FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

JOINT MEETING OF THE ANESTHETIC AND LIFE SUPPORT DRUGS ADVISORY COMMITTEE AND DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE

Friday, January 30, 2009

8:00 a.m.

Gaithersburg Hilton
620 Perry Parkway
Gaithersburg, Maryland

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PARTICIPANTS

John T. Farrar, M.D., Ph.D., Chair
Kalyani Bhatt, Designated Federal Officer

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Jeffrey R. Kirsch, M.D.
Nancy A. Nussmeier, M.D.
Osemowota Omoigui, M.D., Consumer Representative
Donald S. Prough, M.D.
Bartholomew J. Tortella, M.T.S., M.D.,
Industry Representative
Daniel Zelterman, Ph.D.

Drug Safety and Risk Management Advisory Committee Members:

D. Bruce Burlington, M.D., Industry Representative
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Timothy S. Lesar, Pharm.D.

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Lewis Nelson, M.D.
Jack Rosenberg, M.D.
Mary Tinetti, M.D.
James Woods, Ph.D.
Julie Zito, Ph.D.
Rebecca Zavacky, Patient Representative

PARTICIPANTS (Continued)

FDA Staff:

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Curtis Rosebraugh, M.D.
Henry Francis, M.D.
Robert Rappaport, M.D.
Sharon Hertz, M.D.

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Call to Order and Introductions of the Committee

[House Audio System initially off. Call to Order and initial Introductions of the Committee not recorded.]

DR. ROSENBERG: Jack Rosenberg. I am a pain specialist and an addictionist at the University of Michigan and at Veterans Medical Center in Ann Arbor.

DR. EISENACH: Jim Eisenach. I am a professor of anesthesiology, physiology and pharmacology at Wake Forest University.

DR. ZITO: Julie Zito, the University of Maryland.

DR. BRULL: Sorin Brull, professor of anesthesiology at Mayo Clinic and a temporary voting member of the Anesthesia and Life Support.

DR. CIRAULO: Dom Ciraulo. I am an addiction psychiatrist and professor and chairman of psychiatry at Boston University Medical School.

DR. PROUGH: Don Prough, chair of anesthesiology at the University of Texas Medical Branch at Galveston.

DR. NUSSMEIER: Nancy Nussmeier. I am chair of anesthesiology at SUNY Upstate Medical University in Syracuse, New York.

DR. KIRSCH: Jeffrey Kirsch, chair of anesthesiology at Oregon Health and Science University.

DR. FARRAR: John Farrar, neurologist, epidemiologist and pain specialist at the University of Pennsylvania, and serving as chair of this committee.

MS. BHATT: Good morning. I am Kalyani Bhatt, the designated federal official with advisors and consultants management.

DR. WOODS: James Woods, University of Michigan.

DR. CRAWFORD: Good morning. Stephanie Crawford, University of Illinois, Chicago, College of Pharmacy. When my flight took off yesterday I had one governor; when it landed I had another.

MS. ZAVACKY: Rebecca Zavacky. I am a patient representative, pancreatic cancer.

DR. HENNESSEY: Good morning. My name is Sean Hennessey. I do pharmacoepidemiology research at the University of Pennsylvania.

DR. MAXWELL: I am Jane Maxwell, with the Addiction Research Institute at the University of Texas, in Austin.

DR. LESAR: Timothy Lesar, director of pharmacy services at Albany Medical Center in Albany, New York.

DR. GARDNER: Jacqueline Gardner, professor of

pharmacy, University of Washington, Seattle.

DR. KRAMER: Judith Kramer, associate professor of medicine at Duke University, and a member of the Drug Safety and Risk Management Advisory Committee.

MR. GOOZNER: Merrill Goozner, Center for Science in the Public Interest in Washington, D.C.

DR. NELSON: Lewis Nelson, associate professor of emergency medicine and a medical toxicologist from New York University School of Medicine.

DR. DAY: Ruth Day, director of medical cognition laboratory at Duke University.

MR. LEVIN: Arthur Levin, director of Center for Medical Consumers in New York City.

DR. BICKEL: Warren Bickel. I do addiction research at the University of Arkansas for Medical Sciences.

DR. HIATT: William Hiatt, cardiovascular medicine at the University of Colorado, and the former chair of the Cardiovascular Renal Drugs Advisory Committee.

DR. LINCOFF: Mike Lincoff, a cardiologist at the Cleveland Clinic Foundation and director of clinical research at the Cleveland Clinic, also from the Cardiac and Renal Advisory Committee.

DR. ZELTERMAN: Dan Zelterman. I am a professor of

biostatistics at Yale University.

DR. BURLINGTON: Bruce Burlington. I am the industry rep to the Drug Safety.

DR. TORTELLA: Bartholomew Tortella, industry rep to the Anesthetic and Life Support Drugs Committee.

DR. FARRAR: So, to begin this meeting we have some formalities: For topics such as those being discussed at today's meeting there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for the discussion of these issues, and that individuals can express their views without interruption. Thus, as a general reminder, individuals will be allowed to speak into the record only if they are recognized by the chair.

We look forward to a productive meeting. In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting.

We are aware that members of the media are anxious to speak to the FDA about these proceedings, however, the FDA will refrain from discussing the details of this meeting

with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topics during breaks or lunch. Thank you.

Conflict of Interest Statement

MS. BHATT: I will be reading the meeting statement. The Food and Drug Administration (FDA) is convening today's joint meeting of the Anesthetic and Life Support Drugs and the Drug Safety and Risk Management Advisory Committee under the authority of the Federal Advisory Committee Act (FACA) of 1972. With the exception of the industry representatives, all members and temporary voting members of the committees are special government employees (SGEs) or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of the committee's compliance with the federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 U.S.C. Section 208 and Section 712 of the Federal Food, Drug and Cosmetic Act is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of these committees are in compliance with

federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a particular individual's services outweighs his or her potential financial conflict of interest. Under Section 712 of the FD&C Act, Congress has authorized FDA to grant waivers to special government employees and regular federal employees with potential financial conflicts when necessary to afford the committee essential expertise.

Related to the discussions of today's meeting, members and temporary voting members of these committees have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts/grants/CRADAs; teaching/ speaking/writing; patents and royalties; and primary employment.

Today's agenda involves discussions of the available safety and efficacy data for all propoxyphene-

containing products, including HCl and napsylate salts and combination drugs, and whether any regulatory action is appropriate.

Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting.

With respect to FDA's invited industry representative, we would like to disclose that Drs. Bartholomew Tortella and Bruce Burlington are participating in this meetings as non-voting industry representatives, acting on behalf of regulated industry. Drs. Tortella's and Burlington's role at this meeting is to represent industry in general and not any particular company. Dr. Tortella is employed by Novo Nordisk, Inc. and Dr. Burlington is an independent pharmaceutical consultant.

We would like to remind members and temporary voting members that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record.

We would like to note for the record that Dr. Sidney Wolfe, who serves as the consumer representative on the Drug Safety and Risk Management Advisory Committee, will not be serving as a member of the advisory committee at this meeting. Dr. Wolfe is going to make a presentation regarding his views and the views of Public Citizen regarding the safety of drug products containing propoxyphene. For today's meeting, Dr. Wolfe will not be involved in deliberation of the issues regarding propoxyphene, and he will not be voting on any of the issues presented.

FDA encourages all other participants to advise the committee of any financial relationships that they may have with any firms at issue. Thank you.

DR. FARRAR: With that, I would like to ask Sharon Hertz, Deputy Director of the Division of Anesthesia, Analgesia and Rheumatology Products, to provide some opening remarks.

Opening Remarks

DR. HERTZ: Good morning. Dr. Farrar, members of the Anesthesia and Life Support Drugs and Drug Safety and Risk Management Advisory Committees, invited guests, thank you for your participation at this important meeting.

FDA has been asked to withdraw products containing propoxyphene from the market on the basis of inadequate evidence of efficacy and a lack of adequate safety. However, propoxyphene combination products are among the most frequently prescribed analgesics in this country.

We do not take lightly claims of an unfavorable risk/benefit. However, we also do not take lightly the high rate of prescribing and the implications of the relative risks and benefits of the alternatives to propoxyphene. So, today we are asking you to consider the overall risk and benefit of propoxyphene-containing products and whether there is support for the continued marketing of these products.

Other regulatory agencies have considered the balance of risk and benefit for these products in recent years. In the United Kingdom a propoxyphene and paracetamol combination, co-proxamol, was second only to tricyclic antidepressants as a drug associated with fatal prescription drug overdose. This led to the decision to remove co-proxamol from the market in 2005. It is important to note that in the U.K. the combination product was often the only drug used in overdose.

In Denmark, Norway and Sweden propoxyphene was

both commonly prescribed and commonly associated with a large proportion of deaths from drug poisonings, especially suicides. All three countries introduced stricter prescribing rules, such as a prescription registry in Denmark.

You will be presented with information concerning the efficacy and safety of propoxyphene, including nonclinical safety data. As you hear the available evidence to support a finding of efficacy keep in mind that the standards to support approval of analgesic drugs have evolved over the years subsequent to the submission of the propoxyphene NDAs in the 1970's.

So, while we would want more data in an application submitted today, we are left with the available data to understand efficacy. And, as there are only single-dose studies in the NDAs the safety data were limited and we will rely on postmarketing safety reports to fill out the picture.

In order to make the most informed and sound decision possible we will be asking you to address a number of questions today. First, we will ask you to consider the efficacy data presented and whether you agree or disagree that there is evidence of efficacy for propoxyphene as

monotherapy or in combination with acetaminophen.

Second, we will ask you to consider the nonclinical cardiac effects of propoxyphene in the postmarketing reports of deaths in which propoxyphene was identified. We will ask you to consider whether the available information provides evidence that propoxyphene is cardiotoxic in the therapeutic range, or do we need additional data to adequately assess the potential for cardiac effects.

Propoxyphene-containing products are the second most frequently prescribed opioid analgesic in the U.S. We will ask you to consider the potential risks associated with the products available for use in place of propoxyphene-containing products should these products be removed from the market. These include the NSAIDs, Tramadol, butorphanol, codeine-acetaminophen combinations and hydrocodone-acetaminophen combinations.

Finally, we will ask your opinion on the risk/benefit bounds and whether it supports continued marketing of the propoxyphene-containing products for the management of mild to moderate pain.

These questions are difficult to answer and the outcome may have a great impact on the prescribing practices

of many physicians and that is why we have asked you to help us do so. It is also why we have specifically sought to bring together a panel with a very professional expertise to address the challenge. Your responses to our questions, and especially your discussions underlying your responses, will be critical to us as we attempt to make a well informed, fair and reasonable decision regarding the situation with as much transparency as possible in the process. Thank you for undertaking this challenge.

DR. FARRAR: Thank you, Sharon. We will move on now to the presentation by Dr. Sidney Wolfe, representing the Public Citizen's Health Research Group. Dr. Wolfe?

Public Citizen Presentations

DR. WOLFE: Thank you very much. I appreciate the opportunity to go through some of the information that we have collected.

At the outset, I would like to thank the people from the Drug Abuse Warning Network who provided me with some of the data that they are going to be showing today. As you probably know, the publicly available data has mainly categorized all the opioids together and so for the last few years it was difficult, using that data set, to look at propoxyphene alone.

I would also like to thank the people in the State of Florida, which, as I will get into in a couple of minutes, collected even more detailed data where they literally asked the medical examiners to decide whether a drug was the cause of death. They were very cooperative and provided me with not only the publicly available data but some other data runs.

January 31st, 1979, which will be 30 years ago tomorrow, was the first of three days of hearings by the Senate Small Business Subcommittee which, over a decade, conducted about 135 days of hearings on the pharmaceutical industry and the FDA, and this three-day hearing was on the propoxyphene and it was several months after we had filed a petition initially, in 1978, to get this drug taken off the market or, conversely, to put it in Schedule II. And, it was determined that it didn't have the characteristics of narcotics in Schedule II and, therefore, that was not considered.

But the three days of hearings, including extensive testimony by the FDAB-and I was reading through the transcript of the hearings and the hearing book, and the Yogi Berra phrase Adeja vu all over again@ really came back forcefully because there was a lot known then I think

sufficiently enough to have taken it off the market, but now there is even more known.

There is little doubt that were propoxyphene and propoxyphene-containing products to come before these committees today for approval, based on what is now known, they would be rejected because of one of the most unfavorable benefit-to-risk ratios ever seen for a drug. I mean, for me, I cannot think of any drug that has a more unfavorable benefit/risk ratio that is still on the market, that is.

This is not to say that there was insufficient evidence for a ban 30 years ago when we first petitioned FDA to withdraw the approval. But the forceful and successful war then waged by Lilly, which was characterized in a half-page article in The New York Times in 1979 showing how Lilly canceled the vacations of their employees to go after meB- not physically, but to go after our efforts to try and get this drug off the market. It is interesting that some of the same arguments that Lilly made at the Senate hearing were very similar to the ones that you will hear this morning from the successor, so to speak, of Lilly that is now selling the brand name version of Darvocet and Darvon.

So, the successful war waged by Lilly in

opposition to our proposed ban tended to drown out evidence of minimal benefit and rapidly growing evidence of life-threatening and often lethal harm.

You will hear a little bit of this in the DAWN presentation, but the federally-funded Drug Abuse Warning Network collects data from both emergency rooms and medical examiners concerning drugs which have been determined to be related to emergency-room visits or deaths. Contrary to the views of some that any time someone dies and has the drug on board this is reported, the instruction is clear from DAWN. They train people to report only those drugs they believe are related to the death. Those are DAWN's own words.

This medical examiner data has changed over the years so you can't compare necessarily older years with new years in that the number of entities reporting has increased in definitions such as that accidental death have been modified or combined. In 2006 and 2007 the same definitions were used.

[Slide]

The first slide shows the DAWN data for both 2007 and 2007 DPX, standing for propoxyphene-related deaths, 446 in 2006, up to 503 but, again, there is an increase in the reporting jurisdictions over those two years. The majority

of these were deemed by the medical examiners to be accidental deaths, not suicide, and the majority involved multiple drugs. But, again, multiple drugs were thought to be related in the single drug case as the easiest case because it was the only drug there and it is much more likely that that is the sole cause. You can see that in the DAWN data the majority of these are multiple drugs.

The DAWN data do not imply causality but, rather, that the death was related to the drug. It must be noted that these data represent only a fraction of the U.S. population in 2007. The population covered by DAWN in that year was 109 million people or about 36 percent of the total population for that year. However, the population covered by the DAWN mortality component is primarily from metropolitan areas and is not based on a statistical sample. Thus, the DAWN data must not be used to extrapolate to the nation.

As of 2007, there was complete state reporting from only ten states. Most of these are from individual jurisdictions, not states, not including Florida.

[Slide]

I will now get to Florida. The system of collecting and recoding medical examiner data in Florida

provides more details than the DAWN data. The presence of a drug in a decedent is categorized as cause if the medical examiner concluded that there was enough of the drug present to have been either the sole cause or a contributory cause of the death.

Other drugs are listed as merely present if the medical examiner did not conclude that the drug played a role in the patient's death. So, the dichotomy is cause or presence. So, the incidental finding is noted as present. In their own words, quote, the state's medical examiners were asked to distinguish between the drugs being the cause of death or merely present in the body at the time of death.

In the handout you get directly from the report from Florida drugs identified in deceased persons by Florida medical examiners, 2007, the pie chart, and I don't have a slide for this, showing in percent in that year where propoxyphene was the cause and in 75 percent it was present.

[Slide]

The graph here shows that for the last five years, 2003 to 2007, the range of total propoxyphene-related deaths goes from 328 to 368, mainly the same. Those caused in one state in one year by propoxyphene ranges from 108, the highest in 2003, and the last year for which there are data,

85 deaths in that state in one year caused by propoxyphene.

[Slide]

The next tableB-and, again, these are data provided by the state--breaks down these 85 deaths in that one year, 2007, into whether they were accident or suicide and whether it was the sole cause or whether other drugs were involved. Other drugs involved means that each of the drugs was thought to be a cause of the patient's death. What you can see in the left column is that in 25 of these 85 drugs propoxyphene was the sole cause of death and in 60 others it was propoxyphene plus other drugs.

It should be noted that Florida, with a population of about 18.7 million people, represents 1/16 of the U.S. population. Again, one should not extrapolate from that by multiplying by 16, but the point is that this is a state that, at a state level, does not provide data to DAWN so this is some additional data. DAWN does an extraordinarily good job coping with the variety of ways that different states collect the data, and I think that in many ways Florida is a very good model, and I am sure DAWN would probably like it as well if other states got as detailed and meticulous as Florida in instructing the medical examiners to really point towards cause, ruling out other causes, and

so forth.

I will now spend just a couple of minutes on the FDA review of efficacy. The conclusion of FDA's extremely comprehensive, by far the most comprehensive review that has ever been done of the efficacy of this drug-Ba lot of the efficacy reviews were based on meta-analyses that had not been done. Meta-analyses were not as common then, in 1978, as they are now. So, a lot of what FDA relied on, including the new drug application data, has just never been put together before. And, their conclusion was, quote, there is evidence that propoxyphene alone possesses weak analgesic effects in patients with acute pain compared to placebo.

While most of the studies show that in combination with acetaminophen the propoxyphene component appears to contribute little or no additional analgesic effect beyond the efficacy of the acetaminophen when studied in patients with acute pain, there is at least one studyB-there was one study--that does support the contribution. And I think it is one study, pretty isolated.

The FDA review not only included the NDA data submitted to the agency, but a series of meta-analyses and individual published randomized trials. Just to look at one of them, the Hopkinson one in 1973, their conclusions were

that a global evaluation at the end of treatment, 4 hours, showed no difference between propoxyphene and acetaminophen combination and the single ingredient in the percentage of patients reporting effectiveness.

As you can see in the handout hereB-I didn't put a slide up of that, in the combination group 64 percent reported effectiveness; 62 percent reported effectiveness in the single acetaminophen group; 32 percent in the single propoxyphene group; and 30 percent in the placebo group.

In some other studies propoxyphene was superior to placebo. The FDA review stands on its own merits and in essence finds that, (a) the addition of propoxyphene to acetaminophen does not result in a statistically significant improvement in pain relief and we should note, and you will see some of these data later, that 97.5 percent of the prescriptions for propoxyphene in this country are in the form of propoxyphene-acetaminophen. So, it doesn't result in a statistically significant improvement in pain relief compared to acetaminophen alone and, (b) propoxyphene alone has only weak analgesic effects.

I am now going to take a few minutes to present a statement by Dr. Steven Karch. He was unable to be here and I will not pretend I am he because we have different

backgrounds. I am going to show some slides that he prepared. I will introduce him in his own voice, I guess, and go into the slides.

