administration, seizures or other neurological signs and lethargy. Other rare, but more serious reports, include erythema multiforme in 3 cases and autoimmune hemolytic anemia in a low number of patients, most of whom had received vaccines concurrently.

No common predisposing factors have been identified at this time. In rare situations, death has been associated with some of the adverse reactions listed above. While there reactions appear to be idiosyncratic, we want to bring these to your attention so that you may take appropriate measures in the event you encounter one. In the case of allergic reactions, prompt therapy using standard medical intervention (e.g. antihistamine, corticosteroids and fluids as needed; epinephrine as deemed appropriate on an individual case basis) has been found to be curative in most instances.

As is the case when prescribing any medication, careful examination of the dog prior to administration, consideration of appropriate laboratory tests in dogs that may have chronic conditions, and advice to the owner to watch for signs of drug intolerance is good medical practice. If a drug reaction or intolerance is suspected, examine the patient, provide the necessary supportive therapy, and contact Fort Dodge Animal Health Professional Services veterinarians at 1-800-533-8536.

As a manufacturer of novel innovative products, we feel it is important to provide timely information regarding label changes and current information on post-approval experiences. Millions of doses of *ProHeart 6* (moxidectin) have been used safely and effectively during its first year in the market, and we trust that this has been your experience as well. We will continue to provide you with any pertinent information regarding *ProHeart 6.*

Thank you for your attention regarding these important issues. You are encouraged to contact one of our Professional Services veterinarians at the number listed above if you have any additional questions or concerns.

Sincerely,

Stephen A. Connell,
DVM Director,
Professional Services
Fort Dodge Animal Health

ProHeart 6 *is generally well tolerated. Use with caution in sick, debilitated, or underweight animals. A small percentage of dogs showed mild, transient swelling or itching at the injection site. While rare, digestive, neurological or hypersensitivity reactions may occur. Read the attached package insert for more information. To obtain additional information including a copy of the product labeling, visit the website at www.proheart6dvm.com or call 1-800-685-5656.*

ATTACHMENT 48

Fort Dodge Animal Health
Division of Wyeth
9401 Indian Creek Parkway
Overland Park, KS 66210

Stephen A. Connell
Vice President
Professional and Technical Services
800-533-8536

June 19, 2003

Dear Doctor:

This letter is to provide another update of our field experiences with ProHeart® 6 (moxidectin) as we pass the two year anniversary of its launch, and some label additions being made to reflect some of these experiences, as noted below. We trust that this information will be useful and encourage you to call our Professional Services department if you have any additional questions after reviewing this material.

There are two additions to the ProHeart 6 label that have either been made, or are in the process of being made. The first was the label change regarding use of ProHeart 6 in heartworm positive dogs. Briefly, the changes were made in response to a low number of heartworm-positive dogs that experienced coughing or cardiopulmonary signs after receiving ProHeart 6. The pre-approval clinical studies did not identify any such reactions prior to release, and many heartworm positive dogs have received ProHeart 6 without side effects. However, based on reports received on a low number of heartworm positive dogs, Fort Dodge, in conjunction with the Center for Veterinary Medicine, made the following changes:

Under the heading "Post Approval Experience," the following statement was added:

"Cardiopulmonary signs such as coughing and dyspnea may occur in heartworm-positive dogs treated with ProHeart 6."

Additional labeling changes made under the "Precautions" section of the package insert and printed cartons in conjunction with this statement included:

1. Removal of the statement "At the discretion of the veterinarian" before the sentence "Infected dogs should be treated to remove adult heartworms."

2. The following statement was deleted "No adverse reactions were observed in dogs with patent heartworm infections when ProHeart 6 was administered at three times the labeled dose. Higher doses were not tested." (A similar statement was already present in the Animal Safety section, and this statement was left unchanged.)

The second label change is the recent decision to add a statement regarding the rare occurrence of death in a low number of dogs treated with ProHeart 6. Death has been reported in approximately 0.0025 percent of the doses sold into veterinary clinics. Some of the reports are associated with severe allergic events, while others appear to be multifactorial in nature. Some are linked to factors not associated with product use. We continue to investigate all reports as fully as possible. If and when further information becomes available that has clinical implications on product use, we will advise the veterinary community accordingly.

With regard to the label change, the following new statement, "and rare reports of death" has been added to the "Post-Approval Experience" section under the heading "ADVERSE REACTIONS". The full section "Post Approval Experience" section now reads:

Post-Approval Experience: Although not all adverse events are reported, the following reactions are based on voluntary post-approval drug experience reporting: anaphylaxis/toid reactions, depression/lethargy, urticaria, head/facial edema, and rare reports of death. Anaphylactic and anaphylactoid reactions should be treated immediately with the same measures used to treat hypersensitivity reactions to vaccines and other injectable products. Cardiopulmonary signs such as coughing and dyspnea may occur in heartworm-positive dogs treated with ProHeart 6.

This revised "Post-Approval Experience" statement will replace the current wording, which appears in the ProHeart 6 package insert and on all approved ProHeart 6 printed outer boxes.

In order to help educate your clients on both the benefits and potential side effects associated with ProHeart® 6 (moxidectin), Fort Dodge Animal Health has prepared a client information sheet which contains questions and answers about use of the product, and includes the product insert on the reverse side. An example copy is attached for your reference. Additional quantities will be available to you through your Fort Dodge representative and the sheet will soon be posted on our websites for both veterinarians and clients to download and print.

Thank you for your attention to this important information. We feel it is essential to provide you with timely updates on the use of this product. Millions of doses of ProHeart 6 continue to be used safely, and we trust that this reflects your on-going experience, as well. We continue our monitoring activities and will provide any pertinent updates on ProHeart 6 as they become available. Please feel free to contact one of our Professional Services veterinarians at the number listed above if you have additional questions or concerns regarding any of this information.

Sincerely,

Stephen A. Connell, DVM
Vice President,
Professional and Technical Services

ATTACHMENT 49

Questions and Answers regarding the FDA Recall of ProHeart®6

From a Pet Owners Perspective:

Q: Why did CVM ask Fort Dodge Animal Health to recall ProHeart®6?

A: Since the product was approved in June 2001, we have received reports of nearly 5,500 serious adverse drug reactions attributed to ProHeart® 6. After evaluating these reports, the Center for Veterinary Medicine (CVM) determined that at least 1,900 of those were unrelated to the concurrent administration of other drugs or vaccines. The clinical signs contained in those reports were possibly or probably associated with the ProHeart®6 injection. Many of the adverse events were severe, including more than 600 reports of death.

The actual incidence of adverse events is likely to be even higher than reported, because studies show that only a fraction of actual adverse reactions are reported. Based on its experience with adverse drug reactions attributed to animal drugs over the years, CVM considers the number and severity of those attributed to ProHeart®6 to be unacceptable, even when considering the number of doses of the drug that have been administered.

FDA's concern is based on voluntary self-reporting to FDA by veterinarians and owners whose dogs have suffered adverse drug experiences (ADEs) to ProHeart®6 (which contains the drug moxidectin) as well as the mandatory reporting of adverse events by the product's sponsor, Fort Dodge Animal Health (FDAH).

CVM has worked with Fort Dodge to investigate numerous adverse event reports to try to determine the cause of the problem. At FDA's request, the product sponsor has also made three revisions to the label to include post approval safety information including rare reports of death and a caution to practitioners that dogs should have a negative test for heartworm before administration of ProHeart®6. The firm has also added a Client Information Sheet and issued two "Dear Doctor" letters to advise veterinarians and pet owners of the risks associated with use of the product. Despite these label changes and educational efforts, FDA is still receiving an unacceptable number of reports of unexplained and severe adverse events.
Because the cause of the problems associated with ProHeart®6 have not been identified or remedied, and because veterinarians and dog owners have effective alternative heartworm products available to them, CVM believes that removing the product from the market is in the best interest of the dogs and their owners.
As of September 10, 2004, Fort Dodge submitted the more than 5,500 adverse event reports in compliance with federal regulations (21 CFR §514.80) that require sponsors to submit serious and unexpected adverse drug events within 15 working days of first receiving the information.

Q: Had CVM made Fort Dodge aware of the problem before asking for the product recall?

A: CVM has been working with Fort Dodge Animal Health to investigate the numerous adverse event reports to determine the cause of the problem. At FDA's request, the product sponsor has also made three revisions to the label to include post approval safety information including rare reports of death and a caution to practitioners that dogs should test negative for heartworms before administration of ProHeart®6. The firm has also added a Client Information Sheet, and issued two "Dear Doctor" letters to advise veterinarians and pet owners of the risks associated with use of the product. Discussions with Fort Dodge have been ongoing. CVM has requested that the firm continue to conduct research to determine the cause of related adverse reactions and develop a strategy to help prevent such problems in the future before the product is marketed again.

Q: What are Adverse Drug Experience reports? How does the system work?

A: Adverse Drug Experience (ADE) reports are voluntary descriptions of side effects that appear to be caused by a drug. Approximately 99% of the ADE reports are filed by veterinarians with the remaining 1% or so coming from consumers. Typically, the reports are filed with the drug sponsor, who is required to send them all to CVM for review and analysis.

Q: How are ADE reports analyzed?

A: CVM adverse drug experience reviewers, who are experienced veterinarians, use a standardized method to determine whether the side effects are caused by the drug. The multi-part system used by reviewers evaluates the following criteria: previous experience with the drug (the reviewers determine if the side effects have already been predicted), the timing of the reaction, whether the dog was overdosed, whether other disease factors are present, and what happened if the drug was withdrawn or reintroduced. The reports are given a causality score, and only the reports that show the possibility that side effects are associated with the use of the drug are considered when CVM is determining the safety of a product. Those reports that indicate only a remote likelihood that the drug caused the reaction are not considered when determining whether a drug is safe.

Q: Do you get ADE reports on other animal drugs?

A: Yes, in fact we typically receive many ADE reports following a drug's approval, and the Center's experts are constantly reviewing them to identify specific problems and determine the severity or frequency of problems. When problems are detected through this analysis, CVM begins working with the company to determine the cause and potential remedies. The remedies can include label or even dosage changes. In the case of ProHeart®6, the root cause of the severe side effects has not been found, and none of the steps the company has taken, including label changes, has reduced the problem.

