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CVM Posts New Animal Drug Safety Page on Website

The Food and Drug Administration's (FDA) Center for Veterinary Medicine (CVM) has posted a new Animal Drug Safety page (*www.fda.gov/cvm/AnimalDrugSafety.htm*) on the CVM website to help interested individuals easily locate safety information about drug products regulated by CVM.

Although CVM has historically placed considerable information about approved animal drugs on its website, inquiries from the public, particularly pet owners, about drug approvals indicated that people could not readily find the drug information they needed on the CVM website.

At CVM's new Animal Drug Safety page you will find these links:

- "FDA Database of Approved Animal Drug Products," where you can search for approval information, including indications and withdrawal times about animal drugs.
- "Freedom of Information Summaries," which summarize the safety and effectiveness information submitted by the drug sponsor to support the approval of an original or supplemental new animal drug application. The indications for use, dosage form, route of administration, and the recommended dosage, are explained.
- "Current Labels and Client Information Sheets," which are current drug package labels and product information inserts provided by drug manufacturers for a select list of animal drugs.
- "Adverse Drug Experience Reporting," including the "Cumulative Adverse Drug Experiences Summaries Report," mentioned above.
- "Product Safety Information," which includes "Dear Doctor" Letters for Animal Drugs (letters issued to veterinary medicine professionals by drug manufacturers alerting the professionals to important safety information) and other safety notifications, such as company press releases about product recalls (which are also available at *www.fda.gov/cvm/safeinfo1.html*).
- "Notice of Regulatory Activity Letters to Pharmaceutical Companies," which are the regulatory activity letters issued by CVM's Division of Surveillance, Office of Surveillance and Compliance.

The page also includes links to these other sources of safety notifications.

- CVM, FDA, and U.S. Health and Human Services news releases.
- FDA Product Recalls, Alerts, and Warnings.
- FDA Guidance Documents.
- Information on "Judicious Use of Antimicrobials," which is an approach to maximize therapeutic efficacy of antimicrobial drugs and minimize selection of resistant microorganisms.
- Information on the "Withdrawal of New Animal Drug Applications Process," which includes links to regulations and policies CVM follows when it proposes the withdrawal of approval of new animal drugs.

The Animal Drug Safety page also links to a new "Animal Drug Safety Frequently Asked Questions (FAQ)" page (*www.fda.gov/cvm/AnimalDrugSafetyFAQ.htm*). This page gives answers to the questions CVM often receives from the public.

Some of the FAQs are:

- How to report an adverse reaction.
- What extralabel use means.
- How to find information about a drug prescribed by a veterinarian.
- What is a valid veterinarian-client-patient-relationship.
- What drugs are approved for a particular disease, and what the difference is between an over-the-counter drug and a prescription drug.

We hope you will find CVM's new Animal Drug Safety web page both user-friendly and informative. Any questions or comments about these pages may be directed to the CVM Web Manager, Deborah Brooks *(Deborah.Brooks@FDA.HHS.gov)*.

In This Issue

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

CVM Reminds Aquaculture Producers to Use Appropriate Formaldehyde

According to reports reaching officials at the Center for Veterinary Medicine (CVM), some aquaculture producers are using chemical grade formaldehyde as a parasiticide drug for their fish, a use that CVM has not approved.

CVM issued an UPDATE in June to remind aquaculture producers to use the appropriate drugs. Using a formaldehyde compound other than the approved product can be unsafe for fish, and the effectiveness of an unapproved compound is questionable.

Three sponsors have approved new animal drug applications for formaldehyde: Western Chemical, PARASITE-S (NADA 140-989), Argent Chemical Laboratories, Inc., Paracide-F (NADA 140-831), and Natchez Animal Supply Company, Formalin-F (NADA 137-687).

PARASITE-S and Formalin-F are approved for the control of:

- external protozoa (*Chilodonella, Costia, Epistylis, Ichthyophthirius, Scyphidia*, and *Trichodina* spp.) and the monogenetic trematodes (*Cleidodiscus, Dactylogyrus*, and *Gyrodactylus* spp.) on all finfish;
- fungi of the family Saprolegniaceae on all finfish eggs; and
- protozoan parasites (*Bodo, Epistylis*, and *Zoothamnium* spp.) on penaeid shrimp.

Paracide-F is approved for the control of:

- external protozoa and monogenetic trematodes (as above) on salmon, trout, catfish, largemouth bass, and bluegill; and
- fungi (as above) on salmon, trout, and esocid eggs.

Paracide-F is not currently approved for use on penaeid shrimp.

The sponsors of the aquaculture drugs have approved applications filed with the Food and Drug Administration and have demonstrated that their products are safe and effective for the approved uses. Approved formaldehyde products are manufactured under strict good manufacturing practice standards to ensure quality, purity, and strength. The standards by which chemical grade formaldehyde is manufactured are different, and the products are not appropriate for aquaculture use.

Questions about the use of formaldehyde in aquaculture can be directed to Fran Pell, Consumer Safety Officer, FDA/Center for Veterinary Medicine, Division of Compliance, 240-276-9211, e-mail *frances.pell@fda.hhs.gov*.

NAS Completes Review of EPA Dioxin Risk Assessment

by Jon F. Scheid, Editor

The National Academy of Sciences (NAS) on July 11 released its review of a dioxin risk assessment that the Environmental Protection Agency (EPA) has spent more than a decade developing, bringing the Federal government one step closer to finalizing the risk assessment on this complex and sometimes confusing issue.

EPA issued its first draft of the risk assessment in 1994. Developing the report has taken a long time because scientists needed to collect, evaluate, and accurately present the enormous amounts of sometimes inconclusive data available about dioxin.

Information about dioxin is still being developed, and some conclusions are controversial. To help resolve some of the critical questions surrounding the data and conclusions about dioxin, the NAS was asked to conduct an outside, expert review of the risk assessment. Scientists and policy makers consider an NAS review the "gold standard" for a thorough scientific evaluation.

In a summary of its findings, the NAS committee that reviewed the EPA draft risk assessment identified certain scientific underpinnings for the assessment that it said should be strengthened, and offered recommendations for additional review that it said would improve the assessment. The summary of the NAS committee report can be found at the following website *http://darwin.nap.edu/openbook.php?record_id=11688&page=8*. The entire report can also be accessed from this site.

The term "dioxin" actually refers to a group of chemical compounds that

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FDA VETERINARIAN

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NAS Completes Review... *(Continued)*

share chemical structures and biological characteristics. Scientists have identified two forms as the most toxic (2,3,7,8-tetrachlorodibenzo-p-dioxin [TCDD], which is the most studied, and 1,2,3,7,8-pentachlorodibenzo-p-dioxin [PeCDD]) and use those two as a reference in determining the toxicity of other dioxins or mixtures of dioxin. The toxicity of other forms of dioxin is expressed as "toxicity equivalence," or TEQ, to the most toxic forms of dioxins.

Dioxins in high enough concentrations can cause adverse health effects in humans, including cancer. Scientists are also concerned, based on data from animal studies, that low level exposure in humans over long periods, or high levels at key times, might produce reproductive or developmental effects.

The EPA has issued regulations to limit the release of dioxin from significant sources in the United States, including municipal, medical, and hazardous waste incinerators and from cement kilns that burn hazardous waste. For water, EPA has issued regulations to reduce dioxin releases from pulp and paper facilities that rely on chlorine bleaching. These steps and others taken by the Federal government have curtailed known and quantifiable industrial dioxin emissions in the United States by 89 percent from 1987 levels.