I am a former assistant medical examiner in San Francisco where my practice was confined mainly to the investigation of deaths involving drug toxicity. I am a member of the Royal Academy of Physicians, Faculty of Forensic and Legal Medicine. My textbook, Karch's Pathology of Drug Abuse, last edition published last month, is widely used by pathologists and medical examiners in the United States and Europe. The FDA actually used some of the information in it when they were considering banning Ephedra, something that we had brought to FDA's attention. It is generally considered authoritative. This textbook contains a subsection specifically devoted to propoxyphene-related deaths.

I have been asked to confine, by me, to confine my analysis to the cardiological and toxicological issues of the effects of dextropropoxyphene in clinical practice from the viewpoint of a death-investigator interested in evidence-based medicine.

[Slide]

These are his slides. Propoxyphene is a low

affinity mu receptor antagonist that may cause more respiratory depression by only modest pain relief. The oxidation product, norpropoxyphene, accumulates in the heart, is cardiotoxic and this toxicity is not reversed by naloxone.

[Slide]

The industry response, which you will hear shortly, to Public Citizen's petition, states, quote, the petition does not raise any new safety issues that have not already been considered by the FDA, end quote. That statement is clearly untrue. When propoxyphene was first approved over 50 years ago, and a lot of this was true 30 years ago when our first petition was filed, methods for direct quantification of norpropoxyphene did not exist. Genetic polymorphism was unrecognized, and this is both in terms of the metabolizing CYP enzymes and the hERG and SCN5A channels, ion channels, were not yet identified.

[Slide]

In England and Wales in 1977 through '99 18 percent of drug-related suicides involved dextropropoxyphene, constituting five percent of all suicides in that country. Deaths from overdose may occur rapidly. The lethal dose can be relatively low and the

effects are potentiated by alcohol and other CNS depressants. As Dr. Boyd Stevens, the chief medical examiner in San Francisco, said when we consulted with him 30 years ago, maybe twice the recommended dose of propoxyphene and a couple of drinks can be lethal. The majority of dextropropoxyphene-related deaths occur before hospital treatment can be received.

[Slide]

The first step in metabolism is oxidation by the CYP3A4 liver enzyme to form, norpropoxyphene. Norpropoxyphene is cardiotoxic, binding to both the CSN5A and hERG channels. These are things that I certainly never heard of 30 years ago, as was pointed out by Dr. Karch now, annotating his talk. We know a lot more. The hERG channel, for example, is involved in cardiac induction in the sense that if you block it you can prolong the QT interval and some of the arrhythmic problems with this drug and other drugs with long QT intervals are related to blocking of this channel.

The norpropoxyphene is longer acting than the parent compound. I will go over some pharmacokinetic data. It has effects that are not reversed by opioid antagonists.

[Slide]

The CYP3A4 is the major CYP enzyme catalyzing dextropropoxyphene metabolism. The variability in pharmacodynamic and pain relief effectiveness of this drug is likely due to inter-subject variability in the expression of this enzyme and also drug-drug interactions. The majority of drugs are metabolized by this particular subset of CYP enzymes.

[Slide]

Propoxyphene itself is a competitive inhibitor of CYP3A4 and many other drugs also fall in this class, including calcium channel blockers, macrolide antibiotics, isoniazid and proton pump inhibitors. Most importantly because it has been documented more, carbamazepine, a widely prescribed anticonvulsantB-its breakdown has been well recognized as being slowed by propoxyphene and toxic levels may accumulate. And, there are a number of papers documenting this.

[Slide]

In addition to blocking the CYP3A4 enzyme, it also clearly blocks CYP2D6 enzymes. These are the different enzymes in the liver that metabolize different classes of drugs. This opens up the possibility for other types of drug interactions. Most beta blockers are metabolized by

this enzyme, CYP2D6. Reported bradycardia is well documented with blood levels, and everything, in use of metoprolol to suggest that symptomatic drug interactions are occurring.

[Slide]

Norpropoxyphene accumulates in cardiac tissues and its effects are not reversed by naloxone. It may block both the INa and also the IK ion channels. Blockade of the main sodium channel causes conduction delay. Blockade of the hERG, slow/rapid depolarizing K channel, may cause QT interval prolongation leading to Torsades de Pointes and sudden death. There are genetically determined polymorphic forms of hERG that may increase such toxicities so that people who have the genetic abnormality may at even lower doses be getting in serious, life-threatening, fatal trouble with this drug.

[Slide]

QRS is significantly prolonged in DPX overdose. There is a paper showing dose-related prolongation in patients of QRS interval. These findings have clinical relevance to the management of patients with propoxyphene poisoning. Heart block must be anticipated. Certainly, in dog experiments done by Eli Lilly back in the mid-'70s this

was made clear. Some of this was published. Some of it was never published. I turned over some unpublished data to the FDA in 1978. They actually fired an employee in that year who had done some of these studies and was uncomfortable with the idea that they had not been made public and turned them over to us and we turned them over to the FDA.

[Slide]

Increased toxicity with ethyl alcohol-Bwhen it is co-administered with ethyl alcohol, and I mentioned Dr. Stevens' comment about not terribly much more than the recommended dose of propoxyphene and a few drinks can be lethal. First pass hepatic metabolism is decreased, which means that dextropropoxyphene concentrations increase. Ethanol is frequently present in propoxyphene deaths. In the U.K. in a study of 120 suicides by propoxyphene overdose, alcohol was found to be involved in 58.5 percent of the cases, and these individuals generally had lower propoxyphene blood levels and consumed fewer tablets.

[Slide]

Why should it be banned? These are the conclusions of Dr. Karch. It is a dangerous drug. Large amounts are rapidly absorbed from the GI track very quickly, making attempted suicide difficult to treat. Even modest

amounts of this drug might cause lethal cardiac arrhythmias in individuals with undiagnosed hERG genetic polymorphism, again, the point being that this may happen at even lower doses than the ones that are associated with other problems. Use of dextropropoxyphene can lead to dangerous levels of antibiotics and anticonvulsives.

[Slide]

That is the end of Dr. Karch's presentation. I will now go back to the section in your handout that is called clinical pharmacology data. Because there is very little clinical data on patients found with the unexpected deaths typical of coroners' cases, out of hospital deaths which make up the majority of these deaths, it is useful to examine clinical data from patients who lived after their overdoses of propoxyphene. A very unique series of 222 consecutive patients admitted to one hospital in Denmark over a six-year period provides extremely useful data, confirming what FDA has referred to in the presentation they will make in the preclinical studies they described.

This first figure describes the findings on admission of these patients. As can be seen, 48 percent of the patients had circulatory failure, heart failure, impaired circulation; 15 percent had had a cardiac arrest,

asystole; 9 percent had abnormally slow pulse; and 41 percent had an abnormal electrocardiogram, including 19 patients who had ventricular arrhythmia.

The authors, who had also done some preclinical studies, commented on the experimental evidence of a negative chronotropic effect, slower pulse, and a negative inotropic effect, weaker heart contraction, with propoxyphene that would explain some of these clinical findings, including the fact that only a few of the patients with circulatory failure exhibited compensatory tachycardia, in other words a faster pulse, that a normal person would attempt to compensate for the fact that the heart is not pumping as forcefully, and this was not seen because of the negative chronotropic effect.

[Slide]

The next chart looks at further life-threatening clinical findings on admission. Forty-four percent of the patients, or 100 of them, had acute respiratory failure. This is, again, due to the propoxyphene itself not the norpropoxyphene. Other opioids can do that too. They all had to be placed on ventilators. Twenty-two, or 10 percent had convulsions and 163, or 73 percent, were in a stupor or coma.

[Slide]

The final slide from this paper concerns the 17 patients, or 8 percent of all 222, who died despite apparently excellent care in the ICU. The protocol that they administered was compulsively and properly thorough and, obviously, rescued most of these people. Again, most of the deaths are out of hospital and the opportunity to be saved doesn't happen. What you can see here is that 9 or 53 percent of the deaths were from heart failure. A total of 13 or 76 percent of the deaths were from all cardiovascular causes and 4 or 24 percent of the deaths were from brain damage.

As we discussed in our petition, there is a very narrow margin of safety with propoxyphene, partly because of the accumulation, even at normal doses of the cardiotoxic metabolite norpropoxyphene. This is borne out by pharmacokinetic studies, especially the findings with multiple doses over time and mores so in older patients. I am referring to a published study, the data for which are in the next paragraph of the handout and I will just go through it.

They looked at two groups of people, older people, age 70 to 79, healthy older people, and younger people, age

20 to 28. They administered what amounts to one 65 mgB-it was two 32.5 mg of propoxyphene pills three times a day, single dose, and then they did multiple dose studies.

The median maximum blood levels and the ranges in these people for a single dose in healthy elderly people were 156 mcg/L, with a range going up as high as 366 mcg/L for propoxyphene. For the metabolite the median, again, single dose was 193 mcg/L, with a range going up to 283 for multiple sequential doses, three times a day of essentially 65 mg, a relatively low dose. For one week the median level of propoxyphene was 239, up significantly, with a high of 509 mcg/L, and for norpropoxyphene it was 1100 median blood level, with a high of 1500 mcg/L.

Thus, although blood levels of the shorter half-life propoxyphene increased from 156 single dose to 239, an increase of 1.5 times, levels of the longer half-life and cardiotoxic norpropoxyphene metabolite increased from a median value of 193 to 1100, an increase of 5.7 times when the drug was used over time in elderly people, again, at a fairly low dose.

[Slide]

In our petition we had cited data from patients being given chronic doses, some at lower levels and some at

higher levels. I have the chart for that in the handout and here on the screen. What you can see is that there is overlap, particularly with the people taking the three pills, between blood levels here, these are live patients, and the blood levels in the pharmacokinetic study.

It should be noted that in patients with levels between 500 mcg and 1000 mcg/L there have been published case reports of some toxicity. Of course, it matters enormously whether you have become addicted to it and are taking it over a long period of time and are tolerant of it or not but simply to say that there isn't a huge difference even without alcohol or other drugs between the levels that people can achieve of propoxyphene, and particularly norpropoxyphene, and the levels that are getting towards the lethal range. Some people believe that 1000 mcg/L or 1 mg/L is the beginning of the lethal range. So, you can see that there is not much play here.

Mortality compared to codeine-containing combinations with acetaminophen and the effect of the ban in the United Kingdom: A recent study estimated the frequency of overdose and death for the three most popular acetaminophen-opioid compound analgesics, propoxyphene and acetaminophen and two different codeine preparations. One

was codeine itself and one other was a synthetic codeine.

Adjusting for the relative amounts of prescriptions, as you have to do, for these three drugs overdoses involving propoxyphene and acetaminophen were ten times more likely to be fatal when compared with the mortality for the overdoses of the other two codeine or synthetic codeine-containing analgesics. The authors estimated from this study that withdrawal of propoxyphene and acetaminophen would prevent 39 excess deaths per annum in Scotland alone.

A very recently published study measured the effect, the early effect of the U.K. announcement of the ban of propoxyphene and acetaminophen, which is called co-proxamol in the U.K., on suicides in Scotland. The study showed early evidence--and the study included a year before the ban had actually been finalized and a year after it had been announcedB-of reduction even before the ban was finalized, which happened just a year ago. In the five years pre-legislation, 2000 to 2004, there was a mean of 37 co-proxamol deaths per year in Scotland. In the first year after the legislation was announced the number had fallen to 10 per year. The average number of total Scottish drug poisoning deaths in the earlier interval was 171 per year.

Rather than compensatory use of other drugs and suicides attendant to that, there was actually a slight decrease in the overall drug-related poisonings in Scotland, from an average of 171 in the earlier years to 126.

In a personal communication with Dr. Nick Bateman, who is the co-author of both the ten times higher mortality rate study compared to codeine-containing compounds and of the study just published a few months ago on the early returns from Scotland, he told me that in England unpublished data, which he is working on, shows a 90 percent decrease, and that is over an extra year of time apparently. When I asked him whether he supports the petition to ban this drug in the United States he said yes.

[Slide]

You will see other versions of this but it all is pretty much the same. Despite the evidence for the serious dangers of this drug and its marginal effectiveness, for most of the past 35 years or moreB-we don't have the data going back longer and this drug has been on the market for 50-plus yearsB-propoxyphene-containing drugs, now mainly the combination of propoxyphene and acetaminophen, 97.5 percent, have been among the top 25 selling drugs in the U.S.

The data for the most recent eight years shows the

continuation in the top 25 status for the generic combination of propoxyphene and acetaminophen, similar to the brand name Darvocet. In the most recent year for which data are available, 2007, there were 21.3 million prescriptions filled for the generic combination of propoxyphene and acetaminophen, making it the 21st most prescribed generic drug in the country. As the FDA has estimated in the data they will show you, close to ten million people in the United States are estimated to be using this drug now.

Other top 25 drugs with vastly different benefit/risk ratios because, as Dr. Hertz pointed out, that is really the issue, what is the benefit/risk ratio here. It is the issue for any drug either before it is approved or when it is reevaluated after it has been on the market based on information not available at the time of approval.

Two other top 25 drugs, oxycodone, 16th, and warfarin, 22nd, are worth mentioning because, although they too have significant risks, they have clear unequivocal and very significant benefits, in the case of warfarin a unique benefit. That is why it is the drug most used as an anticoagulant in people who are at risk of blood clots because of atrial fibrillation, and so forth. Because of

proven, important efficacy, it would not be sensible to even consider removing either oxycodone or warfarin from the market. Risk mitigation strategies for such drugs, including the criminal prosecution of Perdue for mis-promoting Oxycontin and proper cautions for doctors and patients for both drugs are necessary. For propoxyphene market withdrawal is the only rational alternative.

I will just go over a couple of recent review articles. Again, these were published after the research we did for our petition. In a review entitled Propoxyphene, Dextropropoxyphene: A critical Review of a Weak Opioid Analgesic that Should Remain in Antiquity, the authors--all members of the Barkins family, I have never met them but they all have the same name and are related, I am told--concluded that, quote, propoxyphene offers no therapeutic advantage over any other opioid.

The population-induced iatrogenic events and risk outweigh any perceived benefits that could be achieved. Any therapeutic benefit from this drug has long been overdue for disuse. The time has arrived for its imminent disposal into antiquity. More suitable therapeutic agents are available with a better risk/benefit ratio and less end-organ damage, such as those with the central nervous system, cardiac and

pulmonary systems.

In another review, by Sachs, focusing more on efficacy, found that, quote, propoxyphene has poor efficacy and significant side effects. A meta-analysisB-and, again, this is one of the ones referred to by the FDA-Bof 26 trials involving 2,231 patients compared the combination of acetaminophen and propoxyphene with acetaminophen alone or placebo. The narcotic combination offered little benefit over acetaminophen alone.

I will skip over the rest of this. It is just other analyses. Thus, propoxyphene provides minimal, if any, additional analgesia to acetaminophen alone and is associated with significant adverse effects.

In conclusion, when we first petitioned the FDA to ban propoxyphene-containing drugs 30-plus years ago, our petition for a ban was supported by a number of medical examiners around the country. We have contacted some of those, the ones that are still alive, and they are still supportive.

Our more recent petition was prompted by the conclusion of the U.K. government after a review of all the evidence that efficacy of this product, quote, is poorly established and the risk of toxicity in overdose, both

accidental and deliberate, is unacceptable, end of quote. They further said that, quote, it has not been possible to identify any patient group in whom the risk/benefit ratio may be positive, end quote.

Despite the drug being a weak analgesic as you have seen or probably will be shown this morning, if you look at it, its chemical structure is at first glance almost identical to methadone. I am sure that was the model for which Lilly developed the drug. Unfortunately, it is a poor analgesic compared to methadone and, also unfortunately, like methadone it has some cardiotoxic properties.

In response to an article, and this is interesting, there was a series of randomized placebo-controlled trials done in the late ‘60s, early ‘70s by Dr. Charles Moertel, who was chief of oncology at the Mayo Clinic, and he published an article in The New England Journal of Medicine in 1972 looking at various analgesics and concluding then, essentially 36 years ago, that propoxyphene was not very good. He said in this article, quote, it appears that factors other than intrinsic therapeutic valueB-and he is referring to advertising promotion, misleading promotion claiming that it was as effective as codeine, which it isn’t, and that it was non-

addicting, which it isn't. Anyway, factors other than intrinsic therapeutic value are responsible for the commercial success of propoxyphene.

A representative of Lilly wrote in a letter to The New England Journal in response to Dr. Moertel's article, quote, Darvon products have won remarkable acceptance-BI think remarkable is the key word--by patients and physicians since their introduction, end quote.

In a letter in response to the Lilly letter Dr. Moertel replied, quote, the implication that general acceptance of a therapeutic procedure by physicians in a given era constitutes obligate proof for effectiveness is not tenable. If this were true, we would still be bound to the mummy dust, unicorn's horn, leeching, purgatives and mustard plasters universally endorsed by our forebears. We must constantly offer challenge to all our sacred cows so that our patients may be afforded the highest care at the most reasonable cost, end quote.

I think that is really the issue here. This drug has become almost a sacred cow. The prescribing is testimony to that. It has decreased slightly but at this rate it will take another 30 or 40 years for it to go down to where it should be, which is zero.

Finally, I contacted Dr. Donald Kennedy who was the FDA commissioner when we originally filed our petition to ban propoxyphene in 1978. My calling him was prompted by my reading his testimony before the Senate committee in 1979 and he obviously was torn about this drug. He recognized some of the problems and thought that there needed to be more study and data on the efficacy, and ultimately the FDA rejected our petition.

When I asked him, after sending him our 2006 petition to ban the drug, if he would now support our petition to ban the drug he replied, quote, you can sign me up, end quote.

As I said in the beginning, propoxyphene has one of the most unfavorable benefit-to-risk ratios I have ever seen for a drug. These committees will, hopefully, agree with this and recommend the beginning of a two-year phased withdrawal of these products. The two-year phased withdrawal is necessary because the drug is addicting and it takes that amount of time for patients to be switched to other drugs.

I would just like to comment briefly-Bit is not in the written testimony but it is one of the questions before the advisory committee, what do you switch people to, what

is the alternative?

Well, there are several. Almost by definition, if 97.5 percent of the people are taking a combination of acetaminophen and propoxyphene for which there isn't evidence of a statistically significant increase in benefit with propoxyphene, they could be taking just acetaminophen.

Another alternative is aspirin. Aspirin, in many studies, works better than propoxyphene alone. As mentioned by Dr. Hertz, hydrocodone could be used. It is by far the biggest selling generic opioid, 117 million prescriptions a year. I did some calculations in terms of how likely it is, adjusted for the amount of prescribing, that hydrocodone would cause death, and its propoxyphene-related deaths again, using that phrase, of about 2.5 times higher. Actually, I used the Florida data in terms of deaths caused by hydrocodone, deaths caused by propoxyphene, and adjusting for the amount of prescriptions.