Therefore, CVM requested that Fort Dodge Animal Health remove the product from the market to protect the health of the dogs.

Q: When will the product be allowed back on the market?

A: There is no way to predict that. FDA is requesting that the firm continue to conduct research to determine the cause of related adverse reactions and develop a strategy to help prevent such problems in the future before the product is marketed again. The FDA will convene an independent scientific advisory committee to thoroughly evaluate all available data.

Q: Has Fort Dodge cooperated with CVM in the review of this product?

A: Yes. As of September 10, 2004, Fort Dodge submitted the more than 5,500 adverse event reports in compliance with federal regulations (21 CFR §514.80) that require sponsors to submit serious and unexpected adverse drug events within 15 working days of first receiving the information. Fort Dodge has worked with CVM to make label revisions to include post approval safety information including rare reports of death and a caution to practitioners that dogs should have a negative test for heartworm before administration. The firm has also added a Client Information Sheet, and issued two "Dear Doctor" letters to advise veterinarians and pet owners of the risks associated with use of the product. Also, after consultations with CVM, the company agreed to recall the product.

Q: ProHeart®6 is used in other countries. Are they experiencing problems?

A: We have only sketchy data from other countries, so we cannot answer that with any certainty. We want to point out, though, that ProHeart®6 adverse reactions, while many times severe, occur in only a small percentage of treated animals. Whether other countries see reactions may depend on the number of doses given.

Q: What more can you tell us about the advisory committee that will review the product?

A: The Veterinary Medicine Advisory Committee is made up of various independent scientists who will be asked to evaluate data about the product. No other details about the committee or the meeting dates are available.

Q: My veterinarian just gave my dog a shot of ProHeart®6 before the recall. Why didn't he know that the product was dangerous?

A: Although we have had concerns about ProHeart®6 for several months, it remains an approved product. Therefore, your veterinarian was acting in a completely legal manner when he treated your dog. And neither CVM nor ProHeart®6's sponsor, Fort Dodge Animal Health, issued any statement saying that the drug was not safe prior to the voluntary recall.

The product has produced severe side effects in a limited number of dogs. So most dogs treated with it will not demonstrate any adverse reaction. Nonetheless, because the cause of the problems associated with ProHeart® 6 have not been identified or remedied, and because veterinarians and dog owners have effective alternative heartworm products available to them, CVM believes that removing the product from the market is in the best interest of the dogs and their owners.

The drug manufacturer, Fort Dodge Animal Health, has agreed to voluntarily recall the product.

Q: My dog seems to be having or has had a reaction to ProHeart®6. Should I file a report with you about that?

A: First, return to your veterinarian and ask him or her to file a report for you. If he or she won't, you can file a report by going to CVM's website (<A href="[ioID]1FB93986303A443E810AF23E7CBE7C4A) and go to the Adverse Drug Experience page where you will find a form to use in reporting to FDA. Or you can call 1-888-FDA-VETS to file your report.

Q: When will I hear back from CVM about my report?

A: You will not hear back from CVM. The reports are analyzed by experts at the Center, and the results are entered into a database. You can view data generated from the database on CVM's Website.

Q: My dog has received an injection. What side effects might occur from ProHeart®6, how soon will I see them and how long should I monitor my dog?

A: The side effects that are observable to dog owners that have been reported in association with ProHeart® 6 are anorexia (loss of appetite); lethargy; vomiting; neurologic signs, such as seizures, difficulty walking and reports of blindness; jaundice (a yellowish appearance); and bleeding disorders. Most of these observable clinical signs have occurred within one month of receiving the drug.

Q: If my dog does have an abnormality (adverse reaction), how should he be treated?

A: A thorough veterinary examination including a routine complete blood count and serum chemistry should reveal most problems. There is no specific antidote for the adverse effects of ProHeart®6. Supportive care according to the system and abnormality detected is indicated. Your veterinarian is the best source of treatment advice. Treatment will depend upon the organ system affected and the severity of the abnormality.

Q: My dog got sick or died after an injection. What should I do?

A: Have your veterinarian file an adverse drug experience report with the company or directly with the FDA.

From a Veterinarian's Perspective:

Q: I have had more problems with vaccines. I do not understand why ProHeart®6 is being singled out?

A: CVM does not regulate vaccines. The UDSA monitors adverse drug reactions in vaccines and it is a voluntary, not a mandatory manufacturer reporting process. Vaccines do not receive the same scrutiny as drugs. The testing requirements are different. A more appropriate comparison would be ProHeart®6 and other heartworm preventatives that go through a pre-approval process at FDA.

Q: Every drug has some side effect or reactions. Why is ProHeart®6 any different?

A: It is true that all drugs have some side effects. Many of the adverse drug experiences associated with ProHeart®6 involve serious, life-threatening adverse events, such as anaphylaxis, convulsions, hematopoetic disorders and heptopathies followed, in some instances, by death. CVM has also evaluated reports that include neurologic problems and, unusual cardiac signs. If the adverse drug events ended at transient anaphylaxis or other mild sign, CVM would not have requested FDAH to initiate a recall. Second, ProHeart®6 is a sustained release product which, if dosed according to the label, is never withdrawn from the system.

Q: Was the recall of ProHeart®6 the result of media hype and done at the spur of the moment?

A: No, CVM has evaluated the adverse drug events over the past several years, worked very hard at obtaining accurate follow up information, and all of this information has originated in veterinary hospitals and been reported through the manufacturer to FDA. CVM was concerned about this product before the media became aware of the concerns and had already required three label changes and informed the company that they were concerned about the liver and autoimmune signs and were watching those reports carefully. All of this occurred before March of 2003 when the media became aware them.

Q: I have not had any more problems with ProHeart®6 than other heartworm preventatives in my clinic. How do you explain this fact?

A: There are over 5000 reports of veterinarians who have had a problem with ProHeart®6.

Q: Why were veterinarians not consulted in the decision to remove this product from the market?

A: The decision to remove a product from the market is between FDA and the manufacturer. FDA made the recommendation based on veterinary reporting to the manufacturer in at least 5000 instances.

ATTACHMENT 50

Veterinary Medicine Advisory Committee Meeting
Food and Drug Administration
January 31, 2005, Doubletree Hotel, Rockville, MD
Issue: Voluntary Recall of ProHeart 6® (NADA 141-189)

Committee Members in attendance:
Susanne Aref, Ph.D., John J. McGlone Ph.D., Corrie Brown, DVM, Ph.D., Lisa Nolan, DVM, Ph.D., Gregory Jaffe , Mark G. Papich, DVM, Richard A. Sams, Ph.D[1]., Katrina L. Mealey, DVM, Ph.D., Arthur L. Craigmill, Ph.D. (Acting Chairperson)

Invited, Voting Consultants in attendance:
Charles L. Bennett, MD, Ph.D., M.P.P., Tom Nelson, DVM, Michael I. Luster, Ph.D., Michael R. Peterson, DVM, MPH, Dr.PH, M. Gatz Riddell, Jr., DVM, MS, Sam Groseclose, DVM, MPH, Lauren A. Trepanier, DVM, Ph.D.

Executive Secretary: Aleta Sindelar, R.N.

The meeting began at 8:00 AM EST with a presentation by Dr. Stephen Sundlof, Director of the Center for Veterinary Medicine (CVM), Dr. Sundlof introduced the committee and the invited consultants, and presented the issue before the committee for consideration.
The meeting continued with a presentation by Jennifer Gresock, Food and Drug Administration (FDA), covering the legal framework for reporting adverse drug events (ADEs). Dr. Margarita Brown, FDA/CVM, presented information about how ADEs are reported to and scored by the FDA. Drs. Lynn Post, FDA/CVM, and Margarita Brown presented information about the (ADE) reports which had been received by CVM about ProHeart 6®, the only injectable heartworm prevention product approved for dogs. The reports prompted discussions with Fort Dodge Animal Health (FDAH) and resulted in the voluntary recall of ProHeart 6® last year. Dr. Brown ended the CVM presentation by outlining CVM's view of the information provided by FDAH about ProHeart 6® adverse reactions.

The CVM presentation was followed by presentations by FDAH personnel and consultants. Dr. Rami Cobb, FDAH, introduced Dr. Larry Glickman, an epidemiologist from Purdue University who presented the results of a study done using data from Banfield, The Pet Hospital® databases, with reference to ProHeart 6® and compared it to two approved oral heartworm preventives. The summaries and interpretations by Dr. Glickman were based on data (The Banfield Data) that had not been submitted to the agency for review and response prior to the VMAC meeting. Dr. David Hustead, FDAH, also made a presentation of the FDAH position and interpretation of ADE reports submitted to FDAH.

After these presentations the VMAC committee and consultants began rounds of questions directed to both CVM and FDAH personnel and consultants. Most of the questions related to methodologies used in assessing the cases, how data were collected, pharmacokinetics of the microsphere formulation, and other factors which might affect the potential toxicity or allergenicity of the ProHeart 6® formulation.

After a break for lunch, the rounds of questions continued, and then at 1:00 PM the floor was opened for public comments. Dr. Craigmill, Acting VMAC Chairperson, read a statement about the public comments into the records, and each of the 15 registered speakers was allocated 5

[1] Dr. Sams participated in the discussions, but did not vote on the questions asked by CVM.

minutes time to make his/her presentation. Several speakers also chose to show pictures using the computer screen projector.

After completion of the public comments, the VMAC committee and consultants had additional questions for the CVM and FDAH personnel and consultants. At the conclusion of the questions, Dr. Craigmill read each CVM VMAC question posed to the committee and asked each voting member and consultant to register their opinion.