Keeping food safe

Dioxins are found virtually everywhere in the world. Although dioxins are an environmental contaminant, most human exposure is through the diet. Scientists estimate that approximately 90 percent of human exposure is through dietary intake, primarily animal fats.

The Food and Drug Administration's (FDA) Center for Veterinary Medicine (CVM) has a role in ensuring food and feed safety and has not waited for the final risk assessment report, but instead has already tried to address some of the dioxin issues. CVM has issued assignments each year since 2000 asking FDA's field staff to collect samples of various complete feeds and feed ingredients and then test them to determine whether those feeds/feed ingredients could be contributing to dioxin in food produced from animals. The levels of dioxin CVM has found in these surveillance samples has generally been low.

Dioxins in high enough concentrations can cause adverse health effects in humans, including cancer. Scientists are also concerned that low level exposure in humans over long periods, or high levels at key times, might produce reproductive or developmental effects.

In addition to determining background levels of dioxin, CVM has investigated any time high levels are found in feed or feed ingredients. CVM has taken action three times to reduce dioxin levels in the feed supply.

CVM issued a letter in 1997 to poultry and catfish producers and other users of clay products in feed asking them to stop using "ball clay" because of its high level of dioxins. Investigators found that ball clay from mines in Mississippi, Kentucky, and Tennessee had elevated dioxin concentrations. Some samples had dioxin at concentrations more than 100 times greater than that found in most topsoils.

Ball clay is a type of clay used mostly in the ceramic industry. It got its name by a practice of English miners to roll the clay into 30-50 lb. balls. The clay was used as a anti-caking agent in soybean meal.

In 2002, CVM worked with a mineral ingredient premix manufacturer who was recalling products found to contain high levels of dioxin. CVM determined the high temperature drying process the company used to produce its "protected" minerals was likely responsible for creating dioxin in the products, especially in mineral products containing high copper levels.

In 2003, CVM issued an alert to the feed industry warning against the use of mineral mixes and premixes that are byproducts or coproducts of industrial metal production. Earlier that year, FDA surveillance programs found elevated levels of dioxin in a feed product and traced the problem back to a zinc oxide product produced by a brass foundry.

CVM will continue to collect and analyze feed samples for dioxins and take appropriate actions to try to reduce dioxin levels in feed. Lower dioxin levels in feed should translate to lower dioxin levels in food of animal origin.

JUNE, JULY

Comings and Goings

New Hires

OFFICE OF NEW ANIMAL DRUG EVALUATION

- Dominique Yearwood, Legal Instruments Examiner

Departures

OFFICE OF NEW ANIMAL DRUG EVALUATION

- Mark Robinson, Supervisory Interdisciplinary Scientist
- Wei Guo, Regulatory Review Officer
- Guilin Qiao, Interdisciplinary Scientist

CVM Issues FY 2005 Annual Report

The Center for Veterinary Medicine (CVM) has issued its Annual Report for Fiscal Year 2005. It is the Center's third annual report.

As it had done in previous annual reports, CVM presents a description of its organization and responsibilities (including those of the new Office of Minor Use and Minor Species Animal Drug Development); the Center's mission, guiding principles, and strategic plan; its sphere of influence; and its stakeholders and partners.

In the report, CVM describes the "challenges and accomplishments" it faced in FY 2005, listing specific performance goals the Center worked to achieve during the year, and explains whether the Center achieved the goal or fell short.

Among the Center's significant accomplishments are enhancements to the animal drug review process, availability of new drugs for aquaculture and other minor species, activities to reduce the risk of antimicrobial resistance, and measures to assure the safety of animal feed and control the risk of Bovine Spongiform Encephalopathy in the United States.

2006 is the centennial year for the Food and Drug Administration (FDA), and to celebrate that anniversary, the report includes historical animal drug and animal health "milestones." For example, in a section about increasing the availability of safe and effective drugs, the report lists 1938 as a milestone year. In that year, Congress modified the Federal Food, Drug, and Cosmetic Act to provide the government authority for pre-market approval of animal drugs. Spohn's Udder Aid, Neo-Polycin Ophthalmic, and Glover's Imperial Dog Capsules were some of the earliest approvals under the new authority. The report added that the oldest active approval is "Sulfodene Medication for Dogs," approved in 1943.

As in previous reports, the FY 2005 report lists the scientific publications that CVM employees have written or helped write, and it lists CVM award winners.

New in the FY 2005 report is a list, in Appendix A, of all significant regulations, guidances, and other documents CVM issued during the year. Appendix B lists all significant New Animal Drug Approvals for the year. In other appendixes, the report presents information about staff and budget levels.

CVM has issued its annual report for FY 2005. It is available on CVM's website or by contacting the Center to request a hard copy of the report.

The Report is available on CVM's website (*www.fda.gov/cvm/FY2005AnnualReport.htm*). For a printed copy, contact CVM's Communications Staff, at HFV 12, 7519 Standish Place, Rockville, MD 20855; or call 240-276-9300.

VICH Working Group Making Progress on Agreement on Pharmacovigilance

by Margarita Brown, DVM, Office of Surveillance and Compliance

When a drug is marketed in different countries, the statement is sometimes made that it has been used for years in Country X without problems. But what does that statement really mean? In the past, little thought was given to how other countries manage veterinary pharmacovigilance, or monitoring drug adverse experiences. The assumption tends to be that all countries do things the same way. However, in today's global society, this assumption takes on new importance.

The regulatory agencies of the member nations of the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH), which are the United States, the European Union, and Japan, as well as the pharmaceutical companies that market their products internationally, all have staff dedicated to veterinary pharmacovigilance. However, there may be marked regional differences not only in the criteria defining an adverse event report, but also in when and how these reports are submitted to various regulatory agencies.

The pharmaceutical companies have had to navigate the regulatory shoals of many nations, sending adverse event reports at varying intervals and containing varying information, resulting in tedious and expensive duplication of reports and subsets of reports. Yet, with all this carefully collected data being sent around the world, there has been little or no sharing of adverse event information. Regulators in Japan may have no

(Continued, next page)

...Progress on Agreement on Pharmacovigilance *(Cont.)*

knowledge of label changes made by regulators in the United States. Regulators in the United States may be completely unaware of a cluster of adverse events in Germany.

VICH is an initiative concerned with developing harmonized technical requirements for the approval of veterinary medicinal products in the European Union, Japan, and the United States, and includes input from regulatory and industry representatives. In 1996, VICH was organized after the success of a similar harmonization effort involving human medicines—the International Conference on Harmonisation of Technical Requirements for Approval of Pharmaceuticals for Human Use (ICH).

Since 1997, the VICH Pharmacovigilance Expert Working Group has been meeting with the purpose of standardizing the collection of adverse event information and the timely sharing of that information with member and observer nations. Standardizing serves the dual purpose of vastly expanding the information available for regulators, and decreasing the burden and expense to the pharmaceutical companies of meeting multiple and diverse regulatory requirements.

Challenges

Several challenges become apparent when trying to meet the needs of different regulatory agencies. One of the biggest is how to negotiate around existing regulations. Different countries have varying degrees of flexibility to change a standing regulation, and the representatives' authority to make such changes might be even more variable. Some regulations might be approved for change, but the timeline for implementation might extend into the distant future. The crafting of guidelines that allow circumnavigation of such impediments requires close attention to the use of language and a great deal of patience.

Definitions become extremely important when standards are being set. One country might require notification of a "serious" adverse event within a certain time frame, while another might require notification of a "serious and unexpected" adverse event within that time. But what, exactly, is meant by "serious" in each of those countries? Some countries might market a product that is not exactly the same as the product sold in another country, but the products might be similar. Sharing information for a similar product could expand the knowledge of the active ingredients, or provide adverse event information for a species approved for use on the label for one country, but not in another. Again, the definition of "same" or "similar" seems intuitive, but these concepts are actually nebulous and require exact delineation for international standards. Factor in the need for precise translation into languages other than English, and the inclusion of a single word can make all the difference between agreement and stalemate.