DR. FARRAR: Dr. Wolfe, I need to ask you to finish up, please.

DR. WOLFE: Okay. The last statement I had was thank you for taking time to listen to my presentation. That literally is the end. I would be happy now, or at some other time, to take questions.

DR. FARRAR: We will take questions later during the question and answer session. In the interest of providing the committee with the most complete data on this I have allowed you to go over your time a bit. I just want to assure the pharmaceutical representatives that they will be allowed their full time as well, which will push back on our break a little bit, but at this point I would like to ask the Xanodyne Pharmaceutical group to provide its presentation.

Sponsor Presentation

Xanodyne Pharmaceuticals

Presentation by James B. Jones, M.D., Pharm.D., FACEP

DR. JONES: Members of the Committee, representatives of the FDA, good morning. My name is James Jones and I am the vice president of clinical development and medical affairs at Xanodyne Pharmaceuticals. Just as important, I am also a practicing, board-certified, emergency medicine physician, still seeing patients in the area of pain management, as well as the person who sees and treats suicide attempts and suicide completions. So, I am coming to you today on behalf of my colleagues at Xanodyne as well as Qualitest to thank you for allowing me to present information and data supporting the safety and efficacy of

propoxyphene, propoxyphene-containing compounds, a chemical entity that has over 50 years of history and is widely used but, most importantly, is widely relied upon by physicians and patients in the management of pain.

[Slide]

The outline of what I will present is as follows: I will briefly present the epidemiology of pain and issues regarding pain management. We will then raise some specific issues brought forth by the Citizen's Petition and some initial responses to those issues.

I will provide an overview of the product's safety and efficacy and the years of history of safe and effective use. I will conclude by bringing forth some additional topics raised in the Citizen's Petition, providing a little extra data to answer and address some of those issues that were brought forth.

[Slide]

As we all know, pain is prevalent, under-diagnosed, under-treated, and can be quite debilitating. Currently it is estimated that 25 million Americans annually experience acute pain, which is usually induced by trauma or some form of surgery, most of them presenting to their primary care physicians and the emergency departments.

It is also estimated that 48 million Americans experience chronic pain, of which 40 percent cannot work; 60 percent cannot engage in daily activities; and this all comes at a cost annualized as about 100 billion dollars which include healthcare costs, compensation for lost work, as well as litigation.

[Slide]

I believe we can all agree that the etiology of pain is as diverse as the people it afflicts. These differences between the individuals make managing pain very, very challenging. To adequately treat pain the clinician absolutely requires many options in order to treat the pain. When one treats the individual, and when you talk about the benefit, we have to talk about the benefit for the individual. This often requires a multi-modal approach to managing that pain. This can come in the form of pharmacologic intervention, non-pharmacologic intervention, as well as adding opioids and non-opioid medications.

This requires a clinician to have a large array of opportunities to choose the right therapy and tailor their treatment to that individual patient. Treatment algorithms exist and are supported by many professional associations, and have ranged from simple analgesics like acetaminophen

and aspirin to major opioids such as oxycodone and hydrocodone.

If we continue to shrink the toolbox and the number of tools in that toolbox that we use to treat patients in pain it is going to become extremely problematic in this country.

[Slide]

I would like to turn my attention right now to some specific issues that were raised in the Citizen's Petition and provide an initial response. Later we will talk a little bit more about specific data as it relates to each topic.

[Slide]

As members of the committees, you are keenly aware of the legal standards that are required for the removal of a previously approved product. It requires proof of imminent hazard to public health. This is determined if a product is unsafe under the conditions of use for which it was approved and labeled, or there is a lack of substantial evidence--and this is in the form of adequate and well-controlled trials not case studies, anecdotes, surveys and lettersB-that the drug will have the effect purported under conditions for use and for which it is labeled.

As such, there was a 1978 Citizen's Petition, as was previously mentioned by Dr. Wolfe, that was denied in 1979. The same petition was put forth again in 2006, which is why we are here today. This offers little additional evidence and support to the initial petition, except around the DAWN data and the U.K. experience.

[Slide]

There is an argument that there are many deaths attributed to propoxyphene as a cardiotoxic effect of its metabolite norpropoxyphene. As was mentioned, in 1989 HEW concluded that there was little evidence that the metabolite's effects were a common factor in propoxyphene-associated deaths. This Citizen's Petition provides little new data.

In my literature review there are two articles. One was a myocyte study that had been published and there is an inappropriately controlled, underpowered study in the U.K., with an N of 15, where ECGs were handwritten, hand-read and not uniformly consistent between the individual patients.

[Slide]

It is alleged that propoxyphene can cause death or severe cardiac events when taken as directed. In 1979 the

FDA concluded that there were no well documented examples of death when taken according to label.

HEW determined that there was no clear evidence that propoxyphene can cause death when taken in accordance with the label and, as it is labeled, it is in the absence of tranquilizers and alcohol. HEW did identify that the death presented in the initial Citizen's Petition were the result of drug misuse.

You will hear later from one of our experts, Dr. Jody Green from the Rocky Mountain Poison Center, showing little evidence that the normal use of propoxyphene causes clinical cardiac instability and bad outcomes.

[Slide]

It is proposed that other analgesicsB-and we just heard several minutes agoB-are better alternatives to propoxyphene, including acetaminophen and aspirin. In 1979 the FDA noted that aspirin and acetaminophen have their own risks and are not proper for every patient. NSAIDs have been the subject of significant risk concerns recently, specifically the COX-2 inhibitors, as we have seen with withdrawal of products from the market. There are studies that show that propoxyphene-acetaminophen combinations are superior to acetaminophen alone.

[Slide]

So with that, now I would like to walk you through the history and the approvals of propoxyphene and propoxyphene-containing compounds.

[Slide]

Propoxyphene and propoxyphene-containing compounds have a long history of safe use in the United States, South America, Europe, Africa, Australia and Asia. As has already been mentioned, it is one of the most widely prescribed and accepted treatments by clinicians for the treatment of mild to moderate pain. It is one of the most commonly prescribed drugs in America.

The age distribution in which propoxyphene prescriptions are written is seen here. This will be useful later in assessing age-related issues, adverse events, that will be presented by Dr. Green on data collected not overseas but in the United States.

[Slide]

As was mentioned, Darvon was initially approved based on its safety back in the 1950s. Later it underwent further investigation and evaluation, subsequent to the Kefauver-Harris Drug Amendment, and was approved based on its efficacy.

There have been subsequent approvals for new propoxyphene-containing compounds which include new formulations, strengths and combinations with other drugs. As recently as 2003 there was approval of an NDA for Darvocet A500. There are many, many propoxyphene products on the market. There are over 97 products that have unique identifiers. These are being sold over the last 24 months, and the most recent approval of a propoxyphene-containing compound was within the last year.

[Slide]

Given the limited amount of time that we are going to have today for our presentations, I am going to provide an overview, a summary of the vast quantity of data that has been accumulated over the last 50 years on the safety and efficacy of propoxyphene. For additional details I would refer you to both the industry as well as the agency's briefing packet that was supplied in advance of the meeting.

[Slide]

In order to properly assess the available data, I would like to review with you, the experts, some of the challenging methodologic issues that we have in evaluating pain medicines today. As you know, clinical evaluation of analgesics is quite complex. It is often very difficult for

patients to distinguish among analgesics, specifically when they have different mechanisms of action.

There is also the high placebo rate, with 30 percent of patients getting some temporary relief, especially in mild pain syndromes. We all know that as the pain increases it is a lot easier to get a response from a patient who has a pain score of 10 than someone who has a pain score of 5.

It is also difficult when you compare opioids as they have different potencies. If one is careful in planning of a study and uses equipotent doses of opioids they will get the same pain relief.

There are also changes occurring over time in how we look at the acute pain model, as evidenced by the transition from using third molar extractions to bunionectomies.

[Slide]

I present to you the two initial studies, published, that were used to approve the propoxyphene-hydrochloride back in the 1950s. These studies were both placebo-controlled, positive-controlled, dose-escalating studies. They concluded that the study drugs, codeine and propoxyphene, were indistinguishable from one another and

had better analgesic efficacy than placebo.

[Slide]

Subsequently there were seven additional clinical studies used as evidence of the safety and efficacy of Darvocet, or propoxyphene and acetaminophen, both as a hydrochloride salt, and a napsylate salt.

Three of these studies were completed. Four had the results tabulated before completion. They did a four-point categorical measurement out to eight hours for both pain intensity and pain relief.

[Slide]

Additional data that was assessed was time to onset of analgesia; total analgesic response over six hours, something that we know today as SPID; peak pain relief. And, they also looked at consistencies in medication with regard to initial pain intensity so they were making sure that the groups were evenly matched at baseline, and that the patterns of change in analgesic response were consistent with the pain intensity. As I mentioned earlier, it is much easier to treat someone from a pain score of 10 to 5 than someone from 5 to 2.5.

[Slide]

So, let me summarize these results for you. The

first slide will show that the results of the single entity agent, Darvon, or in this case propoxyphene, were significantly better than placebo, providing analgesia at one or two hours. Acetaminophen was as well. There was no evidence of an interaction between propoxyphene and acetaminophen, rather, they saw additive effects.

[Slide]

When one looked the Darvocet arm-Bthis was the propoxyphene and acetaminophen, there was significantly more effect than placebo in five of the seven studies. This was statistical improvement. The other two studies were numerically improved but not statistically. While I did not conduct the studies, one would assume that it had to do with the ending of the studies early to get the data to the FDA.

Darvocet, the combination product, was also better than Darvon, acetaminophen and placebo in peak pain relief and peak analgesia. These seven studies consistently demonstrated greater analgesic effects of the combination than either of the components alone.

[Slide]

I am going to switch gears for just a minute here and provide you a summary of a document prepared by Eli Lilly in 1973, and submitted and reviewed by the FDA, which

was an overview of 50 studies published comparing Darvon, propoxyphene, to codeine, codeine combinations, aspirin products and placebos. For obvious reasons, due to differences in doses, causes, severity of the pain and experimental designs, these studies could not be grouped for a statistical review.

[Slide]

However, the results showed trends that Darvon and its combinations were effective analgesics. The combination products appear superior to single-product entities. All active medications were superior to placebo. In the 24 studies that were done and summarized that compared Darvon to Darvon combinations and placebo, the analgesic effect of the Darvon combinations was greater than placebo. They reported more side effects in the codeine groups than in the propoxyphene arms of these studies.

[Slide]

We hear that there are two salts. This will become important in further discussions but, needless to say, the study was done to look at the different salts, the hydrochloride salt versus the napsylate saltB-and this is where it was determined that 100 mg of the napsylate salt is equivalent outcome the 65 mg of the hydrochloride salt.

This study was done to obtain the efficacy ratings on these two drugs and safety information using a four-point categorical scale of good, fair, poor and one that I don't use nowadays, don't know.

[Slide]

In this case there was very high inter-rater reliability between the clinician assessing the patient and the patient themselves, agreeing in over 90 percent of the cases. The best ratings of good and fair when asked about pain relief were similar between the two groups, 75 percent in the napsylate group, 79 percent in the hydrochloride group, with a non-statistical p value showing that they were equivalent.

Discontinuation due to lack of efficacy or adverse events, which was a secondary measure of efficacy, was 10 percent in both groups. So, the authors were able to conclude that the salts were not distinguishable when it came to efficacy. They did, however, see a trend in less frequent side effects with the napsylate salt but these were both minor and very infrequent so no determinations could be made.

[Slide]

We present here four clinical studies that are

known to test the combination of propoxyphene and Tylenol with Tylenol alone, with a comparable dose of Tylenol, 650 mg.

To summarize, propoxyphene adds efficacy to Tylenol alone. As you can see, in some of the pain intensity differences there is more pain relief obtained with the combination than the APAP alone. Both are significantly better than placebo.

[Slide]

Now I would like to move and discuss the findings of a recent government review looking at the safety and efficacy of propoxyphene. The VA Administration, in 2006, had to update their 2001 review, and they did this based on additional data on single-dose efficacy of propoxyphene, the additional safety concerns raised, specifically with regard to abuse and accidental fatal overdoses.

They asked the following questions: Does the potential analgesic efficacy of propoxyphene alone or in combination exceed the potential risks? I believe that is the question we are here today to answer again.

Cost effectiveness related to other opioids? If so, what other agents might be used as therapeutic alternatives?

[Slide]

After extensive evaluation and review they concluded there was no substantial evidence found to alter the previous conclusions about the safety and efficacy of propoxyphene and propoxyphene-containing compounds relative to other opioids. Therefore, the VA system recommendations on the use of propoxyphene remains unchanged. In a majority of VA patients with mild to moderate acute pain, who are not at risk for intentional or unintentional overdose, propoxyphene with or without acetaminophen is likely to provide adequate analgesia with an acceptable safety for a single dose or short-term therapy.

[Slide]

Now let's just take a few minutes to address some key points mentioned by Public Citizen in their 2006 petition with some additional data that we were able to find.

[Slide]

The specific topic that we will be addressing is a discussion of the European experience. We feel this is very important specifically to put the U.K. experience into context as it relates to the U.S. We will talk briefly about its abuse liability; use in the elderly; alleged

cardiotoxicity; and the DAWN data.

[Slide]

As you are well aware, in January of 2005 the U.K. ordered a phased withdrawal of co-proxamol from the market based on their determination that the benefit did not outweigh the risk, and that there were up to 400 self-poisoning deaths annually. This phased withdrawal concluded in December of 2007 when the market authorization was cancelled. Yet, physicians were still allowed to prescribe this drug to the patients who need it on a named-patient basis under their own authority and supervision.

We know that this practice is increasing as this drug is being imported significantly since ‘07 to treat patients in the U.K. who have pain, who were unsuccessfully attempted to be transferred to other pain medications and could not have their pain adequately managed.

[Slide]

Here are a few key reasons why the U.K. experience that we have heard so much about cannot be directly translated to the U.S. situation. Number one, the product in the U.K., co-proxamol, had only 32 mg of propoxyphene and 125 mg of acetaminophen. We know that products in the U.S. contain more propoxyphene, 50-100 mg, with and without

appropriate doses of acetaminophen.

Before 2005 propoxyphene in the U.K. was sold without a prescription. Now it is available on a patient-named basis. In the U.S. it has always been required that a healthcare provider write a prescription, and it has been a Schedule IV controlled substance since 1977.

You will hear data that this is an uncommon suicide drug in the U.S., whereas in the U.K. it was more common. In the U.K. they also had propoxyphene hydrochloride and, as I mentioned earlier, it is more soluble and has a faster absorption. For drug-seeking subjects those are two traits that they look for in abusing a drug. Ninety-six percent of the propoxyphene sold in the U.S. if of the napsylate salt, less soluble, slower absorption.

Most importantly, in the U.S. the labeling for propoxyphene and propoxyphene-containing compounds carries extensive warnings and precautions. The doctor is very aware of all of the issues surrounding the use with alcohol and other CNS depressants. In the U.K. they did not have uniform labeling and they lacked such warnings.

[Slide]

There have been other regulatory bodies across

Europe that have looked at this issue as well. Currently there are no restrictions on propoxyphene put forth by EMEA. In January of 2008 they did start a review of propoxyphene due to some safety concerns and related to overdose. This was supposed to be on a time scale of 52 days in order to get final decision. Of note, no decision has been put forth so no changes have been implemented to date.

[Slide]

France had one of the highest use rates of dextropropoxyphene and tramadol. The French National Commission for Pharmacovigilance investigated the safety profile of all medicinal products containing dextropropoxyphene and paracetamol combinations. They discussed their results in 2007.

They did mention the Scottish study that was presented earlier which did have higher rates of suicide than in France. The French attributed these to cultural differences and the less availability of dextropropoxyphene in products due to limited quantities, not over-the-counter.

The Commission concluded that there were no significant safety differences between propoxyphene-containing compounds and codeine-containing compounds and tramadol, a weak opioid. France decided not to ban or to

further regulate dextropropoxyphene.

[Slide]

I just want to briefly mention propoxyphene and its abuse liability and addictiveness. The proper management of a product such as this involves scheduling, not removal from the market. Many, many drugs with addictive properties are being safely prescribed and providing efficacy to patients. There are over 200 such drugs in this country.

The DEA, in 1977, evaluated the abuse liability and addictiveness of propoxyphene and properly scheduled it in Schedule IV based on its low potential for abuse relative to those in Schedule III, and that it has an acceptable medical use. To date, the DEA has not expressed any further interest in putting additional restrictions or a scheduling change.

[Slide]

In the Citizen's Petition there is a recommendation against using propoxyphene in the elderly. This position is not scientifically supported. The study that was referred to was not a randomized study; it was a survey. A survey of experts with credentials is not given. They were handpicked by the author and did not necessarily

reflect the scientific and academic communities. The petitioner, Dr. Sidney Wolfe, was one of those experts. They only included two analgesics to compare when there were many others that should and could have been put into that survey.

When one looks at the questions put forth to the survey participants, the experts, the wording of these questions was significantly biased and could not be used to draw any scientific conclusions.

[Slide]

We are very fortunate in this country to have several academic institutions to take stock in looking at improving patient outcomes. With respect to the clinical effects of propoxyphene on the QT interval and any other cardiac conduction, we are able to review the data that is put forth and updated on an ongoing basis of the Arizona Center for Education and Research on Therapeutics, affectionately known as CERTs, not the breath mint.

The mission is to improve therapeutic outcomes and to reduce adverse events caused by drug interactions and drugs that prolong the QT interval. They also look at special populations such as the elderly. They categorize drugs into three lists based on their review and the use of

the QT Drugs Advisory Board. As I mentioned, they are reviewed on an ongoing basis. To date, propoxyphene is not on any list in which there is a known definite association, possible association, or even a conditional association with any effect clinically on the QT interval. With regards to special populations, they still do not find any reason to list a warning for this medication.

[Slide]

Now, being an emergency-room physician, I take a lot of creditB-not credit personally; I take a lot of stock in DAWN data. I have been at institutions that collect DAWN data. I have been in an emergency department with chaos breaking out as a patient comes in not breathing. The last thing we are worried about is what prescriptions are in their pocket. If anybody has ever seen a paramedic wheel in an overdosed patient, they usually will plop down six or seven pill vials that they have found in a very quick survey of the victim's house. The reason that they don't survive most of the time is because they didn't want to be found. They are found already having passed away. So, for us getting information of what they took is very difficult.