The first question posed to the committee was: ***Based on the presentations and information provided is ProHeart 6® safe for use in dogs? Yes or No***
(It should be noted that almost all of the responses to the first question were qualified with a concern that more information and data were needed to establish the safety or the risks associated with the use of ProHeart 6®.)
Dr. Aref: NO, however we need more data, it is very hard to answer.
Dr. Brown: YES, the Banfield data are pretty convincing.
Mr. Jaffe: NO, but we need real incidence rate information, continue the withdrawal for the time being.
Dr. Mealey: NO, there are safer alternatives; it is hard to determine if it is the drug or the carrier which is causing the anaphylactoid reactions.
Dr. McGlone: NO, but not enough data to do a proper risk-benefit analysis as the risks are very low.
Dr. Nolan: YES, Banfield data are compelling.
Dr. Papich: NO, but much more data needed to decide if it is really safe or not. Need to be more careful with prophylactic medications than therapeutic ones.
Dr. Bennett: YES, and though the reports are worrisome, we need more studies like the Banfield study to truly decide.
Dr. Luster: NO, since there are safer alternatives now, need risk-benefit analysis.
Dr. Groseclose: NO, we need more data however since quality data are lacking.
Dr. Nelson: YES, there are too many other possible causes of the reactions reported.
Dr. Peterson: YES, the Banfield data are not perfect but very good, and the real question should be how this product compares to other heartworm preventives.
Dr. Riddell: YES, we need to consider the risk-benefit perspective and owner compliance issue.
Dr. Trepanier: NO, even though the reactions are rare, really need a 30 day follow-up study to clarify this issue.
Dr. Craigmill: YES, there are certainly a lot of ADE reports, but the incidence rate is very important as are issues of acceptable risk in comparison to other products and disease.

Second Question: ***If there are remaining safety concerns with ProHeart 6®, what additional avenues of research could be explored to mitigate and/or prevent the adverse events?***
Suggestions from the panel and consultants include additional studies, both new prospective cohort and retrospective case-control studies; performance of a risk benefit analysis taking into account owner non-compliance when using oral heartworm preventives; additional clinical trials; additional pharmacokinetic trials to explore the effects of increased body temperature on release of the drug from the injection site; release of the Banfield data to the FDA for analysis; possible "black-box" labeling of the drug to emphasize the possible risks; development of more information about the drug's effects on different life stages of the parasite; meta-analysis of data collected from multiple studies or areas to increase the power of detecting and quantifying the adverse events in comparison to other heartworm preventives.

The meeting was adjourned at 5:15 PM EST

Respectfully submitted: Arthur L. Craigmill, Ph.D. Acting Chairperson, VMAC

ATTACHMENT 51

Nomination for US PHS Achievement Medal
CDR Victoria Hampshire

Accomplishment:

This achievement medal recognizes CDR Hampshire for noteworthy accomplishments and a sustained above average performance of duty in post marketing veterinary drug surveillance. CDR Hampshire has held the position of Adverse Drug Events Coordinator from November 2003 – May 2005. The position CDR Hampshire holds is located in the Division of Surveillance (DS), Office of Surveillance Compliance (OSC), Center for Veterinary Medicine (CVM), US Food and Drug Administration (FDA).

Background:

The Division of Surveillance has undergone extensive pressures over the last two fiscal years due to a rapidly growing number of new animal drug approvals and more recently, due to one drug that has also been associated with human injury. The number and severity of adverse events has nearly doubled the review time necessary to address safety issues; primarily because of the number of endectocides and non-steroidal anti-inflammatory agents developed for companion animals.

In particular, the contacts from consumers and special interest groups who have experienced adverse events in their pets that are suspected to be due to a recently recalled heartworm preventative has been a special hardship of the job. While the new drug approvals require intense surveillance over early post-marketing periods, consumers also require enough information to aid themselves and their veterinarians in safe prescribing and dosing practices.

CDR Hampshire was appointed to the position of Adverse Drug Events Coordinator as an addition to her primary job as a product manager. Her take charge approach, ease in speaking with pet owners and scientists, and her familiarity with the safety reviewer positions enabled her to rapidly become a recognized expert and leader of this office. CDR Hampshire's strong biomedical research and regulatory background, coupled with her experience in emergency medicine and critical care has enabled her to comprehensively and accurately evaluate legacy and new data related to the safety and efficacious use of marketed animal drugs, to take this information forward in a manner that permits the senior leaders in the Division, Office and Center to request label changers or even stiffer regulatory action. She has also helped devise ways to inform the public of risk information without breaching government/industry relations or confidentiality.

Intervention:

CDR Hampshire typically assesses the safety of 22 Tier One or Tier Two priority products each week. She has successfully identified five major product safety or efficacy issues in the first year and a half of her tenure. These are:

- Identification of hepatic enzyme elevation and renal elevation problems and their association with death in a new canine non-steroidal anti-inflammatory
- Identification of hepatic enzyme elevations in one canine anxiolytic drug
- Identification of efficacy problems in three canine heartworm preventatives
- Identification of major signals in a new sustained release canine heartworm product
- Identification of probable ineffectiveness in large animal topical endectocides

At the same time this was occurring, CDR Hampshire discovered significant discrepancies in canine heartworm lack of effect reporting and expended considerable efforts at ensuring that all product sponsors reported equally. Her efforts led to invitations to represent FDA at the American Heartworm Society at the American Veterinary Medical Association Annual Meeting in 2004, the publication of 3 manuscripts in peer-reviewed journals, invitations to speak, and one invited book chapter on the subject of adverse drug event reporting. She led a team of inspectors in one major facility inspection that resulted in the discovery of important withheld information, and also wrote a standard operating procedure for field personnel to more efficiently inspect pharmacovigilance programs at regulated facilities.

Lastly, CDR Hampshire was the stimulus for a revised electronic drug event reporting system which was challenging to navigate because it required a change in administrative culture from a historically custom contract, design-build approach to a modified commercially off the shelf system. This revised electronic drug event reporting system effort is saving the FDA several hundred thousand dollars over the next few years. At times it was so difficult to navigate the status quo in contracting of customized software; most individuals would have given up, but CDR Hampshire did not.

Outcome:

In summary, CDR Hampshire has performed at a level far beyond what was expected and well above the level of her peers and during a tumultuous series of regulatory events at the Center for Veterinary Medicine. She has exemplified qualities that the public relies on to protect the health of their animals and ultimately to maintain their confidence in the FDA so that they can trust that safe and effective drugs continue to be available for their farm and companion animals. We recommend approval of the PHS Achievement Medal for CDR Victoria Hampshire for her significant achievements in post marketing veterinary drug surveillance.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service

INDIVIDUAL HONOR AWARD NOMINATION RECORD
PART I

OFFICER'S NAME (Last)	(First)	(Middle)	ENTRY ON DUTY DATE
Hampshire	Victoria	Anna	10/21/2002
PHS RANK (O - 1 through O - 10)	PHS PROFESSIONAL CATEGORY		PHS SERIAL NO.
05	Veterinarian		55804
CURRENT ORGANIZATION		ORGANIZATIONAL TITLE OR POSITION	
DHHS/FDA/CVM/OSC/DS		Adverse Drug Events Coordinator	
PROPOSED AWARD		PERIOD COVERED (From) 11/2003 (To) 05/2005	
PHS Achievement Medal			

NOTE: *(Synopsis of specific achievement for which the individual is being nominated must be limited to 25 words.)*

CITED FOR Significant Achievement in Post Marketing Veterinary Drug Surveillance

The nominator certifies that the officer is deserving of the proposed award, and that the accompanying documentation accurately and completely reflects the relevant information. Additionally, the nominator certifies that the officer has not received nor is being nominated for another award for which the basis overlaps this nomination (except as specifically cited).

NOMINATOR (SIGNATURE)	NAME AND TITLE (TYPED)	DATE
Lynn O. Post	Lynn Post, DVM, Ph.D. ABVT, Director, DS	06/01/2005

ENDORSEMENTS:

SIGNATURES	NAME AND TITLE (TYPED)	AWARD ENDORSED (See Note below)	DATE
Supervisory / Line Authority			
Dan McChesney	Dan McChesney, Ph.D. Director, Office of Surveillance Compliance	AM	6/3/05
Linda Tollefson	Linda Tollefson, DVM, Deputy Director, CVM	AM	6/3/05
Operating Division (OPDIV) Awards Board Chairperson			
Linda J. Callahan	Linda Callahan, CC Personnel Contact, CVM	AM	6/23/05
Approving Authority			
	Steve Sundlof DVM, Ph.D. CVM Director	AM	6/27/05
OPDIV Awards Coordinator			
Amy F. Anderson	~~LCDR~~ Amy F. Anderson	AM	7/6/05

NOTE: Use abbreviation (i.e., DSM, MSM, OSM, CM, AM, CIT). If no award or a different award is endorsed, give reason in "comment" below. *(Use extra sheet if needed.)*

COMMENT

	DATE	ACTION	COMMENTS
CCAB		☐ Recommended ☐ Not Recommended	
SURGEON GENERAL	DATE	ACTION ☐ Approved ☐ Not Approved	COMMENTS

6F

ATTACHMENT 52

Vioxx Debate Echoed in Battle Over Dog Drugs

By Marc Kaufman
Washington Post Staff Writer
Friday, May 12, 2006; Page A01

The drug came on the market four years ago after being tested in a healthy, young population, although it was intended for use by the old and sick. The manufacturer aggressively advertised it and ultimately made claims deemed by regulators to be beyond what testing had established.

When reports of illness and death linked to the drug surfaced not long after it went on the market, the company was slow to report the problems to the Food and Drug Administration. The agency eventually did issue a reprimand and a formal warning letter, but two years later the drug is still being sold, and some consumers complain that too little is being done to warn pet owners of its dangers.

The medication is Deramaxx, and it's the center of another drug controversy. But this medication isn't for people. It's for dogs.

Enlarge This Photo

Kasi died shortly after taking ProHeart 6 heartworm medication. Owner Staci Walker sued Wyeth. (Www.dogsadversereactions.com)

An anti-inflammatory closely related to the human painkiller Vioxx, which was taken off the market in 2004 and is now the subject of thousands of lawsuits against Merck & Co., Deramaxx has helped relieve many canine aches and pains. But in an echo of the national debate over the dangerous side effects of some popular human drugs, Deramaxx has also proved at times to be deadly.