Since 1997, the VICH Pharmacovigilance Expert Working Group has been meeting with the purpose of standardizing the collection of adverse event information and the timely sharing of that information with member and observer nations.

Although the required grasp of detail and structure can make negotiations seem frustrating and slow, the benefits will be well worth the effort and expense. Considerable time can elapse from the marketing of a new drug to the detection of a serious adverse event that was not identified in the few hundred animals participating in the pre-approval studies. A drug that quickly gains widespread use in hundreds of thousands of animals can provide the necessary basis for recognition of as yet unrecognized serious adverse events. Sharing of adverse event information under different conditions of use will benefit the international recognition of such events. Access to the more than 30,000 reports received annually in the United States will increase the strength of the emerging safety signals from the several thousand anticipated adverse events reported annually across the EU and the approximately 300 adverse events reported annually in Japan.

Crucial ingredients in the sharing of information include not only the standardization of the information collected but also its rapid transmission. The regulatory agencies of the EU and Japan already have systems in place for electronic submission of veterinary adverse drug events, while the Center for Veterinary Medicine is currently in the pilot phase of receiving adverse events electronically from industry. All of these in-house systems are different. The challenge is to establish the means by which manufacturers can send the same reports to their international branches, as well as to all the regulatory agencies. To this purpose, the Pharmacovigilance Expert Working Group is now standardizing the electronic data elements of the adverse event report and evaluating existing systems for widespread distribution so that the information can be received by the member nations, regardless of their internal processing system.

After four years of persistent dedication to negotiation, the members of the Pharmacovigilance Expert Working Group have succeeded in signing

(Continued, page 12)

The Conceptual Basis of Guidance About Biowaivers for Type A Medicated Articles

by Marilyn N. Martinez, Ph.D., Senior Biomedical Research Scientist, Office of New Animal Drug Evaluation

The Center for Veterinary Medicine (CVM) issued an industry guidance in February 2006 that explains the basis under which CVM can grant biowaivers for Type A medicated articles containing drug substances that are classified as water soluble.

"Guidance for Industry on Waivers of In Vivo Demonstration of Bioequivalence of Animal Drugs in Soluble Powder Oral Dosage Form Products and Type A Medicated Articles" (Guidance for Industry #171) is available on CVM's website at *http://www.fda.gov/cvm/Guidance/guide171.doc*.

The Type A medicated article consists of the active pharmaceutical ingredient (API) plus excipients and is not a finished dosage form. Since the Type A medicated article is only a small component of the final product that is ingested by the animal, the composition of the medicated feed can vary with the nutritional content of the foodstuffs with which it is mixed.

Therefore, with few exceptions, if the drug itself is water soluble across a variety of pH values, the composition of the Type A medicated article will not affect the bioavailability of the drug in medicated feed. (See sidebar for definitions of Type A medicated articles and Type B and C medicated feeds.)

CVM's basis for granting biowaivers for Type A medicated feeds is that drugs soluble in aqueous media across a range of pH values go rapidly into solution upon contact with the fluids of the gastrointestinal (GI) tract. If the drug readily goes into solution upon contact with the gastric fluids, then the rate at which the drug reaches a remote site of action or absorption is dependent upon the rate of gastric emptying and intestinal transit. These factors reflect physiological rather than formulation-dependent variables.

While adsorption of the drug to the nutrients in a meal may affect product bioavailability[1], the clinical impact of drug adsorption to the contents of the Type B or C medicated feed will have been addressed in the original application through the evaluation of product safety and efficacy.

Therefore, assuming that the active ingredients of the test and reference formulations are identical, if a drug is water soluble, the bioavailability of that drug when contained in a Type A medicated article will not be influenced by the composition of the Type A medicated article.

The only exceptions of which CVM is aware are when the formulation contains substances that could cause adverse pharmacologic effects (e.g., altered GI transit time, membrane permeability, or drug metabolism), or when there is inactivation of the drug by, for example, an excipient that chelates the API (where chelation is the combining of a metal ion with a chemical compound).

By definition, solubility is the extent to which molecules in a solid are removed from its surface by a solvent. CVM recommends use of the USP definition of drug solubility. In general, ionized drugs tend to exhibit far greater aqueous solubility than their unionized counterparts. Consequently, drug solubility can be markedly affected by the pH of that solvent. For this reason, CVM requires that solubility be tested across a wide range of pH values.

There is no need for statistical comparison of the solubility test results obtained with the pioneer and generic products because, as defined in CVM's biowaivers guidance document, to be eligible for biowaiver, the API must meet the solubility criteria across all pH conditions. A failure to dissolve in any one condition will disqualify products containing this API from being a candidate for a biowaiver.

CVM recognizes that consistent with the Center for Drug Evaluation and Research (CDER) biowaiver guidance[1], there may be occasions when this conservative USP definition of solubility excludes compounds that are administered at doses so low that sink conditions exist in the stomach of the target animal species (i.e., where the concentration of dissolved drug does not influence the further dissolution of that solid dosage form). In other words, the dosage is such that there will be far less than 1 gram of drug per 10 mL of gastric fluid. Therefore, CVM's biowaiver guidance provides for a dosage-adjusted definition of solubility that is based upon gastric fluid volume and targeted dose.

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. . .Biowaivers for Type A Medicated Articles *(Cont.)*

As described in the CDER guidance[1], the entire dose must dissolve in the gastric volume of the targeted species to avoid the possibility of dissolution-rate limited bioavailability.

When using the dosage-adjusted approach, the test conditions and criteria being applied within CVM's Guidance for Industry #171 are consistent with drugs that are classified as "highly soluble" within the framework of CDER's biowaiver guidance.

CDER's biowaiver guidance is applicable to compounds that are highly soluble and highly permeable across the intestinal mucosa (defined by the Biopharmaceutics Classification System as Class I compounds). Unlike CDER's biowaiver guidance, CVM's guidance also allows for the granting of biowaviers for drugs that are highly soluble but that exhibit poor intestinal permeability (Class III compounds). For these molecules, it is not the rate of drug dissolution that is rate-limiting, but rather the rate and extent of drug permeation across biological membranes[2]. Therefore, so long as there are no permeability enhancers included in the formulation, CVM has deemed it appropriate to include both Class I and Class III compounds in its biowaivers guidance.

However, as noted in that guidance, CVM reserves the right to deny a waiver request if there is any component of the Type A medicated article that is believed to either compromise drug solubility or alter intestinal permeability. Examples of "inactive" ingredients that may be of concern include substances known to alter drug solubilization (e.g., a chelating agent), intestinal permeability enhancers (e.g., polysorbate 80) or excipients that can alter GI transit time (e.g., osmotically active substances such as sorbitol and mannitol).[3]

CVM's biowaivers guidance is applicable if a generic drug sponsor or if the sponsor owning the

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Definitions of Medicated Articles, Medicated Feeds

The Type A medicated article and Type B and C medicated feeds are regulated by the Food and Drug Administration's (FDA), Center for Veterinary Medicine. Definitions of new animal drugs approved for use in animal feed are provided in 21 CFR §558.3.