In the DAWN data we do not apply causation. We merely list the drugs that are put on our counter as

possible prescriptions that may have been ingested by this individual. When it goes to the medical examiner, their report will show drugs that are mentioned and they do not give quantities. It is either there or it is not there. So, even if it is in therapeutic quantities it will be listed.

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We actually took a 1999 report that was argued about in the Citizen's Petition and wanted to just present to you the real numbers as we found them in one of the tables.

In 1999 there were over 1,000 total drug abuse deaths. Of these, propoxyphene was a mention only 466 times. That is less than four percent. Of these 466 mentions, it was reported that propoxyphene was the only drug found in only five. The others showed multiple drug ingestion, other events such as physiologic conditions and external physical events such as a car accident, or other medical disorders. Only 26 were listed as unknown.

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Again when looking at trending, one cannot look at old DAWN data to apply trends because the medical examiners that contributed to those changed both in location and in

number. But one can look at DAWN trend information from the DAWN ED data. Here you provide information on mentions--not causation, mentions of propoxyphene being used in the emergency department setting. Most of this was in misuse.

You can see that from 1994 to 2001 the number of propoxyphene mentions is steadily decreasing. Other opioids, hydrocodone, oxycodone, are increasing over this same time period. In 2000 alone you can see that there are only 4,000 mentions of propoxyphene, showing additional reduction since 2001, and the mentions of propoxyphene alone have decreased 53 percent from 1995 to 2002. The other opioids that are mentioned in the ED continue to increase.

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I am going to provide a couple of summary statements before I invite three distinguished guests to present to you this morning.

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Propoxyphene products have had a long history in the U.S. of safe and effective use as it is appropriately labeled here. Propoxyphene products have been used continuously for half a century in many strengths, dosage forms and combinations. Propoxyphene products have well-characterized risks that practitioners in the U.S. are

keenly aware of.

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With that, I would like to introduce our first speaker, Dr. Jody Green, who is the associate research director from the Denver Health Rocky Mountain Poison and Drug Center.

Presentation by Jody L. Green, Ph.D.

DR. GREEN: Good morning. As mentioned, I am Jody Green, from the Denver Health Rocky Mountain Poison and Drug Center. I am also an assistant professor at Vanderbilt University.

I have worked with poison center data for over six years now and have been a co-author on the National Poison Data System Annual Report for the last two years. I am here today to talk about the safety of propoxyphene as reported to the National Poison Data System.

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The National Poison Data System, or NPDS, is the data warehouse of the American Association of Poison Control Centers. This data is often used to evaluate the safety of both prescription and non-prescription drugs. There are 61 regional poison centers, covering the entire United States, that comprise a nationwide network that provides advice to

the public and healthcare professionals.

Each call is managed by a trained professional, namely pharmacists and nurses. Our calls range from mothers worried about their child to healthcare professionals managing a critically ill patient. A nationally standardized system is used to document every call. This system allows for standard definitions and consistent data collection. The vast amount of data available is a valuable tool for assessing drug safety. While these data come from spontaneous reports, poison center data have the advantage of being truly national and involve a large number of exposures.

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Poison centers receive two main types of cases, exposure calls and information calls. An information call does not involve a person actually ingesting a substance, such as a pill identification. An exposure is any call in which a patient reportedly took a drug or chemical involved regardless of dose.

In 2007 poison centers received nearly 2.5 million exposure calls alone. It is very important to understand that an exposure does not mean overdose. Every case is coded for the exposure reason. These include adverse drug

reactions, intentional exposures and unintentional exposures. In addition, every case is graded for outcome, no effect, minimal effect, moderate effect, major effect or death.

With this in mind, let's look at prescription opioid data, specifically propoxyphene as compared to hydrocodone, oxycodone and morphine.

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The objectives of the study were threefold. First, to characterize the exposures reported to NPDS that involved propoxyphene. Next, we set out to describe these data in terms of drug availability using IMS Health prescription data to determine exposure rates. Then we compared these rates to those of other commonly prescribed opioids.

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As mentioned, all poison centers submit their data to NPDS, which is maintained by the American Association of Poison Control Centers. We asked the association to provide all cases of human exposure reported from January 1st of 2005 through December 31st of 2007 that involved a propoxyphene product. NPDS used MicroMedical software to identify substances that are involved in an exposure.

Approximately 200 propoxyphene-containing products were used in our search. These included both single and multiple ingredient products. The same search was then repeated for any product that contained hydrocodone, oxycodone or morphine to use as comparator data sets.

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This chart depicts the total number of human exposures reported to NPDS from 2005 through 2007. The year of the study is on the X axis and the number of human exposures on the Y axis. Of the four drugs studied, the most commonly reported drug was hydrocodone, followed by oxycodone, propoxyphene and morphine. The number of propoxyphene exposures reported to NPDS decreased in percent from 2005 to 2007. The number of exposures for all comparator drugs increased during this time.

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This chart illustrates the distribution of exposure reason for each drug selected. An adverse drug reaction indicates that the reported event occurred with normal, prescribed, labeled or recommended use of the product as opposed to situations involving overdose, misuse or abuse. Intentional or purposeful exposures include abuse, misuse or suicidal intent. Unintentional exposures

are unforeseen or unplanned events. The most common example is a curious child accessing household products or medications. The final category consists of the cases in which the exposure reason was unknown or did not meet the criteria to fit into one of the three categories listed. The most informative groups to understand drug safety are the first two categories, adverse drug reactions and intentional exposures.

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With that in mind, I will now characterize the adverse drug reaction cases reported to NPDS for propoxyphene in relation to the comparator drugs studied. Five percent of all propoxyphene exposures were coded as an adverse drug reaction. Similarly, six percent of all hydrocodone cases, seven percent of oxycodone cases, and eight percent of morphine cases were coded as adverse reactions.

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This chart depicts the total number of adverse drug reactions reported to NPDS from 2005 through 2007. Of the four drugs studied, the most commonly reported adverse drug reactions involved hydrocodone, followed by oxycodone, propoxyphene and morphine. While the number of adverse drug

reactions reported to NPDS decreased for propoxyphene, they remained stable for hydrocodone and morphine and increased for oxycodone.

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While actual numbers give us some indication of frequency, they really don't tell the whole story. Whether these numbers come from DAWN or NPDS, it is really important to look at some sort of denominator to understand the true impact. When we look at the adverse drug reaction rate per 100,000 prescriptions dispensed using IMS Health data morphine had the highest rate, followed by oxycodone, hydrocodone and then propoxyphene. This rate decreased from 2005 to 2007 for all drugs studied.

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In review, propoxyphene ranked third of the four drugs studied for total number of adverse drug reactions and lowest for the rates of adverse drug reactions per 100,000 prescriptions dispensed. The rate of propoxyphene adverse drug reactions, as reported to NPDS, are the lowest of the four common opioids studied.

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Let's now look at the specific clinical effects associated with these events. So, clinical effects related

to exposures are recorded for each case. We standardized these reports using MedDRA coding. This chart displays the five most common system organ classes, or SOCs, associated with adverse drug reaction cases for each drug. These were nervous system disorders, gastrointestinal disorders, ear and labyrinth disorders, skin and subcutaneous tissue disorders, and psychiatric disorders.

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Let's look at the first two SOCs in more detail. Nervous system disorders were the most common type of effect associated with propoxyphene, reported in about 23 percent of the cases. In comparison, 28 percent of morphine adverse drug reaction cases reported nervous system disorders. Specific effects associated with propoxyphene included dizziness, somnolence, lethargy and tremor.

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Gastrointestinal disorders were the second most common type of effect associated with propoxyphene and occurred in 20 percent of the cases. In comparison, 25 percent of hydrocodone adverse drug reaction cases reported gastrointestinal effects. Specific effects associated with propoxyphene included nausea, vomiting and abdominal pain.

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The Citizen Petition highlights concerns regarding respiratory events with therapeutic use of propoxyphene. Events of respiratory, thoracic and mediastinal disorders associated with propoxyphene were not commonly reported to NPDS. Three percent of propoxyphene adverse drug reaction cases reported these types of events. In comparison, three percent of hydrocodone cases, four percent of oxycodone cases and seven percent of morphine cases reported these events. Specific events associated with propoxyphene included dyspnea, respiratory depression and throat irritation.

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The petition also highlights concerns regarding cardiac events with therapeutic use of propoxyphene. Cardiac events associated with propoxyphene were rarely reported to NPDS. One percent of adverse drug reaction cases included a cardiac event associated with propoxyphene, compared to two percent for both hydrocodone and oxycodone and three percent for morphine. Specific events included tachycardia and bradycardia.

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We estimate that the number of prescriptions dispensed for the age group listed by applying the

physician, drug and diagnosis audit results to the number of prescriptions dispensed. Adverse drug reactions associated with propoxyphene were among the lowest of all age groups studied, including the elderly which receives an estimated 30 percent of all propoxyphene prescriptions.

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Overall, the medical outcome following adverse drug reactions associated with propoxyphene was favorable and severe outcomes were rarely reported. Approximately 18 percent of propoxyphene cases did not report any medical effects, reported effects that were determined to be not related to propoxyphene, or the case was judged non-toxic.

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Another 64 percent of propoxyphene cases were judged as minimally toxic and resulted in minor medical effects. These are effects that are minimally bothersome and resolve rapidly.

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Nine percent of propoxyphene cases involved reports of moderate effects, or effects that were more than bothersome, may have needed therapy but eventually resolved.

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Less than one percent of cases resulted in a major

effect. Major effects are life-threatening events.

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In the NPDS data no deaths were reported in cases of adverse drug reactions associated with propoxyphene or hydrocodone. Three deaths were reported for oxycodone and four for morphine.

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Cases not followed to a known outcome are sometimes judged as potentially toxic exposures. Nine percent of adverse drug reactions associated with propoxyphene were estimated to be potentially toxic, with an unknown outcome. In general, the medical outcomes associated with propoxyphene adverse drug reactions were less severe than those associated with other commonly prescribed opioids.

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As mentioned, the second type of exposure to look at regarding drug safety is intentional exposures. The code for intentional includes abuse, misuse and suicide. These are purposeful exposures to achieve psychotropic effects, self-harm or some other desired effect. They may include cases of therapeutic dosing or overdose. These are not cases of labeled use of the drug. Intentional exposures was

indicated in 59 percent of propoxyphene cases, 53 percent of hydrocodone cases, 55 percent of oxycodone cases and 48 percent of morphine cases.

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This chart depicts the total number of intentional exposures reported to NPDS from 2005 through 2007. Of the four drugs studied, the most commonly reported intentional exposures involved hydrocodone, followed by oxycodone, population and morphine. The number of intentional exposures to propoxyphene decreased from 2005 to 2007. The number of intentional exposures for all comparator drugs increased during the same time.

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Again, when we look at the exposure rates per 100,000 prescriptions dispensed morphine had the highest rate, followed by oxycodone, propoxyphene and then hydrocodone. These rates remained relatively consistent for propoxyphene, hydrocodone and oxycodone but have dramatically decreased for morphine.

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To recap, propoxyphene ranked third of the four drugs studied for both total number of intentional exposures and for the rate of intentional exposures per 100,000

prescriptions dispensed. The rate of propoxyphene intentional exposures, as reported to NPDS, are similar to common opioids also studied.

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Overall, the medical outcome following intentional exposures associated with propoxyphene were similar to other opioids studied. Approximately 19 percent of intentional exposures did not report any medical effects, effects that were not related to the drug or were judged non-toxic. Another 36 percent were judged as minimally toxic or resulted in a minor effect.

Twenty-two percent involved reports of moderate effects or effects that were more than bothersome and may have needed therapy but eventually resolved. Six percent resulted in a major effect or life-threatening event. And, less than one percent, a total of 91 deaths, were reported following intentional propoxyphene exposures. In general, the medical outcomes associated with intentional exposures were similar to those associated with other commonly prescribed opioids.

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It is important to review all reported deaths regardless of exposure reasons. The drug associated with

the most deaths was hydrocodone, followed by oxycodone, morphine, then propoxyphene. The change in number of deaths is displayed rather than change in percent due to the small number of cases. The number of deaths reported over the last few years has remained relatively constant for all drugs studied.

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The overall rate of death associated with propoxyphene is 0.14 deaths per 100,000 prescriptions dispensed. This is the second lowest death rate of the four drugs studied. The highest rate of death was associated with morphine. Over time death rates as reported to NPDS have remained relatively stable for all drugs studied, although we do see more variability with morphine than with the other drugs.

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Deaths associated with propoxyphene were most often reported in patients age 35 to 55 years. Propoxyphene has the highest percentage, 15 percent, of deaths reported in patients age 65 and older. However, this is not surprising since an estimated 30 percent of all propoxyphene prescriptions are written for this age group.

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The majority of deaths for all drugs studied were associated with intentional exposures. As a reminder, intentional exposures are those that are purposeful, not labeled use. Adverse drug reactions were associated with deaths involving oxycodone and morphine only as no deaths were reported with propoxyphene following adverse drug reactions.

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More than one substance was reported for 70-80 percent of all deaths. This is also a common finding of all deaths reported to NPDS as polypharmacy is a well-known contributing factor.

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In conclusion, NPDS data indicate that adverse drug reactions and intentional exposures to propoxyphene are decreasing; that overall propoxyphene exposure rates are similar to those reported for other commonly prescribed opioids; and that severe outcomes are rarely associated with propoxyphene exposure.

DR. JONES: Thank you, Dr. Green, for a very thorough evaluation of the experience over the last three-year period in the United States on the adverse events and intentional use of propoxyphene.

Next, I would like to introduce the first of two fellow physicians who are still at the front line, treating pain patients every day. My first speaker will be Dr. Lauren Shaiova, who is the Chief of the Department of Pain Medicine and Palliative Care, Metropolitan Hospital in New York City.

Presentation by Lauren Shaiova, M.D.

DR. SHAIOVA: Good morning. Thank you. I don't have slides. I have a brief talk and I don't need slides.

I am currently the Chief of the Department of Pain Medicine and Palliative Care at Metropolitan Hospital Center. It is one of 11 hospitals under the Health and Hospital Corporation, New York City, which is the largest public care system in the country.

I was trained and worked as an attending physician at Sloan-Kettering so the scope of my practice is mainly palliative medicine, which is the practice of symptom management in patients with a life-threatening illness such as cancer or another advanced disease. Although in my practice I would rarely use propoxyphene, I would rarely use any of the hydrocodone products as well, I still see these drugs as necessary for treating patients with mild to moderate acute pain.

I sat on a committee approximately a year ago when we were looking at methadone. The 40 mg tablet, as you recall, was taken off the market deemed for safety reasons. For us in palliative medicine, especially working with a population that is both chemically addicted and may be on methadone maintenance, and battling a life-threatening illness and dying of their cancer, this posed a huge problem for myself and my fellows. We train six fellows a year. This also posed a huge problem to the cancer centers that use methadone for the treatment of pain in dying patients. We had to use many more tablets.

I view this medication for the mild to moderate acute pain as the same kind of hit that it was for me when the methadone 40 mg tablet went off the market. This drug is used for mild to moderate pain in an acute situation. The difficulties with this drug and the other short-acting drugs that have had problems with suicidality and sudden death are really in patients where there may be a coexisting comorbid psychiatric disease or a comorbid or coexisting harmful situation at home where these drugs are placed in a situation where there is not safety in taking these medications for their mild to moderate pain.

I feel personally and for the fellows that I treat

in the Health and Hospital Corporation system that if more and more opiate analgesics continue to shrink this limits our practice. And, we have been taught, and I teach every day the notion of opioid rotation which is commonly practiced and is efficacious in treating pain syndromes. If our market continues to decrease we really we have less and less options.

Although propoxyphene, again, has little or no role in my practice or end-of-life care, in the treatment of acute mild to moderate pain in an ambulatory practice in patients who are evaluated properly by their physician and deemed appropriate, responsible patients, this deems a role for this analgesic.

The key is really teaching prescribers and fellows and residents and interns to safely prescribe, not ban a drug. The safety of all medications lies within our prescribers' knowledge, the assessment of patients and to look for red flags such as a comorbid psychiatric disease and use extra precaution with the use of propoxyphene and other drugs equally. This really looks at scheduled and non-scheduled drugs.

So, I ask you to look at this drug in the same light that you would look at all drugs, and just to increase

education with prescribing drugs as to their side effects, their limitations and their efficacy, instead of taking another one of our medications that we use in the practice of pain medicine and palliative care off the market. Thanks.

DR. JONES: Thank you, Dr. Shaiova. As our last speaker today I would like to present is another clinical colleague of mine, Dr. Gerald Sacks, board-certified anesthesiologist, pain management specialist and the director of pain management at St. John's Health Center in Santa Monica.

Presentation by Gerald M. Sacks, M.D.

DR. SACKS: Thank you very much. My name is Gerry Sacks. I am an anesthesiologist, pain specialist and, yes, I came all the way from Santa Monica to be here today.

My background is a little bit different and I just want to go through that just so you can see where I am coming from. I did graduate from medical school, then did a year of general surgical training and actually did three years of residency in orthopedic surgery before changing careers and becoming an anesthesiologist and then doing a pain management fellowship. I do practice pain management full time in Santa Monica. I have a very busy practice,

work numerous hours per week, seeing between 150 and 200 pain management patients per week in an average week.

These patients are very difficult to take care of. The easy ones are taken care of by their primary care practitioners, orthopedic surgeons, neurologists, rheumatologists, etc. The difficult and complex pain issues that we see in our practice, these patients are not being able to be taken care of by their primary care practitioners and, therefore, they are referred to us as a pain management center.

The prevalence of acute and chronic pain is increasing. Our population is aging and especially chronic painful conditions such as arthritis and other chronic painful conditions seem to be increasing over time, and what we need is more options to help these patients, not limiting our options to help these patients.

I see, as I said, patients with both acute and chronic pain. I run the acute pain service in the hospital and at any given time we have probably somewhere between 10 and 20 patients who are suffering from acute pain, primarily postoperative pain but also acute exacerbations of chronic cancer pain. It is a big part of what we deal with there.

As I said, we need options for these patients

because there are many patients for whom the available options are inadequate. I see a lot of patients who are referred to me and the first complaint when they come to me is that they failed everything. There is nothing else that is available and they say, you know, Dr. Sacks, what can you do to help us out? What can you do to help me?

In terms of the types of patients that we see, the large majority is chronic back pain, usually with an arthritic component but sometimes with a traumatic component. We see failed back surgery. I see a lot of radiculopathy, radiculitis and other problems such as that. But also I do see patients with cancer, quite a few actually, and see patients with numerous types of neuropathic pain which is extremely difficult to control, postherpetic neuralgia, diabetic neuropathy, migraine headaches, tension headaches and cervicogenic headaches, phantom limb pain, interstitial cystitis, fibromyalgia, complex regional pain syndrome which we used to call RSD.