Before the early 1990s, most drugs given to pets were human medications that appeared to help animals as well. But with dogs in particular living longer and being treated increasingly as members of the family, the demand for better drugs has grown, along with the public's willingness to pay for them. Most companies that now develop and sell pet drugs are subsidiaries or divisions of the major brand-name drug companies, and they must seek FDA approval to market their products much as they do with drugs intended for people.

Deramaxx is not the only drug to run into trouble in the burgeoning world of animal medicine. The widely used ProHeart 6 heartworm treatment was the subject of controversy several years ago and was withdrawn from the market in 2004 following reports that healthy dogs were becoming sick and dying after getting a shot of the preventive medicine.

In both cases, the deadly side effects led to formal -- but by many accounts ineffective -- government and industry efforts to warn veterinarians and dog owners of the drugs' risks.

In 1999, 300 pet owners filed a lawsuit against Pfizer Inc., alleging that its early dog arthritis medicine Rimadyl had seriously harmed their pets. Pfizer settled in 2003, saying it had done nothing wrong but wanted to avoid costly litigation. Each plaintiff was given $1,000.

The ProHeart 6 case also led to allegations that its manufacturer, Wyeth, had sought to discredit the FDA official overseeing the investigation -- a pattern seen with FDA officials who questioned the safety of human drugs.

Victoria Hampshire, the agency official at the center of the ProHeart 6 controversy, was taken off the case and later became a whistle-blower. Her difficulties were documented on the Senate floor last winter by Sen. Charles E. Grassley (R-Iowa). Wyeth maintains that it simply gave the FDA potentially troubling information it found on a Web site about a possible conflict of interest involving Hampshire. The agency cleared her after an investigation, and ProHeart 6 remains off the market.

Hampshire says she became increasingly alarmed after receiving reports of hundreds of dogs dying soon after receiving the heartworm shots, just as more than 350 reports of deaths linked to Deramaxx have come into the FDA's Center for Veterinary Medicine. As with adverse reactions in people, the number of reported cases is generally believed to represent less than 10 percent of the true total.

Hampshire, who now works in a different FDA division, said she learned about many cases from distraught pet owners such as Demitry Herman, a manager with Lehigh Electric in Allentown, Pa.

CONTINUED 1 2 Next >

ATTACHMENT 53

DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of Inspector General

Washington, D.C. 20201

SEP 6 2007

TO: Andrew C. von Eschenbach
Commissioner
Food and Drug Administration

FROM: Daniel R. Levinson
Inspector General

SUBJECT: Memorandum of Understanding Between the Food and Drug Administration and the Office of Inspector General

A Memorandum of Understanding (MOU) between the Food and Drug Administration (FDA) and the Office of Inspector General (OIG) setting forth the roles and responsibilities of each office concerning internal investigations involving FDA employees was negotiated in 1998. For the reasons outlined below, OIG intends to withdraw from the MOU and assume responsibility for investigations of potential criminal misconduct by FDA employees.

First, it is important that there be consistency in the manner in which OIG handles internal investigations involving all departmental employees. OIG does not have an MOU authorizing shared investigative responsibility for criminal investigations of employee misconduct with any other Operating or Staff Division. This important area of OIG investigative responsibility should be handled uniformly throughout the Department, with primary investigative responsibility resting with OIG.

The return of this function to OIG is also consistent with the Inspector General Act of 1978, as well as Federal regulations at 45 CFR §§ 73.735-1301 and 1302 and Chapter 5-10 of the Department's "General Administration Manual," which require Department employees or supervisors to report nonfrivolous allegations of "criminal offenses" (including conflicts of interest) to OIG.

To ensure integrity in the process of conducting sensitive employee misconduct investigations and based on our experience operating under the MOU, this function is more appropriately placed in an investigative office with statutory independence. OIG can more appropriately handle sensitive internal employee misconduct inquiries because OIG investigators are entirely independent of the programs and officials being investigated.

OIG has a dedicated unit of investigators assigned to handle sensitive investigations of Department officials. This Special Investigations Unit (SIU), established in 2004, will independently investigate allegations concerning senior FDA officials and thereby eliminate

any conflict of interest—in fact or appearance—created when FDA Office of Internal Affairs (OIA) agents are asked to investigate allegations of misconduct against a supervisory official.

Since entering into the MOU in 1998, there have been difficulties in consistently applying its terms, both in the exchange of information and the assignment of cases. Although improved during the past year, these problems continue.

Increased congressional and media scrutiny regarding allegations of potential criminal violations of Federal conflict-of-interest statutes and regulations involving FDA and other officials in the Department has resulted in OIG's devoting increased attention and resources to ethics issues. As a result, OIG investigators and attorneys have developed significant expertise in handling these complex cases.

OIG wishes to terminate the MOU with the least disruption possible to FDA and to ongoing cases. We would like to work collaboratively with OIA to ensure a smooth transition and to minimize any adverse impact on OIA staff. In this regard, OIG and OIA can explore the possibility of detailing personnel for a defined time period to assist in coordinating the transfer of cases.

We look forward to working with you and your staff on this important endeavor.

Attachments:
Tab A: April 10, 2007, Memorandum to the Acting Deputy Secretary
Tab B: Memorandum of Understanding - FDA/OIG

ATTACHMENT 54

Outside Activity Process - Private Practice of Veterinarians

Effective July 20, 2005

This memorandum relates to and clarifies the private practice of veterinary medicine as an outside activity by veterinarians employed by the Center for Veterinary Medicine (CVM), Food and Drug Administration (FDA). The practice of veterinary medicine differs from the practice of human medicine by virtue of a greater reliance on the dispensing of drugs by the veterinarian. The difference, in itself, does not create an ethical issue sufficient to prevent CVM veterinarians from legally practicing veterinary medicine as an outside activity; however, certain methods of dispensing animal drugs may create either an actual or a perceived conflict of interest and are unacceptable as an outside activity.

Establishing a business devoted solely to dispensing animal drugs is outside the practice of veterinary medicine. Such a business is a pharmacy, not a veterinary practice. Outside of veterinary or human medicine, FDA employees should not receive monetary benefit from the sale of products which FDA is responsible for regulating (whether this is by owning stock or other interest in such businesses or owning and operating them outright is immaterial). CVM veterinarians, therefore, may not hold an interest in or privately own or operate a pharmacy, separate from veterinary practice as an acceptable outside activity.

Writing valid prescriptions to be filled by an independent pharmacy is entirely within the scope of veterinary practice. It is clearly acceptable as an outside activity for CVM employed veterinarians. However, while it is possible that having a working relationship with a pharmacy which results in the veterinarian receiving compensation from an "independent" pharmacy for prescriptions written and subsequently presented to the pharmacy might be considered an acceptable practice under various state veterinary practice acts, it is unacceptable for CVM-employed veterinarians.

The means by which prescriptions (or more likely, refills of prescriptions) are transmitted to a pharmacy by a CVM-employed veterinarian practicing as an outside activity are immaterial to CVM provided they are in compliance with state veterinary and pharmacy practice acts AND do not create the appearance of a pharmacy in which a veterinarian holds an interest operating independently of that veterinarian's practice of veterinary medicine. Thus, it is acceptable for a privately practicing CVM-employed veterinarian to use a personal (not government) computer and electronically generated messages to serve the same functions as a telephone with respect to generating or transmitting legal prescriptions. A CVM-employed veterinarian practicing as an outside activity may charge his or her clients fees for writing prescriptions in accordance with state pharmacy and veterinary practice acts. However, any outside activity which results in income to a CVM-employed veterinarian from a third party based upon the filling of a prescription written by the CVM-employed veterinarian is unacceptable.

ATTACHMENT 55

[redacted]

[redacted]2005

Steven Sundlof, D.V.M., Ph.D.
Director, Center for Veterinary Medicine
Food and Drug Administration
7519 Standish Place, HFV-12
Rockville, Maryland 20855

Dear Dr. Sundlof,

I am a veterinarian, [redacted] currently working in Private Practice in [redacted] An interaction and disturbing conversation with a representative from Fort Dodge Animal Health this past week regarding ProHeart-6 has prompted me to write directly to you in confidence.

On [redacted] 2005, Fort Dodge Senior Territory Manager [redacted] and another Fort Dodge representative (to whom I was not introduced) made a sales visit to the owner of the practice where I am employed. [redacted] and I have interacted on a business level for [redacted] years, our last contact having been over a year ago. Before leaving the facility, [redacted] stopped in the Treatment Room, where I was completing a procedure, to visit with me. As is my custom, I inquired about what was new with Fort Dodge, [redacted] response shocked me, and dealt primarily with the drug ProHeart-6. He indicated that the drug was soon to be back on the market, that it was a good drug, and that it had been taken off the market because of an individual in the Food and Drug Administration's Adverse Drug Events Section, who had aggressively pursued the withdrawal of the drug for personal financial gain. He continued on without prompting to name FDA employee "Victoria Hampshire" as the culprit, and indicated that she had had an internet website through which she was marketing and selling a competitor's heartworm preventative for personal profit. He stated that she had generated $70,000.00 in one year from these competitor product sales. He stated that Dr. Hampshire also had some association with a rogue "anti ProHeart-6" internet site on which individuals would relate negative experiences with their own animals after an administration of ProHeart-6, and that she would take this unsubstantiated information for inclusion as adverse drug reports of ProHeart-6. He indicated that Fort Dodge Animal Health had Dr. Hampshire investigated by private detectives and that what he was telling me had all been verified. He said that once "she (Dr. Hampshire) was taken care of" the adverse drug reports being submitted for ProHeart-6 had dropped significantly and that after review and public hearings, the adverse drug events for the product were changed by the Agency from over 5,000 to less than 2,000. He mentioned that Fort Dodge had obtained enough data from their association with The Banifield to support the safety of the drug to the Food and Drug Administration and that the drug would soon be available. I had listened in silence and had heard enough more than enough of this propaganda. I changed the subject to [redacted] and shortly thereafter ended our conversation.