- A "Type A medicated article" is intended solely for use in the manufacture of another Type A medicated article or a Type B or Type C medicated feed. It consists of a new animal drug or drugs, with or without carrier (e.g., calcium carbonate, rice hull, corn, gluten) with or without inactive ingredients.
- A "Type B medicated feed" is intended solely for the manufacture of other medicated feeds (Type B or Type C). It contains a substantial quantity of nutrients including vitamins and/or minerals and/or other nutritional ingredients in an amount not less than 25 percent of the weight. It is manufactured by diluting a Type A medicated article or another Type B medicated feed.
- A "Type C medicated feed" is intended as the complete feed for the animal or may be fed "top dressed" (added on top of usual ration) on or offered "free-choice" (e.g., supplement) in conjunction with other animal feed. It contains a substantial quantity of nutrients including vitamins, minerals, and/or other nutritional ingredients. It is manufactured by diluting a Type A medicated article or a Type B medicated feed. A Type C medicated feed may be further diluted to produce another Type C medicated feed.

Companies manufacturing Type A medicated articles must comply with the good manufacturing practice regulations in 21 CFR 226. Type B or Type C medicated feeds are produced using Type A medicated articles or other Type B or Type C medicated feeds. To manufacture some medicated feeds, an approved medicated feed mill license is needed. According to provisions of the Animal Drug Availability Act of 1996, a licensed feed mill may manufacture any approved medicated feed as long as the facility is manufacturing the feed in conformance with the good manufacturing practice regulations for medicated feeds (21 CFR 225).

NRSP-7 Holds Semi-Annual Committee Meeting

by Dr. Meg Oeller, DVM, Office of Minor Use and Minor Species Animal Drug Development

The U.S. Department of Agriculture's (USDA) Minor Species Animal Drug Program, National Research Support Project #7 (NRSP-7), held its semi-annual meeting of the technical committee and Administrative Advisors on May 11 at the offices of the Food and Drug Administration's (FDA) Center for Veterinary Medicine (CVM) in Rockville, MD. While the autumn meeting rotates among the four regions, the spring meeting is held in Rockville to facilitate the participation of CVM reviewers and minor species stakeholders, including producer groups and the regulated industry.

The purpose of the NRSP-7 Minor Use Animal Drug Program is to address the shortage of animal drugs for minor species by funding and overseeing the effectiveness, target animal safety, and human food safety research and the environmental assessment required for the approval of a New Animal Drug Application (NADA). Commercial sponsors are able to use these data in conjunction with their own manufacturing and labeling information to pursue approval of an animal drug for an intended use in the minor species.

Minor species are those species other than humans that are not major species. The major species are horses, cattle, swine, dogs, cats, chickens, and turkeys.

The scope of the program includes minor species of agricultural importance, and generally excludes companion animals.

Opening remarks from Dr. Beaulieu

The Director of the CVM's new Office of Minor Use and Minor Species Animal Drug Development (OMUMS), Dr. Andy Beaulieu, welcomed everyone and discussed issues of major importance to CVM. These issues include the implementation of the Minor Use Minor Species Animal Health Act (MUMS Act), animal drug user fees, minor use issues, and the upcoming personnel changes in OMUMS.

NRSP-7
National Research Support Project No. 7

He reported that the drafting of implementing regulations for provisions of the MUMS Act is moving forward. The final rule for "designation" will publish soon, as will the proposed rule for "indexing." The determination of "minor use in a major species" is being handled on a case-by-case basis until proposed rules are published to help clarify this issue.

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. . .Biowaivers for Type A Medicated Articles *(Cont.)*

rights to the approved New Animal Drug Application (NADA) for the Type A medicated article wishes to develop a revised formulation of the approved Type A medicated article.

However, these same criteria cannot be used to bridge between a Type A medicated article and a water soluble powder. Unlike with tablets, oral boluses, oral suspensions, and injectable formulations, animal behavior (drinking and eating) determines the actual dose received when the drug is administered in the drinking water or in food. While blood level bioequivalence studies employing gavage dosing may confirm the absence of a formulation effect (which is the sole question applied to products that meet the criteria for approval as an abbreviated NADA), it cannot confirm the comparability of rate and extent of drug intake. This difference in intake may be greater in diseased as compared to healthy animals, since diseased animals tend to go off food before they cease to drink.

Therefore, CVM's biowaiver guidance should not be applied in these situations. Similar questions may arise if going from the administration of drug in total feed versus as a top dress.

[1] CDER Guidance For Industry: Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System. Issued 8/2000, Posted 8/31/2000).

[2] Fleisher, D, Li, C, Zhou, Y, Pao, LH, and Karim, A: Drug, meal and formulation interactions influencing drug absorption after oral administration. Clin Pharmacokinetics 1999;36:233-254.

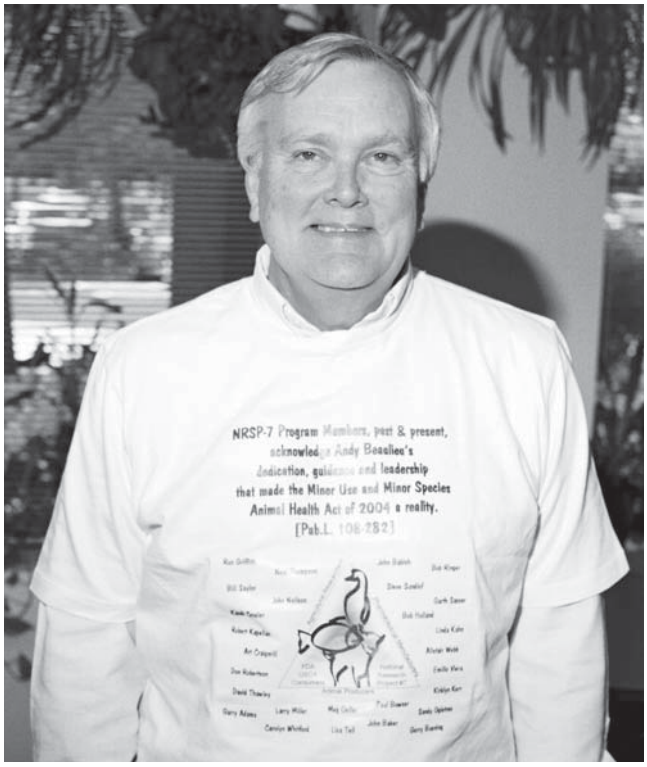
[3] Martinez M, Augsburger L, Johnston T and Jones WW. Applying the biopharmaceutics classification system to veterinary pharmaceutical products. Part I: biopharmaceutics and formulation considerations. Adv Drug Deliv Rev 2002 54; 805-824.

NRSP-7 Holds Semi-Annual Committee Meeting *(Cont.)*

Budget constraints may delay the establishment of a grant program for "designated" MUMS drugs. The MUMS Act authorized funding for a grants program once the designation final rule is published, but funds may not be appropriated for some time.

User fee waivers are available for minor species projects, and we hope the waivers will still be so when the fees are reauthorized by Congress.

The NRSP-7 committee presented Dr. Beaulieu with a special T-shirt and NRSP-7 coffee mug in appreciation for his long-standing support of the program. The T-shirt listed the names of all committee members past and present. Dr. Beaulieu will be retiring from CVM in January 2007 after serving as a champion of minor use and minor species issues for many years. The new OMUMS Director will be Dr. Bernadette Dunham, currently deputy director of the Office of New Animal Drug Evaluation at CVM. She will begin working with Dr. Beaulieu this fall to provide a smooth transition.



Dr. Andy Beaulieu, Director of the CVM's new Office of Minor Use and Minor Species Animal Drug Development, will be retiring at the end of this year, so the NRSP-7 technical committee and administrative advisors presented Dr. Beaulieu this shirt during the May 11 meeting to highlight his contributions to the work of the NRSP-7.