These are all the types of things that we see in a chronic pain medicine practice, each of which is very difficult to treat and each of which tends to present to our clinic in an individual in whom they have already tried and failed many of the options that are available. So, the key

here is to have a lot of options so that we can help these patients to gain control of their painful situations.

Each patient is an individual. Just because I have one patient with metastatic breast cancer, that patient is not comparable to another patient with metastatic breast cancer in terms of how they interpret their painful signals and how they metabolize medications and utilize medications. I have some patients that respond dramatically to one medication and do not respond well to another.

The statistics are great. I love to read pain research and see, you know, good N values and good p values and see, you know, the large majority of patients that may benefit from a certain specific medication. But there is always the group of patients that do not do well with certain specific medications, and for those we do need options available.

Propoxyphene is a valuable tool in my armamentarium for acute and chronic pain. We have quite a few patients who benefit from propoxyphene that did not benefit from other medications. In a couple of minutes I will discuss one of those patients specifically with you. If we remove propoxyphene as one of our optionsB-by the way, we don't use it for chronic severe pain. We are using it

primarily for mild to moderate pain. For chronic use we are talking, you know, about two, sometimes three, occasionally up to four pills per day. It is uncommon that we would go over those dosages but, again, it is a valuable option for our patients. I utilize it for acute exacerbations of chronic pain, sometimes utilizing a long-acting opioid with it. So, that is the way that we use it.

If it is removed it will just eliminate one of the options that we have available. If my patients could take acetaminophen and provide pain relief with it, they would never be sent to our office to begin with. If acetaminophen was adequate for these patients' pain control, again, they would never need a pain management consultation to begin with. We do commonly utilize acetaminophen. It is just not strong enough for most of these patients to control their pain.

In addition, substituting anti-inflammatory analgesicsB-well, most of my patients are already on anti-inflammatory analgesics in addition to a short-acting as well as a long-acting opioid. You can't substitute it if they are already taking it, and the ones who are not taking anti-inflammatory analgesics are the ones for whom it would be inappropriate. Perhaps they have had a GI bleed.

Perhaps they have difficulty with dyspepsia or other side effects, or perhaps they are at too high risk to be placed on an anti-inflammatory analgesic.

So, in my practice I do find that the efficacy of propoxyphene is superior to that of acetaminophen alone. It seems to be approximately on par with tramadol or the codeine preparations, plus/minus acetaminophen or even low dose hydrocodone, say, 2.5 mg or 5 mg.

In terms of abuse, again, I have a very busy chronic pain management practice. My patients do abuse medications occasionally. Their most widely utilized medication for use and/or misuse is not propoxyphene. It is actually hydrocodone. They love hydrocodone. My patients also, in terms of abuse medications, tend to abuse oxycodone. I have never had a patient come in, or find out that they were snorting propoxyphene but they do that with, as you know, long-acting oxycodone preparations, and the overuse of hydrocodone is actually widespread in my patient practice.

Let me tell you about a patient actually that I had recently, within the last couple of weeks, that came to mind when I was preparing these remarks. This is a patient who was referred to me by her orthopedic surgeon to do a

preparatory preoperative pain management consultation because she had had a total knee replacement about two years earlier and had had five days of postoperative intractable nausea and vomiting which, of course, was quite disconcerting to the patient and quite uncomfortable for her.

I was asked to see the patient so that we could plan what we would do in her postoperative period because she was now going to have the other knee replaced by an excellent orthopedic surgeon in our area. I literally went through basically every medication, opioid, non-opioid, analgesic, etc., that could be utilized in the postoperative period. Obviously, aspirin would not be particularly appropriate, but acetaminophen, and she does do okay with acetaminophen but did not find it strong enough to control her pain during her previous knee replacement. We then talked about codeine which in her caused intractable nausea and vomiting. Hydrocodone she couldn't tolerate due to nausea as well as confusion even at very small dosages, 2.5 mg dosage given, you know, every four to six hours. She couldn't tolerate that. Oxycodone, very similar response. Fentanyl, we tried fentanyl in very small dosages, both intravenously and transmucosally. Morphine, oxycodone,

pretty much everything that you can imagine.

The plan that we came up with for her surgical anesthetic as to do it under an epidural anesthetic, which worked great without any use of opioids but then, 24 hours post-op what do we do? We needed to take the epidural out so that she could ambulate and they were starting her on coumadin so we didn't want to, you know, leave the epidural catheter in place. At that point we had to put her on something. We had to find something to control her pain.

Well, we repeated the experiment that they had done five years before, very low dosages of oxycodone, fentanyl, hydrocodone, none of which were adequate for this patient in terms of the side effect profile or in terms of achieving analgesia. We did put her on around-the-clock acetaminophen, making sure that we were not giving her excessive doses of acetaminophen. But the one medication that in her provided analgesia without side effects happened to have been propoxyphene with the acetaminophen in it.

There are patients for whom this is pretty much their only option. It is not the most powerful opioid available. Certainly, you know, we have other options for that. But for this patient it enabled her to undergo her total knee replacement procedure which was done

successfully.

So, in conclusion, I just want to state that we do need options available for our patients and propoxyphene is an important option in a chronic pain management practice. Thank you very much.

Closing Comments

DR. JONES: Thank you, Dr. Sacks. As you were talking about your patient I was just remembering a patient I had recently in the ED who was an elderly patient and had to go home on some analgesic, and I asked her if she wanted hydrocodone, Vicodin, or Percocet. She goes, that makes me too loopy, and we settled on Darvocet because she felt that that was all she needed. She didn't need those heavier opioids to take care of her pain. So, it is always good, patient anecdotes.

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I hope that we have been able to paint a very broad picture for you about the safety, the efficacy, the utility and the need for propoxyphene in the toolbox for the pain management doctors, the primary carers, and the emergency medicine physicians as well.

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So, in conclusion, the petitioner presents no

credible scientific evidence that propoxyphene drugs present an imminent hazard to public health, or that they are unsafe and ineffective when used according to the approved label.

The safety and efficacy of propoxyphene has been reviewed and considered repeatedly by multiple U.S. government agencies, spanning 50 years. The agencies include HEW, the FDA and the VA.

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Today the petitioner raises no new safety or efficacy concerns that have not been previously reviewed, considered and rejected by the FDA. As we heard from our clinicians, pain sufferers should not be deprived of this option, the option of using propoxyphene and propoxyphene-containing products. They should not be withdrawn as treatment options.

With that, I would like to say thank you very much for your time.

DR. FARRAR: Thank you for the presentation. We are about to take a break, a ten-minute break. The committee members are reminded not to discuss any of the meeting topics during the break amongst themselves or with any members of the audience.

I would, however, like committee members in this

break to consider points of clarification from the two morning presentations. What we will do when we come back from the break is to have a 15- or 20-minute session, depending on how long it takes, for the committee members to be able to query first the presentation by Dr. and subsequently the presentation by the company with regard to points of clarification. It is not time yet to have a discussion about this, but if there are specific questions related to their presentations that you would like clarified, I think we would like to do that.

We will then go on to the presentation by the FDA. At the end of the FDA presentation we will have, again, a period where the committee can clarify points with the FDA. It is likely if all the presentations go the prescribed length that we will probably not break for lunch until 12:30. So, that is the plan. It seems to be about 10:10 and I would like to resume again at 10:20.

[Brief recess]

DR. FARRAR: I did fail to mention the FDA contact. Is the FDA press contact here? If he or she could stand? Thank you very much.

One other comment is that the travel desk, as most of you know, is just outside here, in the hall. It is my

very clear intention to finish on time today. Just so people understand what we are going to be doing, the morning session will probably run until around 12:30. We will take an hour for lunch. Currently there is only one scheduled speaker for the open public hearing, which unlikely to take a lot of time so we will make up the time at that point, and then continue with the afternoon events with substantial time for discussion and consideration of the questions. We will plan to adjourn by 3:30. I would ask though that those of you that are here, please, don't plan to leave before that. We really do need you here for the discussion and consideration of the questions at the end.

At the end of the meeting there will be buses and transport to the various airports and train station. I have been asked to announce, and I will announce it again later, that those buses and transports will leave from the front of the hotel within 20 minutes of the end of the meeting. So, if you are going to Dulles or elsewhere, please, do make your way fairly quickly to the front so that the folks with the earlier flights can make their flights.

So, what I would like to do is to spend a few minutes here and open the floor to questions for clarification only. Do try and limit it to clarifications.

If I think we are getting too much into discussion I will take the chairman's prerogative and cut you off. If you are interested in speaking, and this will go on later as well, please put on your light for a minute and when you are recognized by Kalyani you can turn it off and we will try and call you in order as we go around.

Questions of Clarification

DR. BICKEL: This is Warren Bickel. I have a question of clarification for Jody Green. Dr. Green, you said that rate measures are very important and it is good to know the denominator. And on reflecting on the age distribution of deaths reported to the agency she was reporting on, she noted that the medication in question had a greater proportion, percentage of deaths, in 65 and older and also had a greater number of prescriptions associated with the elderly. So, it seems to me that the rate measure would be very helpful in understanding the exact meaning of the percentage of deaths in the 65 or older group. Thank you.

DR. FARRAR: If I can just be sure we know what the question is, the question is whether she has data on the age specific rates.

DR. BICKEL: Yes, per 100,000 prescriptions.

DR. GREEN: Good question. One moment.

DR. BICKEL: I think it is figure 31.

DR. GREEN: I would be happy to get that information for you. We didn't look at the specific rate of death in the older age group. We did look at the medical outcomes including death for all drugs and all outcomes, and death was no greater in the propoxyphene group than it was in the other opioids.

DR. FARRAR: Dr. Lincoff?

DR. LINCOFF: Yes, I wanted to address more specifically the relative efficacy of the combination as compared to acetaminophen alone. I was sort of dismayed by the efficacy presentation by the sponsor in terms of sort of the qualitative nature. This really is the forum to be specific and scientific.

On slide 19 of the sponsor's presentation there is the comment that better than Darvon are acetaminophen and placebo in total pain relief and peak analgesia on the basis of seven acute pain studies. In the FDA's material, on page 10, those seven studies are summarized and all but two of them actually appear to have shown no additional benefit of the combination. It was only, by my count, 175 patients out of 991 in the total seven studies where there was any

evidence of what looked like better benefit with the combination.

Similarly, on slide 24 of the sponsor's presentation where they compare the four clinical studies and again say, summary, propoxyphene adds efficacy to acetaminophen. That actually is what is on page 17 of the FDA meta-analysis by Po and Zhang and that they actually showed no significant benefit.

So, without being qualitative and trying to be somewhat scientific and statistical, is the sponsor aware of data that showed significant benefit of the combination of acetaminophen and propoxyphene as compared to acetaminophen alone? Are there any studies beyond those which seem to be summarized that showed no significant benefit?

DR. FARRAR: I will give the sponsor a minute to respond to that, and perhaps the best thing to do after the sponsor has responded is to then leave that and bring that question back after we have seen the FDA presentation so we can all have that fresh in our minds.

DR. JONES: Yes, in response to the question, we are not aware of any additional studies that compare the combination to acetaminophen alone. Those probably, as was reflected, were some trends and some statistical

significance but I think the FDA will be presenting that as well.

DR. FARRAR: Dr. Hiatt?

DR. HIATT: Most of the efficacy data was performed in a very short-term acute pain setting. I am assuming that most of the safety that we saw was from more chronic use. Can the sponsor tell us what percent of prescriptions currently for propoxyphene compounds are used for very short-term, acute pain management and what percent appear to be used for more chronic, long-term management?

DR. JONES: I am getting some whispers here. I think the best thing that we can estimate is that 60 percent of the use is acute.

DR. HIATT: And that is based on what?

DR. JONES: The NDTA data.

DR. FARRAR: Dr. Tinetti?

DR. TINETTI: Yes, my question is for Dr. Jones. You alluded to but didn't really comment upon the fact that there was a new drug approval, just a few years ago, in 2003, for another Darvocet preparation. Is the FDA going to be presenting the evidence? Presumably at that point it was deemed safe and effective. Is anybody going to actually present us the evidence that led to that approval in 2003?

DR. FARRAR: Dr. Hertz?

DR. RAPPAPORT: That would have had to have been a generic product so it was approved based on the generic regulations which just require a show of bioequivalence.

DR. TINETTI: So they would not have to show that the drug was safe and effective?

DR. RAPPAPORT: We can have somebody from Generics give more of an input on this, but basically generic drugs are approved on their bioequivalence to the approved drugs, with the scientific foundation for that being that if they are bioequivalent they are equally as safe and effective as the approved drug.

DR. TINETTI: Can we then imply that the FDA assumed that they were safe and effective?

DR. RAPPAPORT: Absolutely.

DR. TINETTI: Is that a reasonable assumption?

DR. RAPPAPORT: Yes. They are safe and effective or they wouldn't have been approved.

DR. FARRAR: Dr. Rosenberg?

DR. ROSENBERG: This is for the petitioner, and the sponsor for that matter. What evidence do you have that the patients who are on propoxyphene and its derivatives can be switched to other opiates analgesics successfully without

increased side effects? The same for the sponsor, what portion of the patients who could not tolerate opiates were able to tolerate propoxyphene?

DR. FARRAR: Dr. Wolfe, do you want to start?

DR. WOLFE: I think it is more indirect evidence than anything. As the FDA's presentation will show, 97.5 percent of the use is a combination of acetaminophen and propoxyphene, a combination for which, as just alluded to again, there is no evidence that the propoxyphene significantly adds anything to it.

So, if you are having something that adds only risk, which is the propoxyphene, and no benefit you still have some addiction problem, not the most severe addiction but an addiction problem which is, again, why in BritainB- and, again, I think the experience in Britain is probably the best and we have not seen their--

DR. FARRAR: If I could ask you to restrict to the question with regards to what drugs could they be switched to.

DR. WOLFE: The evidence is simply the lack that there is any additional efficacy. Therefore, we would presume that switching to just acetaminophen for many people would work as it has in Britain apparently.

DR. ROSENBERG: Specifically, I am trying to determine if you have any evidence, as you stated in your presentation, that patients who are on propoxyphene can be switched to a comparable opioid-containing regimen without substantial side effects that they didn't have before.

DR. WOLFE: You meant opioid-containing; you just said switched to something else. No, I don't think there are any data for that. I mean, it would more likely come from somewhere where the drug was taken off the market. In this country there would be no reason for someone to do that unless a patient got into trouble with a drug.

DR. ROSENBERG: So, I guess specifically are there any data from the U.K. experience in terms of this?

DR. WOLFE: Not that I am aware of.

DR. ROSENBERG: Thank you.

DR. JONES: I think the only data that I can share is going back to the data that talks about the increase in the number of importation of Darvocet or co-proxamol into the U.K. since it is no longer available, only on a patient-named basis. And, I don't have those numbers exactly, but there has been a continuous increase since 2007 in importing and bringing co-proxamol into the U.K. because patients were unable to get successfully transferred. That is the only

piece of evidence that I have. Dr. Sacks, do you want to talk about clinical experience?

DR. SACKS: I also have no specific data because I have never done a study on this, but I can tell you as a very busy practicing clinician, seeing patients all day, literally seven days a week, there are numerous patients that I have seen over the last 20 years in practice that could not be successfully transferred or had their medication switched to anything else that didn't either increase their risk, increase their side effect profile or provide inadequate analgesia. For a certain, admittedly small, percentage of patients this is their best option.

DR. FARRAR: Cr. Ciraulo?

DR. CIRAULO: Yes, the sponsor made a statement about the comparison of the salts, the hydrochloride versus napsylate, and related it to abuse liability. Do you have any direct evidence of that or are you just relying on sort of that the general principle of rapid onset is associated with higher liability?

DR. JONES: That is a very good question. I don't have any direct evidence. I have been working in this area for many years and those, for the sake of this compound, are general traits of compounds that are well-known, published,

off the Internet chatter rooms of what they look for when they go to abuse a drug.

DR. CIRAULO: So, the answer is no?

DR. JONES: The answer is no.

DR. CIRAULO: Thank you.

DR. FARRAR: Dr. Nelson?

DR. NELSON: I have a question for Dr. Green. It is actually a fairly simple question. There are several issues surrounding poison center data that we can address perhaps later. But I guess my one question specifically is whether or not the morphine data that you collected was specifically about oral morphine and if IV morphine was excluded.

DR. GREEN: Those were oral products only.

DR. FARRAR: Dr. Zito?

DR. ZITO: I also was going to address a little bit the issue of the poison center data. I do appreciate the value of National Poison Center databases very much, but also wonder about the reporting biases that are likely to be present because in this instance we have a drug that has been around for 30 years, 30-plus years, so we have that issue with serious adverse event reporting in the AERS system as well, so less likely to be reported.

Also, if we think about institutional use, which apparently is a very prominent utilization of these products, what is the likelihood that they would be reporting to a system that really does I think rely on consumer issues? So, I am thinking that the data may be incomplete or more incomplete, or lean a lot on outpatients.

DR. FARRAR: Let me pose that as a question. The question is what are, from your perspective, the limitations of poison control data, and if you know sort of what the estimated effect of reporting bias might be.

DR. GREEN: Sure, and it is a spontaneous reporting system, as AERS, so there are limitations as to reporting bias. There, unfortunately, is not a good estimation as to the percentage of these cases that are actually reported to a poison center. However, the bias should be the same across the drugs that we did study. So, I think it is important to realize that in relation to other drugs the data I think are very valid to use as a tool to assess and compare, knowing that these most likely are under-represented numbers if you look at just actual numbers.

DR. ZITO: I have just a quick one. I guess that would rely on the assumption that consumers perceive the risk of this drug equivalent to other opioids.

DR. GREEN: Well, it is not just consumers that call the poison centers. It is also healthcare professionals that are looking for advice on how to manage patients that have presented either in their clinics or emergency rooms and, you know, I think it is still a very valuable tool in looking at the data.

DR. ZITO: Thank you.

DR. FARRAR: Ms. Zavacky?

MS. ZAVACKY: Yes, this question is for Dr. Wolfe regarding the data on propoxyphene-related deaths in Florida from 2003 to 2007. I was just wondering if the definitions of accidental death were the same during that period, or if they were just the same in 2006, 2007.

DR. WOLFE: I may not have made this clear enough. It was the DAWN system that re-aggregated from more categories to fewer the accidental death definition. The Florida system has not changed their definitions at all during any of these years that I was looking at the data. Does that answer your question?

MS. ZAVACKY: Yes.

DR. FARRAR: Dr. Day?

DR. DAY: There was a theme running through the sponsor's briefing materials and some of the comments this

morning as well that the risks observed, adverse events observed with the drug are not so much the drug as the appropriate use of the drug. In this connection, it was mentioned that Lilly did conduct an educational campaign with doctors, pharmacists, nurses, and so on, and I am wondering whether there was any assessment of the effectiveness of that campaign in terms of prescribing practices or adverse events changes after the campaign. That is question number one.