Victoria A. Hampshire, V.M.D. has been a highly respected [redacted] Her career has been one notable for her

expansive knowledge of veterinary medicine, true professional competency, and great professional achievements. Over the [redacted] I have collaborated and consulted with Dr. Hampshire on a variety of clinical and technical challenges and have found her knowledge and experience base to be of great value. Her personal and professional commitments to exceptional animal care, health, and welfare in the biomedical research arena have positively impacted countless research animals and numerous significant research efforts. Her integrity and ethics, [redacted], are impeccable. It is beyond comprehension that Dr. Hampshire's work in the Food and Drug Administration would be anything other than above reproach.

It appears that Fort Dodge Animal Health has propagated a malicious personal assault against an ethical, professional [redacted] for the competent performance of her duty in the Food and Drug Administration. I am appalled. If a Fort Dodge Senior Territory Manager visiting a small town i[redacted] is well versed and easily relating this apparent fallacious information, I would expect that Fort Dodge representatives throughout the country have been provided this same information for dissemination to veterinary practitioners across the country, to explain away formally documented safety issues with ProHeart-6 in an effort to regain the confidence of practitioners if and when the drug is again released. The financial objective seems clear. If this unsafe drug returns to the market, it is Fort Dodge Animal Health, and not the dog owning consumer, who will benefit.

For this avaricious pharmaceutical company, with a documented unsafe drug, to engage in the private investigation of a federal employee in a regulatory agency seems criminal. For this company to perpetuate the personal and professional character assassination on a competent and ethical professional's career is reprehensible. For the Food and Drug Administration to allow this to continue to Dr. Hampshire would be unconscionable. I believe that your incorporation of this information in the Food and Drug Administration's interactions with Fort Dodge Animal Health is critical, for Fort Dodge's assault on Dr. Hampshire's ethics is also an assault on the ethics and credibility of the Food and Drug Administration as a Regulatory Agency. The Food and Drug Administration should be gratified to have the quality of character and professionalism that they have in Dr. Hampshire. The protection of this employee in the performance of her duty in the public interest seems to remain with the Agency. I, for one, respect and admire Dr. Hampshire and am grateful for my professional association with her.

To hear this information regarding another veterinarian unknown to me would have elicited inquiry into the validity of such scandalous accusation of a co-professional. To have heard it regarding a veterinarian [redacted] compelled me to inform you of this egregious Public Relations tactic by Fort Dodge Animal Health. To engage [redacted] in defense of Dr. Hampshire would have been meaningless. To have remained silent in my outrage would be professionally negligent and out of character for me. An Agency that I believe in and trust, [redacted] are both being disparaged publicly. Neither should be tolerated. I request your attention to the seriousness of Fort Dodge's latest actions. I also request that this correspondence be shared with our colleague Commissioner Lester Crawford, D.V.M., Ph.D.

Respectfully Yours,

[redacted]

ATTACHMENT 56

REQUEST FOR APPROVAL OF OUTSIDE ACTIVITY*

(Ref.: HHS Standards of Conduct Regulations)

[ ] Initial Request
[X] Revised Request
[ ] Renewal

NAME *(Last, First, Initial)*	2. ORGANIZATIONAL LOCATION *(Operating Division, Bureau, Division)*
Hampshire, Victoria	FDA/CVM/OSC
3. TITLE OF POSITION	4. GRADE AND SALARY *(Federal)*
Part time Adverse Drug Events Reviewer; Staff Fellow	GS13-10 Part time 24 hrs/wk
*5. NAME, ADDRESS AND BUSINESS OF PERSON OR ORGANIZATION FOR WHOM OUTSIDE SERVICES WILL BE PERFORMED 1. Metropolitan Emergency Animal Clinic 2. Advanced Veterinary Applications Corp. (AVA)	6. LOCATION WHERE SERVICES WILL BE PERFORMED 1. 12210 Nebel Street, Rockville, MD 20854 2. 7307 Nevis Road, Bethesda, MD 20817

7. NATURE OF ACTIVITY *(Indicate type of activity, e.g., teaching, consultative services, and give full description of specific duties or services to be performed. Specify, when possible, the scheduled days of week and hours of day proposed activity will be performed.)*

1. Emergency consultation, medical treatment and surgery of dogs and cats every other Sunday 2PM-9PM
2. Laboratory Animal Research protocol review, consultation, training and software design: 10-hours weekly around present job hours at FDA.

Total client pool averages 2-3 ; mostly ongoing. Current clients include:

1. The Humane Society of the United States
2. The Charitible Bosack Kruger Foundation
3. Scientists Center for Animal Welfare
4. USDA Beltsville Agricultural Lab; Dr. Neil Talbot.

8. ESTIMATED TIME INVOLVED

a. PERIOD COVERED	b. ESTIMATED TOTAL TIME DEVOTED TO ACTIVITY *(If on a continuing basis, give estimated time per year)*
FROM present time TO 07/01/02	750 hours/year

c. WILL WORK BE PERFORMED ENTIRELY OUTSIDE USUAL WORKING HOURS?
[X] YES [ ] NO IF "NO", INDICATE ESTIMATED NUMBER OF HOURS OR DAYS OF ABSENCE FROM WORK

9. DO YOUR OFFICIAL DUTIES RELATE IN ANY WAY TO THE PROPOSED ACTIVITY?
[X] NO [ ] YES *(Describe)*

*10. IF PROVIDING CONSULTATIVE OR PROFESSIONAL SERVICES, ARE YOUR WOULD-BE ASSOCIATES RECEIVING OR WILL THEY SEEK, A GRANT OR CONTRACT FROM A FEDERAL AGENCY?
[ ] NO [X] YES *(Describe)* Item 7; Associate #2 (See Attachment)

11. METHOD OR BASIS OF COMPENSATION	12. WILL COMPENSATION BE DERIVED FROM A DHHS GRANT OR CONTRACT?
[X] FEE [ ] HONORARIUM [ ] PER DIEM [ ] PER ANNUM [ ] ROYALTY [ ] EXPENSES [ ] OTHER *(Specify)*	[X] NO [ ] YES *(Describe)*

13. THIS REQUEST IS MADE WITH FULL KNOWLEDGE OF DEPARTMENT AND OPERATING DIVISION POLICY AND PROCEDURES ON OUTSIDE ACTIVITIES. THE STATEMENTS I HAVE MADE ARE TRUE, COMPLETE AND CORRECT TO THE BEST OF MY KNOWLEDGE AND BELIEF.

14. SIGNATURE OF EMPLOYEE	15. DATE	*16. ADDITIONAL INFORMATION ATTACHED
Victoria Hampshire	10/3/01	[X] YES [ ] NO

RECEIVED IN ETHICS 2002 APR 22 AM 11:03

17. ACTION RECOMMENDED BY REVIEWING OFFICIAL

a.	b. SIGNATURE	c. TITLE	d. DATE
[ ] APPROVAL [ ] DISAPPROVAL	Clifford G. Johnson	Director, C&S Office	3-13-02

18. ACTION TAKEN

a.	b. SIGNATURE	c. TITLE	d. DATE
[X] APPROVAL [ ] DISAPPROVAL			

*See reverse of form

HHS-520 (Rev. 1/82)

(INSTRUCTION ON BACK OF FORM)

INSTRUCTIONS

Item 5 - Self-Employment: If applicable, indicate self-employment, the type of service (as medical, legal, etc.), whether alone or with partners, giving their names, and, if providing professional services to a large number of clients or patients, estimate the total number rather than listing them separately.

* Item 10 - Federal Grants or Contracts Involved: Describe the Federal grants or contracts (type, granting or contracting department, etc.). Full details must be provided on any aspect of professional and consultative services which involves, directly or indirectly, the preparation of grant applications, contract proposals, program reports, and other material which are designed to become the subject of dealings between institutions and government units and the Federal Government.

* Item 16 - Attachments: Be sure to sign copies of all attachments submitted.

---

* Item 17 - COMMENTS OF REVIEWING OFFICIAL

The employee who submitted this request was provided a copy of the attached "Notice to Applicants for Prior Approval of Outside Activities" on 11/5/01 (date).

Signature

Item 18 - REASON FOR DISAPPROVAL

16. Attachment:

The gene mapping lab, USDA has requested from Advanced Veterinary Applications a small contract for 8-hours/month to review standard operating procedures and animal study proposals for humane care and use. Dr. Hampshire will derive no income from this relationship. The project is being handled by another employee of the company who is proposed to receive 100% of any company income.

301827 4000

REQUEST FOR APPROVAL OF OUTSIDE ACTIVITY*

(Ref.: HHS Standards of Conduct Regulations)

[ ] Initial Request
[X] Revised Request
[ ] Renewal

1. NAME (Last, First, Initial)	2. ORGANIZATIONAL LOCATION (Operating Division, Bureau, Division)
Hampshire, Victoria	FDA/CVM/OSC
3. TITLE OF POSITION	4. GRADE AND SALARY (Federal)
Veterinary Medical Officer	05 PHS
*5. NAME, ADDRESS AND BUSINESS OF PERSON OR ORGANIZATION FOR WHOM OUTSIDE SERVICES WILL BE PERFORMED 1. Metropolitan Emergency Animal Clinic 2. Advanced Veterinary Applications Corp. (AVA)	6. LOCATION WHERE SERVICES WILL BE PERFORMED 1. 12210 Nebel Street, Rockville, MD 20854 2. 7307 Nevis Road, Bethesda, MD 20817

7. NATURE OF ACTIVITY *(Indicate type of activity, e.g., teaching, consultative services, and give full description of specific duties or services to be performed. Specify, when possible, the scheduled days of week and hours of day proposed activity will be performed.)*

1. Emergency consultation, medical treatment and surgery of dogs and cats every other Saturday 2PM-10PM
2. Laboratory Animal Research consultation, training Total client pool averages 2-3 ; mostly ongoing. Current clients include:
   1. The Humane Society of the United States (paid $400.00 per month
   2. The Charitible Bosack Kruger Foundation (volunteer)
   3. Scientists Center for Animal Welfare (volunteer; organization pays perdium and travel to one meeting per year)
   4. Institute for Laboratory Animal Research; National Academies of Science: Invited Editor One Issue July 02