Stakeholders' presentations

The NRSP-7 program's last 5-year review, which was done in August of 2003 and applies to the 5-year term that covers October 2004 through September 2009, recommended that the NRSP-7 committee do more outreach to stakeholders. To forward that goal, the committee decided to invite prominent members of minor species industries to speak at the spring meetings to foster better communication.

This year the committee invited Dr. C. Shane Donley, a veterinarian from Ohio who represented the farmed deer industry. From his early life growing up on a deer farm to his current life in veterinary practice with many deer farm clients, Dr. Donley is well versed in the practices and problems associated with raising deer. He provided an excellent picture of the deer industry that included husbandry practices and veterinary drug needs for management and disease treatment. His insightful and thorough presentation was very helpful to the NRSP-7 committee and will be invaluable in the selection of projects and the design of needed studies.

National Aquaculture NADA Coordinator Roz Schnick gave a presentation, "Aquaculture Drug Approval Highlights of Progress." She described the achievements of several different entities, including the Upper Midwest Environmental Sciences Center, that are conducting studies to support drug approvals. Ms. Schnick reported significant progress on projects exploring claims for the anesthetic AQUI-S® (isoeugenol), chloramine-T, florfenicol, formalin, hydrogen peroxide, 17 alpha methyltestosterone, and oxytetracycline. She also described a survey that she conducted to identify unmet label claims in the public sector. The survey results will soon be distributed to the 38 participating States through the Drug Approval Working Group of the Federal-State Aquaculture Drug Approval Partnership, which is a separate group made up of State and Federal agencies and other aquaculture interests.

Ms. Schnick also described her internet-based drug matrix database, which provides general information and reports on the status of studies supporting aquaculture drug development.

Regional coordinators' reports

There is great concern across the program about the continuing increase in data requested by CVM to support minor species drug approvals. NRSP-7 has not had any increase in funding for several years. More data for each project increase the cost and makes it more difficult for the program to serve the minor species community.

NORTHEAST REGION: Dr. Paul Bowser

Although many of these projects are intended to support species grouping, the data will be accumulated to support individual drug approvals for the drugs under study. (Species grouping is the concept whereby, based on scientific evidence, a few species can represent a larger group of species for the purpose of drug approval. For example, one species of salmon and one of trout can represent all salmonid fish.) Current projects include oxytetracycline for finfish, Romet-30® (sulfadimethoxine/ormetoprim) for finfish, florfenicol for finfish, and Rofenaid® (sulfadimethoxine/ormetoprim) for pheasants. Plans

(Continued, next page)

NRSP-7 Holds Semi-Annual Committee Meeting *(Cont.)*

for a study identifying the needs of the goat industry are in development.

This past year saw the publication of several articles and abstracts dealing with various pharmacokinetic and physiologic effects of oxytetracycline, florfenicol, and hydrogen peroxide.

SOUTHERN REGION: Dr. Alistair Webb

Dr. Webb reported that current projects include ivermectin for rabbits, fenbendazole for deer, lasalocid for deer and goats, fenbendazole for gamebirds, and Crude Carp Pituitary, Ovaprim® (GnRH and domperidone), and metomidate for fish.

Dr. Webb also reported that scientists at his lab at the University of Florida have completed the setup of their Good Laboratory Practices (GLP) lab. (GLP labs follow the rules in 21 Code of Federal Regulations, Part 58). The Ivermectin assay and the in vivo sections of the rabbit project have completed their GLP inspection. Dr. Webb is maintaining the NRSP-7 website (*www.nrsp7.org*), which includes the project tracking database for the use of the committee.

Future projects are under consideration for deer.

NORTH CENTRAL REGION: Dr. Ronald Griffith

The major current project is the Controlled Internal Drug Release, Type G (CIDR-G) intravaginal progesterone device for sheep. The U.S. sheep industry lists this product as its number one need. Target animal safety and effectiveness studies are complete and the human food safety study is nearly done. A project to support approval for this device in goats is in its early stages. A new project for lasalocid for coccidiosis in pheasants is in development. New projects are under consideration for tulathromycin for respiratory disease in sheep and goats, for Regulin® (melatonin) to enhance early estrus in sheep, and for Bioclip® (epidermal growth factor) to induce wool-break in sheep. (Wool-break is breaking of the wool fibers, which causes sheep to shed their fleece without shearing.)

WESTERN REGION: Dr. Arthur Craigmill

Dr. Dr. Lisa Tell presented the region's report on several projects. Several of these are cooperative projects with other regions, such as the CIDR-G for sheep and goats and species grouping of fish. A project concerning florfenicol for respiratory disease in sheep is on hold while additional data requirements are identified. The target animal safety study for the CIDR-G in goats is complete and the report is almost ready for submission to CVM.

Pirlimycin for mastitis in goats is early in development, as is ceftiofur for the same indication.

Work is continuing on species grouping for gamebirds.

The Western Region is also responsible for the recently approved project for tylosin and the in-progress project for lincomycin for American Foulbrood disease in honeybees.

The project for otolith marking of salmonids with strontium chloride immersion is still in the early stages.

There is considerable collaboration across the four regions. Much of the analysis of samples from studies conducted in other regions is done in the laboratory at the University of California, Davis. Some projects are funded and conducted by more than one region to make the best use of equipment and expertise.

The project concerning erythromycin for bacterial kidney disease in salmonids is in its final stages, mainly in need of an environmental assessment.

Collaboration

There is considerable collaboration across the four regions. Much of the analysis of samples from studies conducted in other regions is done in the laboratory at the University of California, Davis. Some projects are funded and conducted by more than one region to make the best use of equipment and expertise. The chart on page 11 lists the region with primary responsibility for each project.

Administrative Advisors' report

The Administrative Advisors discussed the need for reexamination of the program's mission statement in regard to increased requirements and costs for drug approval without corresponding

(Continued, next page)

Dr. Larry Miller served for a number of years at the U.S. Department of Agriculture representative to the NRSP-7 meetings. He recently retired, and was honored by the NRSP-7 Committee at a dinner following the May 11 meeting.

NRSP-7 Holds Semi-Annual Committee Meeting *(Cont.)*

increases in funding. In this climate, it may be necessary to reconsider the prioritization and number of projects.

The Advisors also encouraged continued outreach to stakeholders noting that they can influence congressional support that the committee cannot.

They also encouraged development of a strong relationship between NRSP-7 and the OMUMS in CVM.

USDA representative's report

Dr. Gary Sherman introduced his associate, Jillian Allen, who has been assisting him in his work with the NRSP-7 program. Dr. Sherman also provided an update on responsibilities and personnel changes in his office at USDA. He related that the program's funding is expected to remain at the same level for the foreseeable future. He also discussed the timing and methods for managing NRSP-7 grants in the four regions.

This was the first NRSP-7 meeting for Dr. Sherman since replacing Dr. Larry Miller, who served in this role for many years. Dr. Miller was honored at a dinner with the committee that evening. His contributions to the program cannot be overstated.

FDA'S NRSP-7 liaison report

Dr. Meg Oeller reported on the positive news that NRSP-7's public master files (PMF) have been used to support NADA approvals for several oxytetracycline products for otolith marking of fry and fingerling fish. Another PMF for tylosin for American Foulbrood in honey bees also supported an approval this year.

She noted acceptance of some significant studies for active projects. Also, the full transcript of the NRSP-7/FDA International Workshop on Minor Use and Minor Species is posted on the FDA/CVM website along with copies of the slide presentations. (Go to the "MUMS" page of the CVM website [*www.fda.gov/cvm*], and look under "meetings.") The possibility of a translation into Spanish is being explored.