Question number two, what do you view as the main educational messages for today for safe and appropriate use of this medication?

DR. JONES: If I understood the questions correctly, there was an educational campaign undertaken by Eli Lilly and are we aware of the results or the outcome of that educational campaign. We are not. However, it was given to the FDA upon their conclusion.

Second, I think your question was what about education today for these products.

DR. DAY: If, for example, we recommended some additional practices to mitigate risks, what do you view as the most important? If you had to pick two of three of the most important educational messages for prescribers in order

to have safe and effective prescribing and use of this drug, what would they be?

DR. FARRAR: I think that is a very important issue but I think it is more of a discussion issue than it is a clarification. It wasn't presented in the initial presentation. So, hold that but, please, do bring it back up again at a later time because I think we need to discuss that.

DR. DAY: Right, but one of the presenters did say it was key, Dr. Shaiova.

DR. FARRAR: I think there is a lot of discussion around that point and I think we should bring it up later. In terms of clarification, Dr. Burlington?

DR. BURLINGTON: I had a question for Dr. Wolfe. Dr. Wolfe, in your presentation you presented data on the metabolism of propoxyphene or dextropropoxyphene to norpropoxyphene, and pointed out that in individuals with rapid 34A metabolism they may accumulate to significant quantities. Yet, I did not see any data or information that would associate that with morbidity or mortality. You did talk about the prolonged QTc effect, but you didn't show us any information on arrhythmias, particularly Torsades de Pointes, sudden cardiac death, etc. Do you have such

information?

DR. FARRAR: Before you answer that, unless you are interested in the exercise you are welcome to bring your chair a little closer up.

DR. WOLFE: I am interested in the exercise. It is a low exercise day so we should all be interested in it.

The range in this study that I cited of blood levels in the normal healthy older people and younger people itself suggests some kind of variation. We are still at the infancy of polymorphisms of either the CYP3A4 or the channel blocking problem. So, I don't think there are any data linking the two, but what we do see are such wide ranges of blood levels in people who are given exactly the same amount of drugs, at the same weight, that one can suspect that these differences do exist and that they probably are related clinically.

There is the study I cited briefly relating the level of propoxyphene to the extent of QRS prolongation. That is the only one where there has actually been a regression analysis done relating dose to some electrocardiographic abnormality.

DR. FARRAR: Dr. Gardner?

DR. GARDNER: I wonder whether the FDA will be

talking more about the VA review that the sponsor mentioned in their presentation. If not, I wonder if we could have a reference either to published information about that or a website in which the VA has expounded on it.

DR. FARRAR: We can wait for the FDA presentation and, if not, then maybe someone can provide us with that.

DR. HERTZ: We are not going to be reviewing that in detail but we can get the reference for you.

DR. FARRAR: MR. LEVIN?

MR. LEVIN: I guess I am puzzled by the logic of the sponsor's use of the importation surge after the market authorization was cancelled as sort of evidence for the utility or efficacy of the drug and not simply the fact that the drug is no longer available in the U.K. and had to be imported.

DR. JONES: Right, I would not go as far as saying that that shows efficacy. It was in response to a question as to is there any data out there that shows that patients can be successfully switched as indirect evidence, at best, that because you are making the assumption that the physicians in the U.K. are prescribing what is on the market not successfully and, therefore, having to go back to what was working for them before. So, it is only inferential and

indirect.

DR. FARRAR: Dr. Omoigui?

DR. OMOIGUI: This is for the sponsor. You repeatedly referenced the use of propoxyphene for mild to moderate pain. What part of your data justifies the use in moderate pain? Based on the placebo data and the combination that had a marginal increase in efficacy compared to placebo, how did you separate the use of propoxyphene for mild pain with propoxyphene for mild to moderate pain because mild to moderate pain covers a wider range of pain syndromes than just mild pain?

DR. JONES: So, let me see if I understand the question, how are we justifying an indication of mild to moderate instead of just mild?

DR. OMOIGUI: Yes.

DR. JONES: Based on the studies that were presented to the FDA for Darvon and then subsequently for Darvocet, it was determined that it had efficacy for mild to moderate pain. The pain models at the time included third molar extractions and other surgical procedures. Now we use a different model, bunionectomy, which is a more moderate to severe pain model. So, it was based on the pain models used and the data presented to the FDA.

DR. FARRAR: By way of procedure, I am allowing two more questions and then we need to move on. We can come back to some of these later. Dr. Crawford?

DR. CRAWFORD: Thank you. I have a couple of questions for the sponsor. I will just state them both so the responses can be a little quicker. For Drs. Green and Jones, Dr. Green, with your presentation quite often it was a little difficult for me to understand when you were saying things such as the lowest AER rate with propoxyphene. I might have seen a rate or absolute number sometimes of five percent versus eight percent, however, it is not clear to me when that is a statistically significant difference versus just descriptively seen difference for the lowest.

In general, for the sponsor, I heard the sponsor talk about the limitations of the data presented by the petitioner, for example older studies, case reports and letters to some large extent, and I would like to ask the sponsor to, please, clarify the scientific data that was presented for us today. Sort of related to Dr. Gardner's question, have those data for the poison center data as well as the VA report been subjected to public scrutiny and peer review through publication in peer review journals or some other similar mechanism?

DR. GREEN: So, the presentation was only meant to be descriptive in nature to understand the relationship of these four drugs so we did not look at p values or look for real, true significance between them. We wanted to see where they fit in the world of those four drugs.

Secondly, are you asking specifically about this report of NPDS data and whether it has been subject to peer review? No, it has not. This is brand-new analyses. However, poison center data has been well published throughout many different peer review journals.

DR. FARRAR: Last, Dr. Zelterman?

DR. ZELTERMAN: Just one quick question for Dr. Green. Of all the graphs and data that you presented, only two or three of these graphs actually adjust for the number of prescriptions written for the various drugs. I mean, if there was ten times as much oxycodone out there as there was Darvon then, of course, we would expect ten times the suicide rate and ten times the death rate. Would your graphs look very different if you adjusted all of them for the number of prescriptions?

DR. GREEN: In the ones I presented, the adverse drug reactions and the intentional exposures were adjusted for rate as well as the deaths. So, outside of trying to

keep the presentation within 15 minutes, there certainly are other areas where we can apply those denominators if you have very specific requests, but to do that across the board would take a few more hours.

DR. FARRAR: Thank you very much. If you have other questions, please write them down and we can bring them back later on during the day. I will call on the FDA to begin their presentation, starting with Dr. Chen.

FDA Presentation

Regulatory History and Clinical Efficacy of Propoxyphene Products

DR. CHEN: Good morning.

[Slide]

My name is Jin Chen. I am a medical officer from the Division of Anesthesia, Analgesia and Rheumatology Products in CDER, FDA.

[Slide]

I will present the history of propoxyphene products.

[Slide]

Since the history of propoxyphene products has been covered by previous speakers I will make this 50-year history fit 50 seconds. So, I will go over it very quickly

and I will focus on efficacy data that we identified from the NDA submission in 1971, followed by a brief literature review.

[Slide]

As you know, the propoxyphene product was first approved in 1957 based on safety only; in 1962 under the DESI process.

[Slide]

In 1969 FDA made a DESI conclusion that the drug is effective for mild to moderate pain.

[Slide]

In 1971 a different sort of propoxyphene was approved, which was Darvon-N.

[Slide]

In 1972 two propoxyphene-acetaminophen products were approved. Darvocet, as you heard this name before, and Darvocet-N. The drugs were approved based on a couple of efficacy trials, which I will go through in some detail, as well as a bioequivalent study which I am not going to cover for today's presentation.

[Slide]

Efficacy data submitted in 1971 NDAs included seven single-dose efficacy trials. All seven trials had

identical study design and were conducted by three external investigators, as listed here.

[Slide]

The seven trials were randomized, double-blind, placebo-controlled, full factorial design. The study subjects were patients with mild to severe postpartum pain, and were treated with a single oral dose of Darvocet, which is a propoxyphene-acetaminophen combination, and Darvon, which is propoxyphene, acetaminophen or placebo.

The analgesic efficacy was assessed hourly for six hours and the major efficacy outcomes included the time-course of analgesic response over six hours, and a total analgesic response, including summed pain intensity difference, which was different in the original submission but is equivalent for now, and total pain relief. These three outcomes are most commonly used for an acute pain trial even today.

[Slide]

In the original submission or original study reports the sponsor provided summary tables for efficacy data. However, we couldn't find the standard deviation information for most of the efficacy trial data. So, details of statistical analyses for those major analgesic

outcomes were not available in the original reports. There were only statements by the sponsor on statistical significance for some treatment effects.

The only statistical analysis details shown in the original reports are limited to the first two hours post treatment data. Based on the original report, the efficacy results were different across the seven trials. I am going to go through a little bit of detail.

[Slide]

This is the time course of pain intensity difference taken from study 3a. As you see, I believe this graph was made by special handwriting technology back in that time. This is the pain intensity difference from baseline at each different time point up to six hours. The top line, here, with the crossed circle, is the combination product, which is Darvocet or propoxyphene-acetaminophen combination. The second line with the open circle is acetaminophen alone. The third line with the cross is propoxyphene alone. The fourth line is placebo.

As you see here, the combination clearly separated from acetaminophen and propoxyphene and all three treatments separate from placebo.

[Slide]

The total analgesic outcome from this particular study, 3a, showed that propoxyphene, acetaminophen and the combination were statistically superior to placebo. Propoxyphene alone was comparable to acetaminophen. The combination appears superior to both acetaminophen and propoxyphene, but the statistical significance is not available in the original reports.

[Slide]

Here is another study which is a little bit different than the 3a. This study was conducted by the same investigator and the same study design, and a similar handmade graph.

[Slide]

This is also total pain intensity difference from baseline at different time points up to six hours. As you see here in the top line, the crossed circle is the combination. The second line is acetaminophen. You see that sometimes they overlap, sometimes separate. This line is the propoxyphene. Compared with the placebo there is some separation but some time points showed overlap.

[Slide]

So, the total analgesic effects from this study, 3b, showed that the combination and acetaminophen alone, but

not propoxyphene alone, were statistically significantly superior to placebo. There were no other statistically significant findings among the treatments and placebo in this study report.

[Slide]

For the remaining five studies the total analgesic response showed similar results across those five trials. It was shown that propoxyphene alone was not better than placebo in all five trials. The combination and acetaminophen alone were statistically superior to placebo. The combination was comparable to acetaminophen alone.

[Slide]

I have one graph here, taken from one of the five trials, which was study 1. The top two lines here are combination and acetaminophen alone and you can see clearly that they overlap. The bottom two lines, propoxyphene alone and placebo, overlap.

[Slide]

So, in summary, all seven trials had identical, single-dose, full-factorial design and were conducted in a similar patient population. Six of the trials showed that propoxyphene alone had no statistically significant difference from the placebo. Acetaminophen alone was

statistically superior to placebo in all seven trials. And, the combination was comparable to acetaminophen alone and was statistically superior to placebo in six of the seven trials. One trial did not show statistical significance between the combination and placebo.

[Slide]

We also conducted a literature review by searching PubMed and EMBASE databases and searched citations of relevant articles. We identified the most relevant publications based on the study design, the drugs studied, and the data process.

We found 27 randomized, controlled trials, most of them acute pain trials and some chronic pain trials. We also found ten systematic review articles including meta-analyses. These publications were reviewed and summarized in our background package in Appendix-1 of Backgrounder-4.

[Slide]

The randomized, controlled trials were mostly published between 1960s and ‘70s. The majority of the trials tested a single dose of propoxyphene single-ingredient products in acute pain patients. There are limited literature reports of factorial design trials with combination products. We identified only one full factorial

design trial and a couple of partial factorial design study reports which we reviewed an included in our backgrounder package.

[Slide]

The published systemic review articles, including meta-analyses, all cover similar published randomized, controlled trial data on propoxyphene products. The authors in those review articles made similar conclusions. Propoxyphene, as a single-ingredient product, was a weak analgesic. Propoxyphene has no, or has little, contribution to efficacy of the acetaminophen combination for acute pain. There is limited information available to assess analgesic effects on chronic pain. These conclusions were consistent with what we found from reviewing the individual trials in the literature.

[Slide]

Next I am going to focus on two meta-analyses and go through these two review articles in some detail. The first meta-analysis was published in the Cochrane Database in 1999, followed by two updates. The latest update was in 2008. The analysis included ten published randomized, controlled trials, and one pooled data which included eight randomized, controlled trials on combination product only

from the same research group, which was published previously which was also a meta-analysis in the Cochrane Database.

The study subjects in those trials were adult patients with post-surgical moderate to severe pain and were treated with a single oral dose of a propoxyphene-acetaminophen combination, propoxyphene alone or placebo. The pain intensity scores or pain relief scores were standardized to 50 percent of maximal SPID or TOTPAR, which is total analgesic response, across all individual trials.

The analyses outcomes included relative benefit between the treatment and placebo; number needed to benefit; and percentage of subjects requiring re-medication within four to eight hours.

[Slide]

I am going to just present relative benefit here with two forest plots in the next two slides. This slide shows the relative benefit of propoxyphene compared with placebo. The six individual trials included in this analysis and the pooled data analysis show the relative benefit here, 1.5. As you see here, the point estimate of relative benefit across six trials actually slid them more than 1.0. Even with 1.0 there is no benefit compared to placebo. Sliding them more would be a little bit of

benefit. As you see, the 95 percent confidence interval, this bar here, crosses 1.09 on the left side. So, this data may suggest that propoxyphene alone had a little bit of effect compared to placebo.

[Slide]

This slide shows the relative benefit of the acetaminophen-propoxyphene combination compared to placebo in four individual trials, and one here from the same research group in 1997, as I said in the beginning, included eight trials. So, the total here is 12 trials. The relative benefit from pooling the data showed 2.5; the lower bound of 95 percent of the confidence interval around 2. I don't have data to show you the relative benefit of acetaminophen compared with placebo. Actually, that analysis from the same research group, with the same analysis and method, showed that the relative benefit is around 2.4. The 95 percent confidence interval actually overlapped.

[Slide]

This is another meta-analysis published by a different research group in the BMJ, in 1997. The analysis included 26 published randomized, controlled trials. The study subjects in those trials were adult patients with

post-surgical pain and were treated with single oral dose combination products, acetaminophen alone or placebo. Remember, there was no propoxyphene alone in those trials.

The analysis outcomes included standardized SPID, with the same pain intensity difference from baseline, and a response rate ratio. They also conducted two different comparisons. One is a head-to-head comparison which is only for factorial design studies, three arms in the same study so they can do head-to-head comparison. The indirect comparison, which was placebo-referenced comparison because most of the studies do not have a third arm so they used a placebo as a comparator for cross study comparison.

[Slide]

These are the results from this meta-analysis. The results from this meta-analysis show that the difference between the combination and acetaminophen was not statistically significant. But if you look at the forest plot in our background, the combination was numerically better than acetaminophen but not statistically significant.

The combination and acetaminophen were statistically superior to placebo, but the effect between the combination and acetaminophen alone overlapped with a 95 percent confidence interval. The authors' conclusion was

that acetaminophen was the primary contributor to the combination product.

[Slide]

In summary, based on the evidence from the DESI process, the original NDA submissions and our literature review, we found that propoxyphene shows weak analgesic effects in some acute pain trials. The contribution of propoxyphene to the analgesic effects of the combination is variable across acute pain trials.

With regard to chronic pain, the NDAs contain no data, and there are insufficient data in the literature to assess the analgesic effects of propoxyphene products. Thank you.

DR. FARRAR: Next is Dr. Sheetal Agarwal, the clinical pharmacology reviewer, Office of Clinical Pharmacology at CDER, FDA, talking about clinical pharmacology of propoxyphene.

Clinical Pharmacology of Propoxyphene

DR. AGARWAL: Good morning.

[Slide]

My name is Sheetal Agarwal, and I am a clinical pharmacology reviewer at the agency.

Today I will be presenting some clinical

pharmacology-related information on propoxyphene and its active metabolite norpropoxyphene. Since Sharon pointed out in the morning that propoxyphene is an old drug, we need to remember that the information that we have is limited, and also it is not to the same extent as you would expect presently from a new chemical entity. As such, the presentation today contains information that we gathered from a review of relevant literature.

[Slide]

Coming to the aspects of propoxyphene that I will be covering today in my presentation, we mainly try to concentrate on situations where pharmacokinetics of propoxyphene may be altered. The reason for that was that we knew that relatively high plasma levels of propoxyphene have been observed in cases related with deaths which were related to suicide or overdose. So, we cannot review the literature to see situations where pharmacokinetics of propoxyphene and norpropoxyphene may be altered.

As such, in today's presentation I will be covering metabolism of propoxyphene; effect of food intake; and effect of hepatic and renal impairment; and effect of age on pharmacokinetics of propoxyphene and norpropoxyphene. Finally, I will present some postmortem systemic levels of

propoxyphene in relation to therapeutic levels of propoxyphene.

[Slide]

I will start with the metabolism of propoxyphene. The major pathway for metabolism of propoxyphene is N-demethylation to norpropoxyphene. Some metabolic pathways include ring hydroxylation and glucuronidation. Historically, CYP2D6 was thought to be the main enzyme involved in metabolism of propoxyphene.

With this information, the implication is that there would be potential pharmacokinetic differences in populations having polymorphic differences in CYP2D6 expression. So, saying that CYP2D6 expression is higher or the activity is higher in patients having increased amounts of CYP2D6; that is, the extensive metabolizers. We could expect that norpropoxyphene levels may be higher in those populations, versus poor metabolizers who have less activity, or less expression of CYP2D6, and we may expect lower levels of norpropoxyphene in those populations.

Also, drug-drug interactions involving strong CYP2D6 inhibitors and inducers which can change the activity of CYP2D6 and, thereby, alter pharmacokinetics of propoxyphene and norpropoxyphene could be observed.

So, in the review of the literature we found a study by Somogyi et al., who assessed propoxyphene and norpropoxyphene pharmacokinetics in extensive and poor metabolizers after a single-dose administration of propoxyphene.

[Slide]

Let's look at the data. This slide shows the Cmax, AUC and elimination half-life for propoxyphene and norpropoxyphene in a population of extensive metabolizers that have limited levels of CYP2D6 versus poor metabolizers who have either low levels or low activity of CYP2D6.