Average time spent= 1 hr/week from home

8. ESTIMATED TIME INVOLVED

a. PERIOD COVERED	b. ESTIMATED TOTAL TIME DEVOTED TO ACTIVITY (If on a continuing basis, give estimated time per year)
FROM present time TO 07/01/03	170 hrs/year

c. WILL WORK BE PERFORMED ENTIRELY OUTSIDE USUAL WORKING HOURS?
[ ] YES [X] NO IF "NO", INDICATE ESTIMATED NUMBER OF HOURS OR DAYS OF ABSENCE FROM WORK 5 1 Day Dec 10/02

9. DO YOUR OFFICIAL DUTIES RELATE IN ANY WAY TO THE PROPOSED ACTIVITY?
[X] NO [ ] YES *(Describe)*

*10. IF PROVIDING CONSULTATIVE OR PROFESSIONAL SERVICES, ARE YOUR WOULD-BE ASSOCIATES RECEIVING OR WILL THEY SEEK A GRANT OR CONTRACT FROM A FEDERAL AGENCY?
[X] NO [ ] YES *(Describe)*

11. METHOD OR BASIS OF COMPENSATION	12. WILL COMPENSATION BE DERIVED FROM A DHHS GRANT OR CONTRACT?
[X] FEE [ ] HONORARIUM [ ] PER DIEM [ ] PER ANNUM [ ] ROYALTY [X] EXPENSES [ ] OTHER *(Specify)*	[X] NO [ ] YES *(Describe)*

13. THIS REQUEST IS MADE WITH FULL KNOWLEDGE OF DEPARTMENT AND OPERATING DIVISION POLICY AND PROCEDURES ON OUTSIDE ACTIVITIES. THE STATEMENTS I HAVE MADE ARE TRUE, COMPLETE AND CORRECT TO THE BEST OF MY KNOWLEDGE AND BELIEF.

14. SIGNATURE OF EMPLOYEE	15. DATE	*16. ADDITIONAL INFORMATION ATTACHED
Victoria Hampshire	10/24/02	[ ] YES [ ] NO

17. ACTION RECOMMENDED BY REVIEWING OFFICIAL

a.	b. SIGNATURE	c. TITLE	d. DATE
[X] APPROVAL [ ] DISAPPROVAL	Lynn O. Cat	DIR, OS	10/24/02

18. ACTION TAKEN

a.	b. SIGNATURE	c. TITLE	d. DATE
[X] APPROVAL [ ] DISAPPROVAL	Clifford Johnson	Director Center for Veterinary Medicine	10/29/02

*See reverse of form
HHS-520 (Rev. 1/82)

(INSTRUCTION ON BACK OF FORM)

RECEIVED IN ETHICS 2003 MAR 18 PM 1:04

per Callahan 10-29-02

Clifford I. Johnson — Director, OS&C — 10-24-02 Date

INSTRUCTIONS

* Item 5 - Self-Employment: If applicable, indicate self-employment, the type of service (as medical, legal, etc.), whether alone or with partners, giving their names, and if providing professional services to a large number of clients or patients, estimate the total number rather than listing them separately.

* Item 10 - Federal Grants or Contracts involved: Describe the Federal grants or contracts (type, granting or contracting department, etc.). Full details must be provided on any aspect of professional and consultative services which involves, directly or indirectly, the preparation of grant applications, contract proposals, program reports, and other material which are designed to become the subject of dealings between institutions and government units and the Federal Government.

* Item 16 - Attachments: Be sure to sign copies of all attachments submitted.

---

* ITEM 17 - COMMENTS OF REVIEWING OFFICIAL

Requester has signed "Notice to Applicants..." and "Standards of Ethical Conduct"

Lynn O Cort
Reviewing Official

---

* ITEM 18 - REASON FOR DISAPPROVAL

THE NATIONAL ACADEMIES
Advisers to the Nation on Science, Engineering, and Medicine

National Academy of Sciences
National Academy of Engineering
Institute of Medicine
National Research Council

Institute for Laboratory Animal Research

October 21, 2002

Victoria Hampshire, VMD
Adverse Veterinary Drug Events
Office of Surveillance Compliance
Center for Veterinary Medicine
Food and Drug Administration
7500 Standish Pl
Rockville, MD 20854

Dear Dr. Hampshire:

I am writing to acknowledge your continued work on production of the *ILAR Journal* issue devoted to Behavioral Research Outside the Laboratory, which is scheduled to publish June 1, 2003. *ILAR Journal* is the quarterly, peer-reviewed, theme-oriented publication of the Institute for Laboratory Animal Research (ILAR), National Research Council.

You are contributing as one of the two Issue Editors. Your role involves working with co-Issue Editor Lilly-Marlene Russow (Professor of Philosophy, Purdue University) as well as the ILAR Council Journal Committee. Responsibilities include planning the issue, reviewing submitted manuscripts, recommending reviewers, assessing reviews and author revisions, and approving the final draft of the issue. You are investing additional time and skill in writing an article you have tentatively titled "Regulatory Guidelines Covering the Use of Companion Animals for Clinical Trials," for prospective inclusion.

Publication of this issue will involve many experts from the scientific community. The issue will serve as a reference to a broad constituency of biomedical investigators and laboratory animal scientists. The information is intended to benefit institutional officials for research and members of animal care and use committees.

I will gladly provide any additional information upon request.

Sincerely,

Susan Vaupel

Susan Vaupel, ELS
Managing Editor, *ILAR Journal*

2101 Constitution Avenue, NW, Washington, DC 20418 *Telephone* (202) 334 2590 *Fax* (202) 334 1687 ilar@nas.edu www.national-academies.org/ilar

Callahan, Linda J

From: Hampshire, Victoria
Sent: Wednesday, October 30, 2002 12:56 PM
To: Callahan, Linda J
Cc: Post, Lynn O; Johnson, Clifford; Tollefson, Linda R
Subject: RE: The National Academies Outside Activity Request

No discrepancy. Thanks very much for that very rapid review. I will certainly write Ms. Vaupel as soon as I receive it from you. I'd asked her to mail the information to me at home and she did that but she addressed the letter using this address. It was probably my fault for not being detailed enough in my request of her. I also hope this takes care of the last of this kind of thing from my former life. Thanks for your understanding, support and efficiency!

Tory Hampshire

-----Original Message-----
From: Callahan, Linda J
Sent: Wednesday, October 30, 2002 12:50 PM
To: Hampshire, Victoria
Cc: Post, Lynn O; Johnson, Clifford; Tollefson, Linda R
Subject: The National Academies Outside Activity Request

Hello Victoria:

I have received your ***Request for Approval of Outside Activity*** for your continued work on production of the *ILAR Journal* as an editor and writer.

In reviewing your request, it states that your official duties do not relate to the proposed activity, but the letter is sent to your at your official government address (CVM/FDA). You may serve as an editor and writer in your "personal capacity" as a scientist and review or write the articles, but to delineate between your "official FDA duties" and your "personal capacity" as a scientist, it is preferable that all correspondence related to Outside Activities be sent to your home address and not to your work address (that of the FDA). Also, if your current employment is used in any way with your name while participating in this outside activity, please be sure to use a disclaimer statement.

I recommend that you contact ILAR Journal in writing (after approval of the Outside Activity request), stating that all future correspondence be directed to your home address and that you will be performing this work in your personal capacity as a scientist (this is where you would add your expertise or specialty).

Please e-mail me back if you concur with the recommended changes, and I will sign-off on your request and forward to Dr. Tollefson for her final review and approval.

If you wish to discuss, please feel free to call me on x78565.

Thank you,

Linda J. Callahan
CVM Ethics Contact

NOTICE TO APPLICANTS FOR PRIOR APPROVAL OF OUTSIDE ACTIVITIES

APPROVAL OF AN HHS FORM 520 DOES NOT RELEASE YOU FROM A CONTINUING LEGAL OBLIGATION TO DISQUALIFY YOURSELF FROM OFFICIAL ASSIGNMENTS AFFECTING YOUR OUTSIDE EMPLOYER. WHILE PERFORMING AN APPROVED OUTSIDE ACTIVITY, ANY ACTIONS TAKEN IN CONFLICT WITH APPLICABLE ETHICS LAWS MAY SUBJECT YOU TO CRIMINAL PROSECUTION OR DISCIPLINARY PROCEEDINGS.

Caution. When you work for a company, organization, or other employer outside your government job, your relationship with that outside employer has certain legal and ethical consequences. The approval of an outside activity does not mean that you are free of conflicts of interest. You must still follow all substantive ethics requirements after approval is granted. Consult the ethics regulations at 5 C.F.R. Sections 2635.802 and 5501.106(d)(4) which are reprinted on the reverse side of this notice.

Conflicts Resolution. An approved HHS Form 520 does not signify that you need not be concerned about conflicts of interest. Under the law, conflicts of interest arising out of outside employment can be resolved in advance in only three ways: (1) you can inform your supervisor and disqualify yourself from participating in a conflicting government matter (often called a recusal); (2) you can ask for and receive, if certain legal requirements are satisfied, a separate legal document from your appointing official or designee that specifically permits you to work on the government matter (known as a waiver, an exemption, or an authorization); or (3) you can resign from either your government or outside job.

Effect of Prior Approval. The outside activities prior approval process has very limited purposes. When a supervisor or other reviewer approves an HHS Form 520 for your outside activity, only two assessments are being made, which are discussed below. You reasonably may rely on these specific determinations only if you provided all relevant information on the form and the circumstances under review do not thereafter change. You remain responsible for the legal consequences of any change in personal or business affairs.

First, based on the information which you provide, the reviewer determines whether your proposed activity is plainly prohibited by applicable statutes or regulations. For example, if you want to lobby federal agencies on behalf of a non-profit organization that employs you, prior approval will be denied because a criminal statute prohibits such representational activities.