On the other hand, a problem remains with timely submission of data. Each regional coordinator was strongly encouraged to pressure investigators to complete study reports and notices of drug shipment as quickly as possible.

She also gave an update about the expected timing of the publication of regulations to implement the MUMS Act as well as the personnel changes in the OMUMS.

(Continued, next page)

Active and New NRSP-7 Projects

Drug	*Route of Administration*	*Species*	*Indication*	*Region*
Ivermectin	injection	rabbits	ear mites	S
Erythromycin	oral (feed)	salmonids	bacterial kidney disease	W
Fenbendazole	oral (feed)	deer	GI parasites	S
Lasalocid	oral (feed)	pheasants	coccidiosis	NC
Progesterone	CIDR-G®	sheep/goats	estrus synchronization	NC
Carp Pituitary	injection	various fish	spawning aid	S
Sulfadimethoxine/ ormetoprim	oral (feed)	pheasants	bacterial infections and coccidiosis	NE
Fenbendazole	oral (feed)	pheasants, partridges & quail	gapeworm, capillaria	S
Oxytetracycline	oral (feed)	finfish	bacterial infections	NE
Lasalocid	oral (feed)	deer/goats	coccidiosis	S
Strontium chloride	immersion	finfish	otolith marking	W
Florfenicol	oral (feed)	finfish	bacterial infections	NE
Pirlimycin	intramammary	goats	mastitis	W
Lincomycin	soluble powder	honey bees	American Foulbrood	W
Florfenicol	injection	sheep	respiratory infections	W
Sulfadimethoxine/ ormetoprim	oral (feed)	finfish	bacterial infections	NE
Ceftiofur	intramammary	goats	mastitis	W
Tulathromycin	injection	sheep/goats	respiratory infections	NC
Ovaprim®	injection	ornamental fish	spawning aid	S
Metomidate	injection	ornamental fish	anesthetic	S

NRSP-7 Holds Semi-Annual Committee Meeting *(Continued)*

National coordinator's report

Dr. Dr. John Babish reported on the need for more outreach to stakeholders to solicit increased funding of the program. He led a discussion about increasing needs in a time of decreasing resources.

Conclusion

The meeting was an excellent opportunity to provide an update on the status of all aspects of the program as well as an opportunity to expand partnerships with other organizations and stakeholders.

For more information about NRSP-7, please visit the website *www.nrsp7.org*. For more information on Minor Use & Minor Species issues at FDA, please visit the website *www.fda.gov/cvm/minortoc.htm* or call Dr. Meg Oeller at (240) 276-9005.

NRSP-7 Representatives, Attendance at Recent Meeting

The National Research Support Project #7 (NRSP-7) technical committee is made up of a National Coordinator, four Regional Coordinators, four regional Administrative Advisors, and liaisons from the U.S. Department of Agriculture (USDA) and the Food and Drug Administration (FDA).

Here are the representatives to NRSP-7.

The National Coordinator
Dr. John Babish (Cornell University).

The Regional Coordinators
- WESTERN REGION – Dr. Arthur Craigmill and Dr. Lisa Tell (University of California, Davis)
- SOUTHERN REGION – Dr. Alistair Webb (University of Florida)
- NORTH CENTRAL REGION – Dr. Ronald Griffith (Iowa State University)
- NORTHEAST REGION – Dr. Paul Bowser (Cornell University)

The Administrative Advisors
- Dr. Kirklyn Kerr (University of Connecticut)
- Dr. Garry Adams (Texas A&M)
- Dr. David Thawley (University of Nevada)
- Dr. John Baker (Michigan State University)

The USDA representative
Dr. Gary Sherman (Washington, DC)

The FDA liaison
Dr. Meg Oeller (Rockville, MD)
(Dr. Craigmill was unable to attend and the Western Region was represented by Co-Coordinator, Dr. Tell. Dr. Kerr was also unable to attend.)

The May 11 meeting was attended by the National Aquaculture New Animal Drug Application Coordinator, Rosalie "Roz" Schnick, as well as by other stakeholders and several reviewers and managers from FDA's Center for Veterinary Medicine.

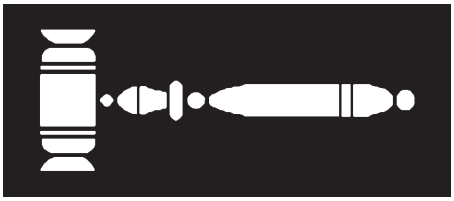
...Progress on Agreement on Pharmacovigilance *(Continued)*

four of the five VICH Guidelines in their jurisdiction:

- Management of Adverse Event Reports (GL24 Draft Guidance), which is CVM's Guidance for Industry #117: Pharmacovigilance of Veterinary Medicinal Products: Management of Adverse Event Reports (AER's)
- Periodic Safety/Summary Updates (GL29 Draft Guidance), which is CVM's Guidance for Industry #142: Pharmacovigilance Of Veterinary Medicinal Products: Management Of Periodic Summary Update Reports (PSUs)
- Controlled List of Terms (GL30 Draft Guidance), which is CVM Guidance for Industry #143: Pharmacovigilance of Veterinary Medicinal Products: Controlled List of Terms
- Data Elements for Submission of Adverse Event Reports (GL42 Draft Guidance), which is CVM's Guidance for Industry #182, Pharmacovigilance of Veterinary Medicinal Products: Data Elements for Submission of Adverse Event Reports

All members of the Pharmacovigilance Expert Working Group have a strong commitment to reaching agreement on the Electronic Standards for Transfer of Data (GL35). With this remarkable achievement so close at hand, electronic submission and automatic population of the databases of the regulatory agencies will be a very big step towards even more rapid recognition of adverse events and the appropriate actions needed to maximize the safe and effective use of veterinary drugs.

Regulatory Activities



A WARNING LETTER was sent to Kenneth L. Wagler, Wagler Farms, Morgantown, IN, for offering a bull for sale for slaughter as food that was adulterated because of the presence of illegal tissue residues. Analysis of tissue samples collected from the animal identified the presence of gentamicin and flunixin. No tolerance has been established for residues of gentamicin in the edible tissues of cattle as codified in Title 21 of the Code of Federal Regulations (21 CFR). The amount of flunixin found exceeded the tolerance of 125 parts per billion established for residues of flunixin in the liver tissue of cattle as codified in 21 CFR 556.286. The presence of these drug residues in the edible tissues of this animal causes the food to be adulterated within the meaning of the Federal Food, Drug, and Cosmetic Act (FFDCA).

The following individuals and firms received WARNING LETTERS for offering animals for slaughter as food that was adulterated because of the presence of illegal tissue residues:

- William G. Vandenberg, owner, Vandenberg Dairy, Caldwell, ID
- Ronald J. Vander Poel and Joseph M. Vander Poel, co-owners, Bar VP Dairy, Pixley, CA
- Edward Imsand, owner, Meadowbrook Dairy, Phelan, CA
- Theo and Cheryl Van Berkum, owners, Theo & Cheryl Van Berkum Dairy, Everson, WA
- Edward DeRuyter, owner, Desertland Dairy, Mesquite, NM
- David B. Van Heel, owner, Swanville, MN

Animals at these facilities were held under conditions so inadequate that medicated animals bearing potentially harmful drug residues were likely to enter the food supply. For example, each operation lacked an adequate system to ensure that animals medicated by the operation were withheld from slaughter for appropriate periods of time to permit depletion of potentially hazardous residues of drugs from edible tissues. In addition, new animal drugs were adulterated when each of the operations failed to use a drug in conformance with its approved labeling. "Extralabel use," i.e., the actual or intended use of a drug in an animal in a manner that is not in accordance with the approved labeling, is permitted only if the use is by or on the lawful order of a licensed veterinarian within the context of a valid veterinarian-client-patient relationship. The extralabel use of approved veterinary or human drugs must comply with sections 512(a)(4) and 512(a)(5) of the FFDCA and 21 CFR Part 530. FDA investigations found that the extralabel use of new animal drugs at these operations failed to comply with these requirements and resulted in illegal drug residues. Because the extralabel uses of the drugs were not in compliance with Part 530, the drugs were caused to be unsafe and adulterated. The above violations involved sulfadimethoxine, penicillin G procaine, flunixin, penicillin, and gentamicin in dairy cows.