So, if CYP2D6 were to be involved in metabolism of propoxyphene to norpropoxyphene, then ideally in the population of extensive metabolizers which have increased activity of CYP2D6 we would expect to see higher levels of norpropoxyphene as compared to poor metabolizers. But that was not found to be the case. As you can see here, the Cmax, AUC and elimination half-life for norpropoxyphene was similar in extensive metabolizers as well as in poor metabolizers.

Also, for propoxyphene there was no significant change in the pharmacokinetic parameters between both the extensive and poor metabolizers. The Cmax, AUC and

elimination half-life were similar. So, this study clearly showed us that CYP2D6 is probably not involved primarily in the metabolism of propoxyphene.

In the same study the authors also showed through an in vitro liver microsome study that CYP3A4 was actually involved in the metabolism of propoxyphene to norpropoxyphene.

[Slide]

So, now with this new information there are new implications, the first one being that we need to pay close attention to drug-drug interactions involving CYP3A4 inducers and inhibitors that can influence the level of CYP3A4 in our bodies. So, strong inhibitors, such as clarithromycin, HIV protease inhibitors, and ketoconazole, grapefruit juice, these can inhibit the expression of CYP3A4, thereby causing an increase in the level of norpropoxyphene.

Also, CYP3A4 inducers, such as carbamazepine and rifampin, can induce CYP3A4 and cause decreased levels of norpropoxyphene. Also, since we know that CYP 3A4 is a major enzyme involved in the metabolism of several drugs, we can expect a greater potential of drug-drug interactions with this new information.

So, from this study two things were clear. One was that CYP2D6 was not the primary enzyme involved in metabolism of propoxyphene, the other one being that we need to pay close attention to drugs that are co-administered with propoxyphene that may induce or inhibit CYP3A4.

[Slide]

Coming next to the food effect, since we know that administration of food can alter the pharmacokinetics of drugs we reviewed a study to see if there was any change in pharmacokinetics of propoxyphene and norpropoxyphene in the presence of food. So, in a study by Welling et al., who assessed the pharmacokinetics of propoxyphene when it was given following a high carbohydrate meal or a high-fat meal or a high protein meal--I will show you the data on the next slide but overall similar plasma profiles of propoxyphene and norpropoxyphene were observed.

[Slide]

Now let’s look at the data. This slide shows the Cmax, AUC and Tmax for propoxyphene when it was administered on an empty stomach with just 250 mL of water and when it was administered immediately following consumption of a high carbohydrate meal or a high-fat meal or a high-protein meal.

As you can see here, with the exception of a high-

carbohydrate meal which caused a 40 percent increase in Cmax, there were no statistically significant differences between any of the three parameters when it was administered on an empty stomach versus when it was administered after food. So, this study showed us that food will probably not have an effect on propoxyphene pharmacokinetics. Similar results were observed for norpropoxyphene.

[Slide]

Coming next to the effect of hepatic impairment on pharmacokinetics of propoxyphene and norpropoxyphene, we do not know in terms of percentage how much propoxyphene is metabolized and how much is excreted unchanged in urine. But we do know that propoxyphene is extensively metabolized. As such, we had reasonable expectations to believe that in conditions of hepatic impairment pharmacokinetics of propoxyphene and norpropoxyphene may be altered. Now, the level of alteration of pharmacokinetic will depend on the degree of hepatic impairment, that is, mild, moderate or severe.

We reviewed a study by Giacomini et al., who assessed the pharmacokinetics of propoxyphene and norpropoxyphene in patients with hepatic cirrhosis after a single-dose administration of propoxyphene.

[Slide]

Let's look at the data from that study. This slide has the Cmax and AUC for propoxyphene and norpropoxyphene in cirrhotic patients versus normal, healthy volunteers. As you can see here, the Cmax and AUC of propoxyphene were significantly increased in the cirrhotic patients, and norpropoxyphene Cmax and AUC was significantly decreased in cirrhotic patients.

This was a good study to review because although we don't have information on different levels of hepatic impairment and how pharmacokinetics will change as a function of degree of hepatic impairment, we still have a good idea that in cases of hepatic impairment, where the liver is not functioning properly and the levels of metabolizing enzymes may change, we may see decreased levels of norpropoxyphene and increased levels of propoxyphene.

[Slide]

On similar lines, we reviewed a study for effect on renal impairment and pharmacokinetics of propoxyphene and norpropoxyphene. We do know that renal excretion is a major pathway for norpropoxyphene elimination. As such, it is reasonably acceptable to believe that pharmacokinetics of propoxyphene and norpropoxyphene may be altered in

conditions of renal impairment. Just like in the case of hepatic impairment, the level of change in pharmacokinetics will depend on the degree of renal impairment, that is, mild, moderate or severe.

We reviewed a study by Giacomini et al, who assessed pharmacokinetics of propoxyphene and norpropoxyphene in anephric patients after a single dose administration of propoxyphene.

[Slide]

Let's look at the data. This slide has the Cmax and AUC for propoxyphene and norpropoxyphene in anephric patients and in normal, healthy volunteers. So, for propoxyphene, as you can see here, the Cmax and AUC were approximately twofold higher in the anephric patients compared to the normal volunteers. For norpropoxyphene, for which the kidney is the major route of excretion, the Cmax was not different in the anephric patients. However, AUC--that is, the exposure of norpropoxyphene--was close to two times higher.

So, again, this study, just like the hepatic impairment study, does not tell us how we can relate the degree of renal impairment to change in pharmacokinetics. But this study does give us useful information that in cases

of renal impairment we can see altered levels of norpropoxyphene and propoxyphene.

[Slide]

Coming to the next study that we reviewed, since we know that in the elderly population organ function is considerably reduced, we have a reasonable expectation to believe that, since renal and haptic function in the elderly might go down, the pharmacokinetics of propoxyphene and norpropoxyphene will be altered in the elderly.

As such, we reviewed a study by Flanagan et al., who evaluated effect of age on pharmacokinetics of propoxyphene and norpropoxyphene after single and multiple dose administration of propoxyphene.

[Slide]

Let’s look at the data. This slide shows the effect of age on single-dose pharmacokinetics of propoxyphene and norpropoxyphene. So, the young population in this study was 21 to 28 years and the elderly population was 70 to 79 years.

This slide has the Cmax, AUC and elimination half-life for propoxyphene and norpropoxyphene. As you can see here, in the elderly population all the three pharmacokinetic parameters were significantly altered. In

fact, they were two to three times higher in the elderly population versus the young population. For norpropoxyphene, however, there was no change in the Cmax. AUC was not determined and the elimination half-life was close to double. So, this study clearly showed us that we need to pay close attention to the dosing regimen in the elderly because they might show altered pharmacokinetics.

[Slide]

From the same study we also have data from single and multiple dose administrations. This slide shows single and multiple dose pharmacokinetics of propoxyphene and norpropoxyphene in the elderly population. We can see the Cmax and the half-life for propoxyphene after a multiple dose administration. The Cmax was significantly higher as compared with the single-dose administration. But for norpropoxyphene it was significantly higher. It was close to 5.7 times higher after a multiple dose administration versus a single dose administration of propoxyphene. So, this study clearly showed us that, in addition to the dosing regimen, we also probably need to pay attention to dosing frequency of propoxyphene in the elderly population.

[Slide]

Finally coming to some postmortem propoxyphene

levels, we reviewed the Adverse Event Reporting System database, the AERS database, for some plasma levels of propoxyphene in suicide and accidental overdose cases, but we found that the levels were highly variable. For example, we found levels ranging from 0.43 mcg/mL for an 86-year old patient to 2.46 mcg/mL for a 24-year old patient.

It is important to remember that these patients were consuming several other medications, such as opioids, along with propoxyphene. When put in perspective, when you compare these levels with therapeutic level they were only threefold higher for an elderly patient versus 42-fold higher when you compare this level with a 24-year old patient. So, when you put these levels in perspective of therapeutic levels, they are not very much higher when compared to therapeutic levels but, on the other hand, there are several conflicting factors that don't let us make a judgment on exactly how toxic propoxyphene will be at therapeutic levels.

[Slide]

The reasons for that are that we do not know the propoxyphene levels at the exact time of death because we do not know the postmortem sampling time. In addition to the postmortem sampling time, we also do not know the

norpropoxyphene plasma levels so we cannot predict the toxicity of propoxyphene because we do not know how much norpropoxyphene was present at the time of death. Also, we do not know how much propoxyphene the patients were consuming. We do not know the number of tablets that they took.

Then, there were several concomitant medications that they were taking and by CYP3A4 inhibitors or inducers or they could be CNS depressants and that could lead to death. In addition, the phenomenon of postmortem redistribution can lead to a change in blood levels of propoxyphene post death and, therefore, the quality of data of these levels cannot be trusted.

[Slide]

Finally coming to the summary of findings from my presentation, for metabolism of propoxyphene we now can pay attention to CYP3A4 inhibitors and inducers, and just pay close attention to what drugs we are co-administering with propoxyphene.

We also now know that food will not have an effect on propoxyphene or norpropoxyphene pharmacokinetics so propoxyphene can be taken without regard to meals.

We also know that in cases of hepatic and renal

impairment we will probably see elevated levels of propoxyphene and elevated or reduced levels of norpropoxyphene. So, we need to be cautious in those patients. For the elderly population we need to pay close attention to the dosing regimen and dosing frequency of propoxyphene. Finally, for postmortem propoxyphene levels, since there are several conflicting factors that complicate the picture, we cannot judge the quality of the data that was presented to us from the AERS database and it was really difficult to predict the toxic levels of propoxyphene at therapeutic or at toxic levels.

This concludes my presentation. Thank you.

DR. FARRAR: Next is Steve Leshin. He is a pharmacology and toxicology reviewer, Division of Anesthesia, Analgesia and Rheumatology Products, CDER, FDA. He will be talking about nonclinical pharmacologic findings.

Nonclinical Toxicology Findings

DR. LESHIN: Good morning.

[Slide]

I will present nonclinical pharmacology and toxicology information concerning propoxyphene and its major metabolite norpropoxyphene, focusing briefly on the receptors involved in analgesics, then highlight some of the

effects demonstrated in animal studies dealing with cardiac effects that were alluded to earlier this morning.

As mentioned earlier, at the time of approval propoxyphene was characterized as a weak opioid analgesic. This was based on comparative behavioral and pharmacological studies with other opioids of the day, such as morphine, codeine and methadone.

[Slide]

Presented here, in the early ‘80s after opioid receptors were characterized, studies were conducted with propoxyphene on the three different opioid receptors, mu, delta and kappa. Propoxyphene was approximately equipotent at mu and delta receptors, much less potent than morphine however, but more potent than codeine. At the kappa receptors the actual quantification was limited by the maximal dose used although it was determined that it is much less potent than morphine.

Norpropoxyphene, along the bottom column, showed very low affinity for all three receptors. However, again, it is limited by the dose that was used.

This led to one of the points of our conclusions, that propoxyphene was a weak opioid analgesic and that norpropoxyphene lacks significant opiate activity in

comparison to morphine. In vitro receptor study data does not always correlate with clinical analgesia. However, as Dr. Chen noted earlier, numerous studies have indicated a weak opioid effect.

[Slide]

Recent studies have revealed a diverse series of receptors for which propoxyphene and norpropoxyphene may also interact. These were studied in the determination of additional opioids and related compounds that may be involved in pain modulation through different mechanisms.

It was found that population and norpropoxyphene have activity at N-methyl D-aspartate receptors, NMDA receptors and at the neural nicotinic subtype of the acetylcholine receptor. At both receptors an antagonistic effect was demonstrated. The binding was non-competitive.

Thus, both compounds appear to have potential for non-opioid interactions. The significance of these findings for the overall analgesia and toxicological profile has not yet been elucidated.

[Slide]

At the 1979 advisory committee meeting concerns were raised about the potential abuse and toxicity of propoxyphene, particularly cardiotoxicity. Previously

submitted studies to the FDA provided no signals suggesting heart-related concerns. These were studies conducted from the ‘50s to the ‘70s.

Additional nonclinical studies were then submitted that focused on cardiovascular effects. These were mostly manuscripts or published papers. The original data was not submitted. Norpropoxyphene was thought to contribute at the time to cardiotoxicity due to its longer half-life, its being present in plasma and tissues at levels greater than propoxyphene and approximately twofold greater local anesthetic activity, which I will address later.

[Slide]

ECG recordings were conducted in some animals and the results for rabbits are presented here. We have propoxyphene infusions on this side. These are conscious rabbits. Norpropoxyphene infusions are on the right side. Heart rate, PQ interval, QRS complex, durations and plasma concentrations are presented.

The propoxyphene infusions resulted in deaths of a couple of the rabbits. Those were separated out in the data and are presented on the far left. The animals that survived are presented in the middle. Note that the pattern of responses for those that survived and those that did not

are very similar.

The data indicates that with increasing dose the PR interval increased. The QRS complex increased. Similarly with increasing doses of norpropoxyphene, the PQ interval increased and the QRS complex increased or widened. Also, it is important to note that at the end of infusion interval durations tended to fall down toward the control levels.

[Slide]

ECG recordings were also conducted in dogs and are summarized here. Dogs were given weekly doses of either 0, 2.1, 6.4 or 21 mcmol/kg and one dose of norpropoxyphene was administered. The results indicate that the PR interval was prolonged. It was a dose-related effect. QTc was also prolonged only at the high dose, which is at the termination of infusion of 12 mcg/kg. QRS was also prolonged, however, statistically it was not determined to be significant because there was large variation between animals.

For norpropoxyphene the only data provided was for the PR interval. In the paper that is cited they just alluded to the fact that similar effects were noted for norpropoxyphene as were found for propoxyphene, but no data was provided.

[Slide]

Further investigation of specific heart tissues, either isolated or intact, indicated that within the atria sinus frequency was slowed; contractility was reduced. Conduction through the His fiber bundle and Purkinje fibers were slowed and shortened. Papillary muscle maximal tension was also reduced. The potency either was greater either for propoxyphene or norpropoxyphene. There wasn't any consistency in which was more potent than the other.

[Slide]

Turning to potassium channels, the action of drugs on potassium channel repolarization current is a common aspect of today's cardiovascular safety studies. It is used to indicate the potential for drug-induced cardiac arrhythmias such as Torsades which can be lethal.

A study conducted in the late '90s found that propoxyphene and norpropoxyphene both altered potassium channel currents similarly. Low concentrations increased currents. High concentrations blocked currents. They also looked at gating properties of these currents and they were able to show that both compounds slowed the channel activation and accelerated deactivation kinetics.

A signal of this nature today would be considered

together with other animal safety studies or human studies and, if warranted, would lead to ECG studies in human subjects.

[Slide]

From the early days of propoxyphene's characterization, it was known to have what is commonly called a local anesthetic effect. This is illustrated here where is plotted the action potential height decrease, percent decrease versus concentration. For propoxyphene note that from 10^{-5} molar to 10^{-4} molar there is reduced height with electrically stimulated nerve fibers. Norpropoxyphene's was about twofold greater effectiveness and lidocaine was substantially less effective in reducing action potential height.

[Slide]

There is a case report from Whitcomb, in '89, that brings this local anesthetic sodium channel effect into the clinical realm. He reported on an overdose case. I will skip through the initial treatments, but the important points I would like to illustrate are that over the time period that this patient was in hospital after admission, the QRS complex widened. It was reversed by administration of lidocaine and the patient did recover. Propoxyphene

levels were around 14 mcg/mL, I believe. Norpropoxyphene levels were not measured. The propoxyphene effect was somewhat paradoxical because both of them are sodium channel blockers.

Further studies were, therefore, conducted in rabbit atrial cells in culture in which they looked at the kinetics of lidocaine and propoxyphene and found that the faster kinetics of lidocaine were probably able to displace the propoxyphene and possibly the norpropoxyphene that was present to facilitate recovery of normal heart function.

[Slide]

In summary, propoxyphene and norpropoxyphene affect cardiac conduction and contractility. Evidence exists for possible mechanisms of action through sodium channels and potassium channels. Evidence exists for potential activity at diverse types of receptors, opioid, NMDA and cholinergic.

However, the available nonclinical information is insufficient to enable a determination of a safety margin for therapeutic use of the propoxyphene drug products, as would be found in today's types of studies. The design at that time in response to the AC meeting was to determine if there was an effect on cardiac tissues.

[Slide]

In terms of therapeutic relevance, as described in the animal studies, similar cardiac-related findings can be found in human case reports. The drug concentrations exceed those, at least in the reports that I have seen, expected at the clinical therapeutic level. What we don't know is whether the cardiac effects noted in these studies occur in individuals exposed to therapeutic concentrations of propoxyphene drugs.

This concludes my presentation. Thank you.

DR. FARRAR: Thank you. Next is Hina Mehta, a drug utilization analyst from the Office of Surveillance and Epidemiology at CDER, talking about the utilization trends for propoxyphene products.

Utilization Trends for Propoxyphene Products

DR. MEHTA: Good morning.

[Slide]

My name is Hina Mehta and I am a drug use analyst, from the Division of Epidemiology in the Office of Surveillance and Epidemiology. Today I will be presenting the outpatient drug utilization trends for propoxyphene products.

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The outline of my presentation is in the following order: First I will present the sales distribution analysis for propoxyphene products using the IMS Health, IMS National Sales Perspectives. Then I will present the dispensed prescription analysis using the SDI, formally known as Verispan Vector One National database.

I will begin with the different single-ingredient and combination propoxyphene products and then do further breakdowns of selective products by age as well as prescribing specialty. My presentation will also cover patient-level analysis using the SDI Vector One National and the SDI Total Patient Tracker. Finally, I will conclude with a summary of my presentation.

[Slide]

Before I begin I want to show you how the propoxyphene products were grouped for the analysis. All combination products of propoxyphene and acetaminophen were grouped together. From this point forward these products will be referred to as propoxyphene/APAP. All single ingredient-propoxyphene products were grouped together. Finally, all combination products of propoxyphene, aspirin and caffeine were grouped together.

[Slide]

Sales distribution data were provided from the IMS Health, IMA National Sales Perspectives database.

[Slide]

Beginning with the sales distribution data, we used the IMS Health, IMS National Sales Perspectives database to get a sense of where these products were distributed and determine the primary settings of care.

This database measures the volume of products in units and dollars moving from the manufacturers to retail and non-retail channels of distribution. The volume measured in this case was eaches, or the number of bottles, packets of pills, syringes or vials in each shipping unit. Retail channels included chain, independent, mass merchandisers, food stores with pharmacies and mail-order pharmacies. Non-retail channels include federal facilities, non-federal hospitals, clinics, long-term care facilities, home health care, HMOs and miscellaneous channels.