Second, assuming your proposed activity is not specifically prohibited, the reviewer determines whether, under the circumstances, approval should be denied for other reasons specified under the law. For example, the reviewer may deny approval if the facts show that you used your government position to obtain an outside compensated business opportunity. Another common reason for denying approval is that the outside activity may prevent you from handling work that is expected of you. Because the outside activity may cause you to have to disqualify yourself from a broad range of job assignments, or even a few crucial projects, that will affect your outside employer, it may be impossible for you to discharge fully your government duties. If, however, your outside activity is approved, the reviewer has determined that the matters in which you will not be allowed to participate are not "so central or critical to the performance of [your] official duties" that your ability to perform the duties of your position would be materially impaired. In other words, you cannot work on a government matter affecting your outside employer, but the reviewer expects that you will be able to stay away from these assignments and still do your job.

Recusal Obligation. When performing your federal duties, you must avoid participating in any government matter that will affect your own self-interest in continuing your outside job. For example, you would have to disqualify yourself from participating in any official matter that might put your outside employer out of business or seriously affect its finances, either positively or negatively, so that the odds of your remaining employed are also affected. Also, when you work for an outside employer, the financial interests of that company or organization are considered to be your own. This means that you cannot participate in government matters that will affect that company or organization. You cannot work on a government matter that involves your outside employer as a specific party, such as a contract, grant, audit, or investigation. The law also requires you to stay away from government matters that are larger in scope, such as deliberations and decisions on developing, implementing, or enforcing statutes, regulations, policies, studies, or proposals, that will have an effect on a large class of employers like the one for which you work on the outside. For example, if you have an outside position as an employee of a hospital, a drug company, or a nonprofit organization, you cannot participate personally in any significant way in a policy decision that affects the financial interests of the industry or organizational sector in which these employers operate. A waiver often can be granted for such "particular matters of general applicability," if you notify your appointing official in advance and receive a written determination.

Scope of Recusal. Although many employees understand the need to disqualify themselves from participating in an official matter that affects their outside employer, they often believe erroneously that they can pick and choose among the various aspects of a particular matter and stay away only from the important decisions. Such incomplete recusals will not protect you from a criminal conflict of interest violation. Unless a waiver, approved in advance, identifies specific permitted activities, you must refrain entirely and absolutely from participating personally and substantially in a government matter that affects your own financial interest or that of an outside employer. When you are involved significantly in proposing, planning, advising, deciding, or implementing some official action, and you do so individually or by actively directing subordinates, your participation is personal and substantial.

EXCERPTS FROM THE STANDARDS OF ETHICAL CONDUCT FOR EMPLOYEES OF THE EXECUTIVE BRANCH AND THE DEPARTMENT OF HEALTH AND HUMAN SERVICES SUPPLEMENTAL AGENCY ETHICS REGULATIONS:

TITLE 5 CODE OF FEDERAL REGULATIONS

Section 2635.802 Conflicting outside employment and activities.

An employee shall not engage in outside employment or any other outside activity that conflicts with his official duties. An activity conflicts with an employee's official duties:

(a) If it is prohibited by statute or by an agency supplemental regulation; or

(b) If, under the standards set forth in Sections 2635.402 and 2635.502, it would require the employee's disqualification from matters so central or critical to the performance of his official duties that the employee's ability to perform the duties of his position would be materially impaired.

Employees are cautioned that even though an outside activity may not be prohibited under this section, it may violate other principles or standards set forth in this part or require the employee to disqualify himself from participation in certain particular matters under either subpart D or subpart E of this part.

Example 1: *An employee of the Environmental Protection Agency has just been promoted. His principal duty in his new position is to write regulations relating to the disposal or hazardous waste. The employee may not continue to serve as president of a nonprofit environmental organization that routinely submits comments on such regulations. His service as an officer would require his disqualification from duties critical to the performance of his official duties on a basis so frequent as to materially impair his ability to perform the duties of his position.*

Example 2: *An employee of the Occupational Safety and Health Administration who was and is expected again to be instrumental in formulating new OSHA safety standards applicable to manufacturers that use chemical solvents has been offered a consulting contract to provide advice to an affected company in restructuring its manufacturing operations to comply with the OSHA standards. The employee should not enter into the consulting arrangement even though he is not currently workin on OSHA standards affecting this industry and his consulting contract can be expected to be completed before he again works on such standards. Even though the consulting arrangement would not be a conflicting activity within the meaning of Sec. 2635.802, it would create an appearance that the employee had used his official position to obtain the compensated outside business opportunity and it would create the further appearance of using his public office for the private gain of the manufacturer.*

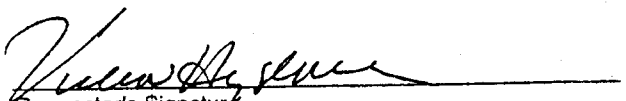
Section 5501.106(d)(4) Standard for approval.

Approval shall be granted unless it is determined that the outside employment or other outside activity is expected to involve conduct prohibited by statute or Federal regulation, including 5 CFR part 2635 and this part.

Note: The granting of approval for an outside activity does not relieve the employee of the obligation to abide by all applicable laws governing employee conduct nor does approval constitute a sanction of any violation. Approval involves an assessment that the general activity as described on the submission does not appear likely to violate any criminal statutes or other ethics rules. Employees are reminded that during the course of an otherwise approvable activity, situations may arise, or actions may be contemplated, that, nevertheless, pose ethical concerns.

Example 1: *A clerical employee with a degree in library science volunteers to work on the acquisitions committee at a local public library. Serving on a panel that renders advice to a non-Federal entity is subject to prior approval. Because recommending books for the library collection normally would not pose a conflict with the typing duties assigned the employee, the request would be approved.*

Example 2: *While serving on the library acquisitions committee, the clerical employee in the preceding example is asked to help the library business office locate a missing book order. Shipment of the order is delayed because the publisher has declared bankruptcy and its assets, including inventory in the warehouse, have been frozen to satisfy the claims of the Internal Revenue Service and other creditors. The employee may not contact the Federal bankruptcy trustee to seek, on behalf of the public library, the release of the books. Even though the employee's service on the acquisitions committee had been approved, a criminal statute, 18 U.S.C. 205, would preclude any representation by a Federal employee of an outside entity before a Federal court or agency with respect to a matter in which the United States is a party or has a direct and substantial interest.*



Requester's Signature

OGE Form 450, 5 CFR Part 2634, Subpart I
U.S. Office of Government Ethics (9/02)
(Replaces 4/99 edition)

Form Approved:
OMB No. 3209-0006

Executive Branch CONFIDENTIAL FINANCIAL DISCLOSURE REPORT

FOR OGE USE ONLY

Page Number 1

Employee's Name (Last, first, middle initial) Hampshire, Victoria A.	Position/Title Adverse Drug Events Coordinator	Grade 2003 MAR 17 GM-15	Reporting Status: [illegible] Annual
Agency FDA	Branch/Unit and Address CDER/OSE/DS	Work Phone [redacted]	If New Entrant, Date of Appointment 10/21/02
Check box if special Government employee (SGE) ☐	If an SGE, Home Address (Number, Street, City, State and ZIP Code)		
I certify that the statements I have made on this form and all attached statements are true, complete, and correct to the best of my knowledge.	Signature of Employee [signature]		Date 03/10/03
Date Received by Agency	On the basis of information contained in this report, I conclude that the filer is in compliance with applicable laws and regulations (except as noted in "comments" box below).	Signature and Title of Supervisor/Other Intermediate Reviewer (if agency requires)	Date
Signature of Agency's Final Reviewing Official and Title [signature]	Date 3/17/03	Comments of Reviewing Officials [signature] Solet. (Check box if continued on reverse) ☐	3/17/03 per Gail

Part I: Assets and Income

None ☐

Identify for you, your spouse, and dependent children: 1) assets with a fair market value greater than $1,000 at the close of the reporting period or producing income over $200; and 2) sources of earned income such as salaries, fees, honoraria (other than U.S. Government salary or retirement benefits, such as the Thrift Savings Plan) which generated over $200 in income during the reporting period. Earned income sources of your spouse must be reported if greater than $1,000 (greater than $200 for honoraria). No earned income needs to be reported for dependent children.

Assets include (but are not limited to): stocks, bonds, tax shelters, real estate, mutual funds, pensions, annuities, IRAs, trusts, commodity futures, trades and businesses, and partnership interests.

Exclude your personal residence, unless you rent it out, and deposit accounts in financial institutions. See instructions for additional exclusions.

	Assets and Income Sources (Identify specific employer, business, stock, bond, mutual fund, type/location of real estate, etc.)	(X) if no longer held	Nature of Income over $200 (Rent, interest dividends, capital gains, salary, etc.)	Date (Only for honoraria)
Examples	Rental Condo, Anchorage, Alaska		Rent	
	Doe, Jones & Smith, Hometown, USA	X	Salary	
	(S) Alexandria Medical Clinic, Alexandria, VA		Salary	
	Franklin Equity Mutual Fund		Dividends/Capital Gains	
1	Rental Income Bethesda, MD		[redacted]	
2	Salary Howard - NIH		[redacted]	
3	Salary PHS - FDA - self		[redacted]	
4	Income - outside activity AVA		$600.00/yr	
5	Income - outside activity MAC		$12,500/yr	
6	6000 Shares AIRG Aviation Int'l (Direct)		non tech stock	
7	430 Shares AMPB		American Pacific Bank	
8	4500 Shares CMDI Comprehensive Medical Diagnostic Group (Bankruptcy)			
9	13 Shares 76 ICF mutual Fund		Investors group Inc.	
10	100 Shares SIRIUS Satellite Radio		- Sirius Satellite Radio Inc.	

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U.S. Office of Government Ethics (9:02)
(Replaces 4/99 edition)

Executive Branch CONFIDENTIAL FINANCIAL DISCLOSURE REPORT

Page Number 2

Employee's Name (Last, first, middle initial) Hampshire, Victoria, A.