WARNING LETTERS were issued to the following individuals and firms because investigations of their operations revealed that they offered animals for slaughter as food that was adulterated because of the presence of illegal tissue residues:

- Benjamin Byma, Ilion, NY
- Richard S. Hunter, owner, H & H Farms, Baileyton, AL
- Rodger W. Camping, president, Eagle Livestock, Inc., Chino, CA

Animals were held under conditions so inadequate that medicated animals bearing potentially harmful drug residues are likely to enter the food supply. The operations lack an adequate system to ensure that animals medicated by the facilities are withheld from slaughter for appropriate periods of time to permit depletion of potentially hazardous residues of drugs from edible tissues. The above violations involved sulfadimethoxine in a cow; gentamicin in a beef cow; and neomycin, flunixin, sulfamethazine, and gentamicin in a culled calf.

A WARNING LETTER was issued to David C. Timmermann, president, J.B. Timmermann Farms, Limited, Breese, IL, because an investigation of the dairy operation revealed that a dairy cow was offered for sale for slaughter as food that was adulterated because of the presence of illegal tissue residues. The amount of sulfadimethoxine found exceeded the tolerance of 0.1 parts per million established for residues of sulfadimethoxine in the uncooked edible tissues of cattle as codified in 21 CFR 556.640. The presence of these drug residues in the edible tissues of this animal causes the food to be adulterated within the meaning of the FFDCA. In addition, new animal drugs Terra-Vet 100 (oxytetracycline hydrochloride injection) and Sulfadimethoxine Injection 40% were adulterated when the operation failed to use the drugs in conformance with their approved labeling. For example, the facility administered a mixture of oxytetracycline and sulfadimethoxine to a dairy cow without the supervision of a licensed veterinarian, and the extralabel use of these drugs resulted in illegal drug residues. Extralabel use is permitted only if the use is by or on the lawful order of a licensed veterinarian within the context of a valid veterinarian-client-patient relationship. The extralabel use of approved veterinary or human drugs must comply with sections 512(a)(4) and 512(a)(5) of the FFDCA and 21 CFR Part 530. FDA investigations found that the extralabel use of new animal drugs at these operations failed to comply with these requirements and resulted in illegal drug residues. Because the extralabel use of the drugs were not in compliance with Part 530, the drugs were caused to be unsafe and adulterated.

A WARNING LETTER was issued to Ed M. Pomeroy, Ferndale, WA, because an investigation of the dairy operation in Custer, WA, revealed that it caused the

(Continued, next page)

Regulatory Activities *(Continued)*

new animal drug Neomycin 325 (neomycin sulfate power packet) and the medicated feed Instant Amplifier Max NT Medicated Dairy Herd & Beef Calf Milk Replacer (containing neomycin) to become adulterated within the meaning of sections 501(a)(5) and (a)(6) of the FFDCA and unsafe under section 512 of the FFDCA. The drug Neomycin 325 was adulterated within the meaning of section 501(a)(5) of the FFDCA when the dairy operation used it in a calf to be processed for veal, which is contrary to the warning on the label. Specifically the operation administered the drug Neomycin 325 by adding it to Instant Amplifier Max NT Medicated Dairy Herd & Beef Calf Milk Replacer, the liquid milk replacer supplement the operation feeds its calves, contrary to the directions set forth in the approved labeling that states it is not for use in liquid supplements and contrary to the label statement that it is not to be used in calves to be processed for veal. Because the FFDCA does not permit the extralabel use of drugs in or on medicated feeds, the actions caused the neomycin to be unsafe under Section 512(a) of the FFDCA and adulterated within the meaning of Section 501(a)(5) of the FFDCA. In addition, the operation caused the adulteration of an animal feed bearing or containing a new animal drug under Section 501(a)(6) of the FFDCA when it failed to use the milk replacer in conformance with its approved labeling by feeding it to calves to be processed for veal and adding the drug neomycin to it.

A WARNING LETTER was issued to Paul M. Kalmbach, president and owner, Kalmbach Feeds, Inc, Upper Sandusky, OH, because an investigation of the licensed medicated feed mill found significant violations of the FFDCA. His firm uses the new animal drug Coban 60 (a Type A medicated article) in an extralabel manner. The extralabel use of a new animal drug in or on animal feed is prohibited by section 512(a)(4)(A) of the FFDCA and 21 CFR 530.11(b). The extralabel use of Coban 60 to produce feed for cattle causes the new animal drug to be deemed unsafe and adulterated within the meaning of the FFDCA. In addition, the use of Coban 60 to produce medicated feed for cattle causes the medicated feed to be unsafe and adulterated within the meaning of the FFDCA. In addition, the feed mill failed to conduct potency assays on at least three representative samples at periodic intervals during the calendar year of each feed required to be manufactured by a licensed feed mill, which is a failure to comply with current Good Manufacturing Practice (cGMP) regulations for medicated feeds. Such deviations cause medicated feeds manufactured at this facility to be adulterated under of the FFDCA.

A WARNING LETTER was issued to John Johnson, president and CEO, CHS, Incorporated, Invergrove Heights, MN, because an investigation of the medicated feed mill located in Great Falls, MT, found significant deviations from cGMP regulations for medicated feeds. Such deviations cause the medicated feeds manufactured at this facility to be adulterated. The investigation found the firm was not conducting potency assays on at least three representative samples at periodic intervals during the calendar year of each feed required to be manufactured by a licensed medicated feed mill. Specifically, during calendar year 2005, the medicated feed mill manufactured batches of medicated feed containing a Category II, Type A medicated article with chlortetracycline and sulfamethazine and batches of medicated feed containing a Category II, Type A medicated article with amprolium, without performing any of the required assays.

A WARNING LETTER was issued to Gil Carrier, president, West Feeds, Inc., Billings, MT, because an inspection of the licensed medicated feed mill located in Great Falls, MT, found significant violations of the FFDCA. The feed mill used the Category II, Type A medicated article amprolium in Type B or Type C medicated feeds containing bentonite. Amprolium is not approved for use in Type B or Type C medicated feeds that contain bentonite. This use causes the new animal drug amprolium to be deemed unsafe and adulterated. In addition, this use of amprolium to produce medicated feed causes the medicated feed to be unsafe and adulterated. Also, the firm failed to conduct potency assays on at least three representative samples at periodic intervals during the calendar year of each feed required to be manufactured by a licensed feed mill. Specifically, the facility manufactured batches of medicated feed containing amprolium, a Category II, Type A medicated article, during calendar year 2005 without performing the required assays. This failure to comply with the cGMP regulations for medicated feeds causes medicated feeds manufactured at this facility to be adulterated.

A WARNING LETTER was issued to Bart Krisle, CEO, Tennessee Farmers Cooperative, LaVergne, TN, because an inspection of the medicated feed mill located in Rockford, TN, revealed significant violations of the FFDCA. Samples of the mill's equine feed, formula 93638, 10% Grain Mix, lot number 4287593638, collected during the investigation were analyzed by FDA's Forensic Chemistry Center (FCC). Analytical results reported by FCC revealed the samples contained monensin. Monensin is not approved for use in equine feed. The manufacture of equine feed containing monensin causes the feed to be deemed unsafe and adulterated. In addition, FDA is aware the mill conducted recalls of the following products due to monensin contamination: 10% Grain Mix, formula 93638, with the lot numbers 4276593638, 4283593638, 4287593638, and 4290593638; and 11% Sweet Horse Feed Course, lot number 43125327. Also recalled were 16% Pelleted Goat Ration, lot number 4313593840, because the quantity of detectable decoquinate was below specifications; Co-op Chick Starter/Grower, Medicated, lot number 43045104 and 43055104, because the quantity of detectable amprolium was below specifications; and Dairy Cattle Rumensin Premix 10000, Medicated Type B Premix, lot number 4287592997, because the amount of detectable rumensin was below specifications.

A WARNING LETTER was issued to Jeffrey Burton, president, Boesl Packing

(Continued, next page)

Regulatory Activities *(Continued)*

Company, Inc., Baltimore, MD, because an inspection of this producer of animal food determined that the facility is subject to the registration requirement in section 415 of the FFDCA. The failure to register a facility as required is a prohibited act under section 301(dd) of the FFDCA. In addition, FDA reviewed the firm's product labels and a brochure entitled "What Does Your Dog Krave." The therapeutic claims contained in the product brochure for K-9 Kraving Dog Food establish that this product is a drug because it is intended for use in the cure, mitigation, treatment, or prevention of a disease. The product K-9 Kraving Dog Food is a drug as defined in section 201(g) of the FFDCA and a new animal drug as defined in section 201(v) of the FFDCA. The product is adulterated within the meaning of section 501(a)(5) of the FFDCA, in that it is a new animal drug that is unsafe within the meaning of section 512(a)(1)(A) of the FFDCA. Under sections 512(a)(1)(A) of the FFDCA, a new animal drug is considered to be unsafe unless there is an approved New Animal Drug Application (NADA) for the product. FDA advised this producer of animal food that it must cease marketing K-9 Kraving Dog Food and file a NADA, or remove the therapeutic claims from the product brochures. Furthermore, the food manufacturing facility needs to register with FDA.

A WARNING LETTER was issued to William Shirley, Jr., owner, Louisiana Proteins, dba Riegel By-Products, Dallas, TX, because inspection of the rendering plant located in Shreveport, LA, revealed significant deviations from the requirements sent forth in Title 21 CFR, Part 589.2000 - Animal Proteins Prohibited in Ruminant Feed. This regulation is intended to prevent the establishment and amplification of Bovine Spongiform Encephalopathy. The inspection found that the rendering plant failed to provide measures, including sufficient written procedures, to prevent commingling or cross-contamination and to maintain sufficient written procedures as required by 21 CFR 589.2000(e). The plant failed to use clean-out procedures or other means adequate to prevent carryover of protein derived from mammalian tissues into animal protein or feeds that may be used for ruminants. For example, the facility uses the same equipment to process mammalian and poultry tissues. However, it uses only hot water to clean the cookers between processing tissues from each species, and does not clean the auger, hammer mill, grinder, and spouts after processing mammalian tissues. Also, the facility failed to maintain written procedures specifying the clean-out procedures or other means to prevent carryover of protein derived from mammalian tissues into feeds that may be used for ruminants. As a result, the poultry meal the facility manufactures may contain protein derived from mammalian tissues prohibited in ruminant. Any product containing or that may contain protein derived from mammalian tissues must be labeled "Do not feed to cattle or other ruminants." Because the facility failed to label their product with the required cautionary statement, the protein meal is misbranded under the FFDCA.

Approvals for New Animal Drugs for May and June 2006

CVM has published in the *Federal Register* notice of the approval of these Supplemental New Animal Drug Applications (NADA)

TRIBRISSEN (trimethoprim and sulfadiazine) 400 Paste (NADA 131-918), filed by Schering-Plough Animal Health Corp. The supplemental NADA provides for revised food safety labeling for trimethoprim and sulfadiazine oral paste administered orally to horses as a systemic antibacterial. The product is used for the control of bacterial infections during treatment of acute strangles, respiratory tract infections, acute urogenital infections, wound infections, and abscesses. The revised labeling adds post-approval experience information, revises the warning statement, and updates the label format. The following post-approval experience was added to the label: "Horses have developed diarrhea during TRIBISSEN 400 Oral Paste treatment, which could be fatal. If fecal consistency changes during TRIBRISSEN 400 Oral Paste therapy, discontinue treatment immediately and contact your veterinarian." Warnings are provided on the product label as follows: "Keep out of reach of children. Do not use in horses intended for human consumption." Notice of approval was published May 31, 2006.

TRIBRISSEN (trimethoprim and sulfadiazine) 48% Injection (NADA 106-965), filed by Schering-Plough Animal Health Corp. The supplemental NADA provides for revised food safety labeling for trimethoprim and sulfadiazine injectable suspension administered to horses as a

(Continued, next page)

Approvals for May and June 2006 *(Continued)*

Supplemental New Animal Drug Applications (Continued)

systemic antibacterial. The product is used for the control of bacterial infections during treatment of acute strangles, respiratory tract infections, acute urogenital infections, wound infections, and abscesses. The revised labeling adds post-approval experience information, revises the warning statement, and updates the label format. The following post-approval experience was added to the label: "Horses have developed diarrhea during TRIBISSEN 400 Oral Paste treatment, which could be fatal. If fecal consistency changes during TRIBRISSEN 400 Oral Paste therapy, discontinue treatment immediately and contact your veterinarian." Warnings are provided on the product label as follows: "Keep out of reach of children. Do not use in horses intended for human consumption." Notice of approval was published May 31, 2006.

CVM has published in the *Federal Register* notice of the approval of these Abbreviated NADAs (ANADA)

HEIFERMAX 500 (melengestrol acetate) Liquid Premix, OPTAFLEXX (ractopamine hydrochloride), RUMENSIN (monensin sodium), and TYLAN (tylosin phosphate) single-ingredient Type A medicated articles to make dry and liquid, four-way combination drug Type C medicated feeds (ANADA 200-424), filed by Ivy Laboratories, Division of Ivy Animal Health, Inc. The ANADA provides for use of single-ingredient Type A medicated articles containing melengestrol, ractopamine, monensin, and tylosin to make four-way combination drug Type C medicated feeds for heifers fed in confinement for slaughter. Ivy Laboratories' ANADA 200-424 is approved as a generic copy of Elanco Animal Health's NADA 141-233 for combination feed use of MGA (melengestrol acetate), OPTAFLEXX, RUMENSIN, and TYLAN. Notice of approval was published June 1, 2006.

HEIFERMAX 500 (melengestrol acetate) Liquid Premix and TYLAN (tylosin phosphate) single-ingredient Type A medicated articles to make two-way combination Type C medicated feeds (ANADA 200-427), filed by Ivy Laboratories, Division of Ivy Animal Health, Inc. The ANADA provides for use of single-ingredient Type A medicated articles containing melengestrol and tylosin to make two-way combination Type C medicated feeds for heifers fed in confinement for slaughter. Ivy Laboratories' ANADA 200-427 is approved as a generic copy of Pharmacia and Upjohn Co.'s new animal drug application NADA 139-192 for combination use of MGA 500 (melengestrol acetate) Liquid Premix and TYLAN in cattle feed. Notice of approval was published May 12, 2006.

DEPARTMENT OF HEALTH & HUMAN SERVICES

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