Part I: Assets and Income

Assets and Income Sources (Identify specific employer, business, stock, bond, mutual fund, type/location of real estate, etc.)	(x) If no longer held	Nature of Income over $200 (Rent, interest, dividends, capital gains, salary, etc.)	Date (Only for honoraria)
9 shares Nabsnvide Healthpptys Inc - Real Estate.			
600 shares Vital Living Products @ .013¢/share - Vital Living			
100 shares Stem cells @ $1.0[illegible]/sh for the employee's fund		[redacted]	
Asset: Home [redacted]		[redacted]	
Asset: [redacted]			
TSP account [redacted]			

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2003

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U.S. Office of Government Ethics (9/02)
(Replaces 4/99 edition)

Employee's Name (Last, first, middle initial) Hampshire, Vachss, B | Work Phone [redacted]

Part II: Liabilities None ☐

Report for you, your spouse, and dependent children, liabilities over $10,000 owed at any time during the reporting period (over $10,000 at the end of the period if revolving charge accounts). Exclude a mortgage on your personal residence unless it is rented out; loans for autos, household furniture or appliances; and liabilities owed to certain family members (see instructions).

	Creditors (Name and address)	Type of Liability (Mortgage, promissory note, etc.)
Example	First Alaska Bank, Anchorage, Alaska	Mortgage on rental property in Anchorage, AK
1	[redacted]	[redacted]
2	[redacted]	[redacted]
3	[redacted]	[redacted]

Part III: Outside Positions None ☐

Report any positions, whether or not compensated, which you held outside the U.S. Government during the reporting period. Positions include (but are not limited to) an employee, officer, director, trustee, general partner, proprietor, representative, executor, or consultant for a business, nonprofit or labor organization, or educational institution. Exclude positions with religious, social, fraternal, or political entities or those solely of an honorary nature. You need not report any positions of your spouse or dependent children.

	Organization (Name and address)	Type of Organization	Position	(X) If no longer held
Example	Doe, Jones & Smith, Hometown, USA	Law Firm	Associate	X
1	Director, AVA Consolly	Consolly	Director	7/1/03
2	Employee Metropolitan SB	Animal Hospital	Employee	
3				
4				

Part IV: Agreements or Arrangements None ☒

Report your agreement or arrangements for current or future employment, leaves of absence, continuation of payment by a former employer (including severance payments), or continuing participation in an employee benefit plan. You need not report agreements or arrangements of your spouse or dependent children.

	Terms of Any Agreement or Arrangement	Parties	Date
Example	Will receive retained pension benefits (independently managed, fully funded, defined contribution plan)	Doe, Jones & Smith, Hometown, USA	2/99
1			
2			
3			

Part V: Gifts and Travel Reimbursements None ☒

Do not complete this part if you are a new entrant or special Government employee.

Report for you, your spouse, and dependent children, gifts or travel reimbursements you have received from one source totaling more than $285. Exclude anything valued at $114 or less; anything received by your spouse or dependent child totally independent of their relationship to you; anything from a relative or from the U.S. Government; anything given to your agency in connection with your official travel; and food, lodging, or entertainment received as personal hospitality at the donor's residence or property.

	Source	Description (For travel-related items, include itinerary)	Date
Example	Doe, Jones & Smith, Hometown, USA	Leather briefcase as a departing gift	2/99
1			
2			
3			
4			

If Part III —
outside position still on-going
need an update HHS-520.
The one on file has been
expired on 2/03.

Thanks.
Holly

OGE Form 450, 5 CFR Part 2634, Subpart I
U.S. Office of Government Ethics (9/02)
(Replaces 4/99 edition)

2003-2004

Form Approved:
OMB No. 3209-0006

Executive Branch CONFIDENTIAL FINANCIAL DISCLOSURE REPORT

Employee's Name (Last, first, middle initial)	Position/Title	Grade	Page Number
Hampshire Victoria A.	Adverse Drug Events Coordinator	CDR-05	
Agency	**Branch/Unit and Address**	**Work Phone**	**Reporting Status:**
FDA	CDRH/OSC/DS	3018270158	☐ New entrant ☑ Annual
Check box if special Government employee (SGE) ☐	If an SGE, Home Address (Number, Street, City, State and ZIP Code)		If New Entrant, Date of Appointment

I certify that the statements I have made on this form and all attached statements are true, complete, and correct to the best of my knowledge.

Signature of Employee: Victoria Hampshire — Date: 10/9/03

Date Received by Agency	*On the basis of information contained in this report, I conclude that the filer is in compliance with applicable laws and regulations (except as noted in "comments" box below).*	Signature and Title of Supervisor/Other Intermediate Reviewer *(If agency requires)*	Date
Signature of Agency's Final Reviewing Official and Title		Date	Comments of Reviewing Officials (Check box if continued on reverse) ☐

Part I: Assets and Income

None ☐

Identify for you, your spouse, and dependent children: 1) assets with a fair market value greater than $1,000 at the close of the reporting period or producing income over $200; and 2) sources of earned income such as salaries, fees, honoraria (other than U.S. Government salary or retirement benefits, such as the Thrift Savings Plan) which generated over $200 in income during the reporting period. Earned income sources of your spouse must be reported if greater than $1,000 (greater than $200 for honoraria). No earned income needs to be reported for dependent children.

Assets include (but are not limited to): stocks, bonds, tax shelters, real estate, mutual funds, pensions, annuities, IRAs, trusts, commodity futures, trades and businesses, and partnership interests.

Exclude your personal residence, unless you rent it out, and deposit accounts in financial institutions. See instructions for additional exclusions.

	Assets and Income Sources *(Identify specific employer, business, stock, bond, mutual fund, type/location of real estate, etc.)*	(X) if no longer held	Nature of Income over $200 *(Rent, interest, dividends, capital gains, salary, etc.)*	Date *(Only for honoraria)*
Examples	Rental Condo, Anchorage, Alaska		Rent	
	Dee, Jones & Smith, Hometown, USA	X	Salary	
	(S) Alexandria Medical Clinic, Alexandria, VA		Salary	
	Franklin Equity Mutual Fund		Dividends/Capital Gains	
1	Rental Income [redacted]		[redacted]	
2	Salary husband previously reported is government W2			
3	Income outside activity AVA Consulting		none this year	
4	Income MSAC (metropolitan emergency clinic)		$12,500/year	
5	600 shares AIRG (Airtech, Int)	X		
6	6500 shares CMDJ Comprehensive medical diagnostics	X		
7	430 shares American Pacific Bank (AMPB)	Bank	stock	
8	B shares Investors group IGICF	X	(mutual fund)	
9	100 shares SIRIUS Satellite Radio Inc	X		
10				

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Note: This is the copy of what I submitted but I never received a signed copy back from OGE (HHS)

OGE Form 450, 5 CFR Part 2634, Subpart I
U.S. Office of Government Ethics (9/02)
(Replaces 4/99 edition)

Executive Branch CONFIDENTIAL FINANCIAL DISCLOSURE REPORT

Employee's Name *(Last, first, middle initial)* Hampshire, Victoria A

Page Number 2

Part I: Assets and Income

Assets and Income Sources *(Identify specific employer, business, stock, bond, mutual fund, type/location of real estate, etc.)*	(x) If no longer held	Nature of Income over $200 *(Rent, interest, dividends, capital gains, salary, etc.)*	Date *(Only for honoraria)*
11 9 shares Nationwide Health Inc	X		
12 600 shares V. Val Hwy Products	X		
13 100 shares AirTran Airways		(Airline Stock	
14			
15			
16			
17			
18			
19			
20			
21			
22			
23			
24			
25			
26			
27			

OGE Form 450, 5 CFR Part 2634, Subpart I
U.S. Office of Government Ethics (9/02)
(Replaces 4/99 edition)

Employee's Name (Last, first, middle initial): [redacted] | Work Phone: 2018270158

Part II: Liabilities

None ☐

Report for you, your spouse, and dependent children, liabilities over $10,000 owed at any time during the reporting period (over $10,000 at the end of the period if revolving charge accounts). Exclude a mortgage on your personal residence unless it is rented out; loans for autos, household furniture or appliances; and liabilities owed to certain family members (see instructions).

	Creditors (Name and address)	Type of Liability (Mortgage, promissory note, etc.)
Example	First Alaska Bank, Anchorage, Alaska	Mortgage on rental property in Anchorage, AK
1	[redacted]	[redacted]
2	[redacted]	[redacted]
3	[redacted]	[redacted]

Part III: Outside Positions

None ☐

Report any positions, whether or not compensated, which you held outside the U.S. Government during the reporting period. Positions include (but are not limited to) an employee, officer, director, trustee, general partner, proprietor, representative, executive, or consultant for a business, nonprofit or labor organization, or educational institution. Exclude positions with religious, social, fraternal, or political entities or those solely of an honorary nature. You need not report any positions of your spouse or dependent children.

	Organization (Name and address)	Type of Organization	Position	(X) If no longer held
Example	Dee, Jones & Smith, Hometown, USA	Law Firm	Associate	X
1	Director AWA	Consulting		
2	Employee Metropolitan ER	Animal Hospital		
3				
4				

Part IV: Agreements or Arrangements

None ☐

Report your agreements or arrangements for current or future employment, leaves of absence, continuation of payment by a former employer (including severance payments), or continuing participation in an employee benefit plan. You need not report agreements or arrangements of your spouse or dependent children.

	Terms of Any Agreement or Arrangement	Parties	Date
Example	Will receive retained pension benefits (independently managed, fully funded, defined contribution plan)	Dee, Jones & Smith, Hometown, USA	2/99
1			
2			
3			

Part V: Gifts and Travel Reimbursements

Do not complete this part if you are a new entrant or special Government employee.

None ☐

Report for you, your spouse, and dependent children, gifts or travel reimbursements you have received from one source totaling more than $285. Exclude anything valued at $114 or less; anything received by your spouse or dependent child totally independent of their relationship to you; anything from a relative or from the U.S. Government; anything given to your agency in connection with your official travel; and food, lodging, or entertainment received as personal hospitality at the donor's residence or premises.

	Source	Description (For travel-related items, include itinerary)	Date
Example	Dee, Jones & Smith, Hometown, USA	Leather briefcase as a departing gift	2/99
1			
2			
3			
4			