[Slide]

This slide shows the total number of bottles or packets of single-ingredient and combination propoxyphene products being sold from the manufacturers to the back door of retail and non-retail pharmacy channels. For year 2007, approximately 90 percent of propoxyphene sales are as

combination product propoxyphene/APAP, of which 55 percent is sold toward retail pharmacy channels. Ten percent of population sales are as single-ingredient propoxyphene, of which 80 percent are distributed toward retail channels. One percent of propoxyphene sales are as combination product propoxyphene-aspirin-caffeine, of which 60 percent are distributed toward retail pharmacy channels. Thus, we focused our analysis on the outpatient retail pharmacy setting.

[Slide]

Dispensed prescription and patient-level data were provided from the SDI Vector One National and Total Patient Tracker databases.

[Slide]

SDI, or Surveillance Data, Inc., is the national-level projected prescription and patient-centric tracking service. It receives over two billion prescription claims per year and represents over 160 million unique patients.

The number of dispensed prescriptions is obtained from a sample of approximately 59,000 pharmacies throughout the U.S., which accounts for nearly all retail pharmacies in the country, and represents nearly half of all retail prescriptions dispensed nationwide. The types of pharmacies

and the retail sample include national retail chains, mass merchandisers, pharmacy benefits managers and their data systems, and physician providers. From this database we can also obtain data on prescribing specialty as well as patient demographic factors such as age and gender.

[Slide]

We looked at the ten-year trend for the volume of prescriptions dispensed for single-ingredient and combination propoxyphene products in the outpatient retail pharmacy setting.

As you can see, the combination product, propoxyphene/APAP, is the most widely dispensed out of the entire propoxyphene prescription drug market for the past ten years. Over 21 million propoxyphene/APAP prescriptions were dispensed in year 2007, accounting for over 97 percent of the market. However, its use has been gradually decreasing, approximately 26 percent from 1998 to 2007. Single-agent propoxyphene and combination product propoxyphene, aspirin and caffeine fall far behind, and combined account for less than three percent of the market in year 2007, or 557,343 prescriptions.

[Slide]

This chart looks specifically at the number of

prescriptions dispensed for combination product propoxyphene/APAP by age. During year 2007 elderly, represented by the bars in this chart, aged 65 years and greater accounted for approximately 8.3 million prescriptions, or 38 percent dispensed; followed by adults, aged 45 to 64 years, with approximately 8.2 million prescriptions, or nearly 38 percent. Adults aged 18 to 44 years accounted for approximately five million prescriptions dispensed, or 23 percent.

[Slide]

In this chart we see the total number of patients receiving a prescription for propoxyphene products from outpatient retail pharmacies for years 2002 through 2007 and year to date, October, 2008.

The majority of patients, approximately 9.7 million, received a prescription for combination product propoxyphene/APAP in year 2007. Single-ingredient propoxyphene and combination product propoxyphene, aspirin and caffeine, fall far behind, with only 182,312 patients and 367 patients respectively, receiving a prescription in year 2007.

[Slide]

This slide takes a look at the number of patients

receiving prescription for propoxyphene/APAP product by age. During year 2007 approximately 3.4 million patients aged 45 to 64 years received a prescription for propoxyphene/APAP; followed by patients aged 18 to 44 years and 65 years and older, with over three million patients each receiving a prescription. There has been a 20 percent decrease in the number of patients aged 18 to 44 years receiving a prescription for propoxyphene/APAP between the years 2002 and 2007. The age group 45 to 64 years has seen a 12 percent decrease in the same time period, while the elderly, aged 65 years and older, have seen an 18 percent decrease.

[Slide]

We also examined the top 15 prescribers of combination product propoxyphene/APAP over the past ten years. The leading prescribers in year 2007 were general practice and family medicine specialists with approximately 6.3 million prescriptions, or 29 percent of the market; internal medicine, with 4.2 million prescriptions, or 19 percent of the market; and orthopedic surgery with 1.9 million prescriptions, or 9 percent of the market.

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In addition, we examined the overall duration of use by gender for combination product propoxyphene/APA in

year 2007 by age. In the age group 0-17 years, approximately 70 percent of drug use mentions by physicians in office-based practice settings was 0-7 days. In the age group 18-44 years, approximately 54 percent of drug use mentions were for 0-7 days. In the age groups 45-64 years and age 65 years and greater the drug use mentions were for 0-7 days in about 35 percent and 37 percent respectively.

[Slide]

This slide breaks down prescriptions for propoxyphene products by new, continuing, and switch-add on prescriptions in year 2007. About 58 percent of prescriptions were dispensed to those who did not have a previous prescription for propoxyphene/APAP products within the past three months.

Approximately 41 percent did have a prior propoxyphene/APAP product in the past three months, and less than one percent of new prescriptions were either add-on or switch from another pain product. Forty-four percent of new prescriptions were dispensed to those who did not have a previous prescription for single-ingredient propoxyphene within the past three months. Fifty-five percent did have a single-ingredient propoxyphene product in the past three months.

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In summary, dispensed prescriptions and number of patients for propoxyphene products have been declining over the past ten years. The largest decrease in use has been seen in the age group 18-44 years. Propoxyphene/APAP accounted for 21.8 million prescriptions and 9.7 million patients in year 2007. The elderly, aged 65 years and greater, account for 8.3 million prescriptions and three million patients for propoxyphene/APAP in year 2007. Adults aged 45-64 years account for 8.2 million prescriptions and 3.4 million patients for propoxyphene/APAP in year 2007. The leading prescribers are general practice and family medicine, internal medicine and orthopedic surgeons.

[Slide]

Average days of therapy of prescription for propoxyphene/APA is 0-7 days for all age groups. Approximately 58 percent of new prescriptions were dispensed to those who did not have a previous prescription for propoxyphene/APAP product within the past three months. Approximately 55 percent did have a prior single-ingredient propoxyphene product in the past three months.

This concludes my presentation.

DR. FARRAR: Thank you. Next is Joann Lee,

Division of Pharmacovigilance, Office of Surveillance and Epidemiology at CDER, talking about the AERS reporting of cardiotoxicity.

Finding from AERS Analysis and Epidemiological Review of Cardiotoxicities Associated with Propoxyphene

DR. LEE: Good morning.

[Slide]

My name is Joann Lee. I am a safety evaluator from the Division of Pharmacovigilance II within the Office of Surveillance and Epidemiology. Today I will be presenting the reviews of postmarketing adverse events and literature findings of propoxyphene-containing products.

[Slide]

Here is the outline of my presentation. First I will go over the Adverse Event Reporting System database, referred to as AERS. There are two AERS reviews which will be discussed today. The first AERS review covers the data from 1969 through 2005, focusing on death cases. The second updated AERS review of serious adverse events reported between 2006 and 2007 will also be discussed in detail.

Before going into the details, I will summarize the key findings from these two propoxyphene AERS reviews and the cardiac literature review. Then I will further

discuss both AERS reviews and follow up with a literature review of cardiac effects of propoxyphene products. Finally, I will wrap it up with concluding statements.

[Slide]

Let’s briefly go over the AERS reporting system.

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Spontaneous adverse event reporting is a voluntary system for consumers and healthcare professionals to report the adverse events. Under the Code of Federal Regulations, sponsors of an approved NDA product are required to report the adverse events. These reports are sent to the agency through the FDA MedWatch program and stored in the AERS database.

[Slide]

Spontaneous adverse event reporting is useful since it does include all U.S. marketed products. It is best to detect events not seen in clinical trials and it is a good tool for rare background rates.

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However, there are some limitations. Since it is a voluntary system there is extensive under-reporting. The quality of reports may be variable depending on who the actual reporters are. There may be reporting biases based

on notoriety and media attention a particular drug product will be receiving at a given time or if it is a new drug product. The actual numerator and denominator are not known so the quantification of risk assessment is subject to limitations. Lastly, causality of drug event association is often in question. So, these are some of the advantages and challenges, as I further discuss AERS data, to bear in mind.

[Slide]

First I will provide a summary of the two AERS reviews and the literature review, followed by a more detailed discussion of the findings.

[Slide]

For the first AERS data we reviewed cases of death associated with the use of Darvocet that were reported between 1969 and 2005. From this search there were 91 death cases. To summarize, majority of the death cases were related to drug overdoses and suicides involving multiple drugs. Most commonly reported overdoses included narcotics, antidepressants, benzodiazepines and/or alcohol. There were no other notable trends or characteristics found in the non-overdose cases. Lastly, a causal role of Darvocet could not be determined in these cases given the underlying medical history or multiple drug use.

[Slide]

Here is a summary of the second updated AERS review of serious adverse events reported in association with propoxyphene between 2006 and 2007. Forty percent of the 65 cases reviewed involved elderly patients, 65 years or older. In this population psychiatric events such as hallucination, which is already labeled in the current product labeling, or mental status changes were most commonly noted. Eighteen percent of the cases involved mortalities, mostly from accidental overdoses, and the majority of the cardiac cases were heavily confounded.

Overall, of these 65 cases evaluated in this updated review, there was a strong temporal relationship and positive dechallenge, most notably in psychiatric cases. However, given the underlying medical history and the polypharmacy, these reports were qualitatively similar to the first AERS review where the direct causal association of propoxyphene could not be established in the majority of the cases.

[Slide]

Lastly, the literature data for cardiotoxicity were mostly anecdotal reports. There was insufficient evidence to support an association between propoxyphene and

cardiotoxicity.

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Now, with that summary in mind, I will briefly discuss the first AERS review. Then I will mainly focus on the updated review of serious events for the purpose of today's AC meeting.

[Slide]

For the first AERS review we reviewed individual cases of death involving Darvocet that were reported between 1969 and 2005. We did not include all propoxyphene products in this search because at that time, in 2005, the U.K. initiated a phased withdrawal of co-proxamol which contained both propoxyphene and acetaminophen. We limited the search to death cases primarily to capture the most serious cases. As a result of this search, a total of 91 death cases were evaluated.

As mentioned in the summary slide, just to recap, a direct causal association with Darvocet could not be determined in these cases given the use of multiple drug products in overdoses and suicides. In the interest of time I will refer you to the background package for the details to the first AERS review.

[Slide]

Now I will discuss the second updated AERS review. This table contains the top 20 adverse events from the AERS crude counts. AERS was searched using all trade and generic drug names for propoxyphene. The search was limited to domestic cases for all adverse events, serious and non-serious, from 1969 through September of 2008. This search produced a total of 3,038 reports.

Here I want to highlight the most commonly reported events which appear to be suicides. It is at the top and I highlighted it in yellow. The most common ones were completed suicide and overdoses. Notably, these events represent almost half of the 3,038 reports. There were also over 1,400 fatalities from these 3,038 reports. Again, that is almost half of these reports.

One caveat, I do want to remind you that these reports have not been individually evaluated so these numbers, as they are called, are crude counts which may contain duplicate reports, and there is no certainty that propoxyphene caused the adverse event. Also, a report may have more than one outcome.

[Slide]

This is a pictorial representation of the top ten adverse events that were just presented in the previous

slide. As you can see, overdose, which includes multiple overdose, intentional overdose and just standard overdose, were all combined and that was the most common reported adverse event, followed by completed suicide.

[Slide]

Now I will focus on the details of the second AERS review. For today's meeting we wanted to provide a safety profile of this drug product looking at some recent AERS data. So, the search was limited to the two-year time period, from 2006 to 2007. In addition, since death cases were already evaluated in the prior AERS review, this search was expanded to include all serious events. Finally, all generic and trade propoxyphene drug names were used to search the AERS database.

Just to remind you, serious events include death, hospitalization, life-threatening and other medically significant outcomes. So, from this search, a total of 192 reports were retrieved.

[Slide]

This slide shows the reasons for excluding the cases. Since we already know that propoxyphene-containing products are implicated in suicides and overdoses, these reports were excluded. Our primary focus for the second

AERS review was on safety of propoxyphene products used under therapeutic conditions.

[Slide]

After exclusion, 65 unique cases were individually evaluated. Here we see twice the females reported adverse events with this drug product. The median age was 62 years of age. The most common indication was for unspecified pain and back pain. The dose was reported in approximately one-fifth of the cases, with a median of 200 mg per day. Similar to the drug utilization trend presented before, almost 80 percent of these cases reported using the propoxyphene-acetaminophen formulation. Nine percent used a single propoxyphene ingredient, and the formulation was unknown in the remaining 12 percent of the cases.

[Slide]

This slide shows the time to onset, duration of therapy and outcome. The time to onset was reported in approximately one-third of the cases, with the median time to onset of one day. The median duration of therapy was 15 days, with one-fourth of the cases reporting this information. There were 12 fatal cases involving two or more drugs, including alcohol. The majority of these death cases involved accidental overdose.

[Slide]

Overall, almost half of the cases reported confounding factors such as contributing medical history and/or use of concomitant drugs which were labeled for the reported events. The most common drugs used concomitantly with propoxyphene products were narcotics, benzodiazepines and psychotropics, which was also noted in the first AERS review that I described earlier.

[Slide]

This is a breakdown of adverse events. Mental status changes and hallucinations were most common among the psychiatric related events. This was especially true in the elderly population. There were three notable cardiac cases, two of which involved life-threatening bradycardia. The third case involved arrhythmia resulting in death. These were notable based on plausible drug interactions or strong temporal association in one case. That is, the patient experienced bradycardia after two days of taking Darvocet for dental pain.

So, in these three cases the role of propoxyphene could not be ruled out in spite of the confounding factors. In the remaining eight cardiac cases the causal association of propoxyphene could not be determined, either due to lack

of clinical details or the cases were heavily confounded with another drug more likely associated with the events.

[Slide]

Interestingly, among the cases reporting drug ineffective, over half of the cases consisted of product complaint when switching from one manufacturer to another generic brand. For the accidental overdose the majority of the cases reported that as an outcome. There were no notable trends or characteristics in the remaining 35 percent of the cases, with the majority reporting another drug as the primary suspect drug.

[Slide]

Next I will describe the findings from the cardiotoxicity literature review that was completed by Dr. Kuyateh, from the Division of Epidemiology.

[Slide]

A search of PubMed and EMBASE yielded 16 publications focusing on associations between propoxyphene and cardiotoxicity, three of which were epidemiology studies. For this presentation I will talk about these three epidemiology studies.

[Slide]

The study findings were mixed. One study found no

association between cardiac conduction and propoxyphene, while a second study found a significant association which was also found to be dose-dependent. The third study found no clinically significant change in cardiac output in relation to propoxyphene.

[Slide]

I just want to remind you that any interpretations of these findings should take into account the study limitations but, most importantly, a negative finding does not necessarily translate into no association but, rather, it is better interpreted as the study could not find an association.

[Slide]

In conclusion, and to reiterate the main findings for the first AERS review, a direct causal role could not be established given the comorbidities and use of multiple drugs, including narcotics, antidepressants or alcohol.

For the second updated AERS review, some cases did show strong temporal association and a few reported positive dechallenge. This was most commonly noted among the psychiatric cases and in the elderly patients.

Overall, the reports were qualitatively similar to the first AERS data where causal association for

propoxyphene could not be determined in majority of the cases. However, in some cases the additive role of propoxyphene could not be ruled out.

With respect to the literature review, there was inadequate data to support cardiotoxicity with use of propoxyphene products.

A final point I would like to leave you with is that propoxyphene continues to be implicated in overdoses and suicides, particularly when used with narcotics and CNS-related drugs. This was true despite the warnings in the current propoxyphene labeling, and it was also reflected in the two AERS reviews presented today.

With that, I would like to thank you for your attention.

DR. FARRAR: The last presentation today is by CAPT Katy Poneleit, from the Public Health Service, Director of the Division of Facility Surveys, Office of Applied Studies at SAMHSA,

Misuse/Abuse of Propoxyphene Products:

Findings from the Drug Abuse Warning Network (DAWN)

CAPT PONELEIT: You just promoted me. Thanks. That was my boss, prior boss.

[Slide]

Good morning. I am CAPT Kathy Poneleit. I am with the Drug Abuse Warning Network. Today I am going to be presenting findings from our network on propoxyphene and some comparators.

[Slide]

DAWN is a stratified probability sample of hospitals. Hospitals have to be short-term, general, non-federal, and have a 24-hour emergency department. We produce national estimates, and from a retrospective review of emergency department charts we collect about ten million, and we find about three percent of cases and these represent an estimated four million ED visits each year. We also produce metropolitan estimates. DAWN also, I should mention, collects data for all drugs, not just drugs of abuse, and this has been since our 2003 redesign.

[Slide]

To give a sense of what we are going to be looking at today, for 2007 emergency department visits I am looking at propoxyphene, propoxyphene-acetaminophen and codeine as a comparator. I look at adverse reactions in all cases. Then I also provide the percent adverse reactions.

So, as you can see, the number of adverse reactions are far fewer than the propoxyphene-acetaminophen

reactions. Then, if you add up the propoxyphene and the propoxyphene-acetaminophen, you get a very similar number in terms of the codeine. That is for the adverse reactions and similarly for all cases. We define all cases as including such things as suicide, the adverse reactions, accidental ingestion, over-medication and alcohol.

[Slide]

As part of this review, I looked at cardiovascular involvement. We have a system where we are able to code diagnosis conditions, and one of those is cardiovascular. As part of that coding process, cardiovascular involvement can include heart attacks, chest pain, abnormal EKGs or enzymes, various cardiac arrhythmias, hypertension and stroke, although this is not an inclusive list.

[Slide]

So, we looked at the number of all cases and the number of adverse reactions that had a cardio event or no cardio event for the propoxyphene, propoxyphene-acetaminophen and codeine. What you can see both for all cases and for adverse reactions is that the pattern is very similar for both all cases and adverse reactions, and that the number of cardio cases versus non-cardio cases is much lower.

[Slide]

So, then we looked at the percent with the cardiovascular event. Again, these data are for 2007, our most recently available data. What you can see is that the percent of all cases is roughly around 12 percent, with the propoxyphene-acetaminophen being slightly higher. Then, when you look at propoxyphene for the adverse events, propoxyphene alone was considerably less than the propoxyphene-acetaminophen and the comparator, codeine. These numbers on the bottom are the totals that I showed in the previous slide.

[Slide]

So then, we looked at a couple of different drugs in combination with the propoxyphene, propoxyphene-acetaminophen and codeine in addition to things like the benzodiazepines. Here what you see is that the adverse reactions with that kind of combination were very low in comparison to all cases, almost non-existent. Similarly with alcohol, the same thing. And, you can see that the number of propoxyphene cases overall were very, very low in comparison to the propoxyphene-acetaminophen and codeine.

[Slide]

So, then we looked at the rate by age and gender

for propoxyphene and we will track through propoxyphene and then the other comparators. In this case, you can see that for males and females the rates are very similar. I should point out that I put everything on the same scale for the next couple of slides so this is not a mistake. The rates for the 25 through 55 are sort of the same and you see this drop at 35-44.

[Slide]

Then they jump up considerably for the propoxyphene-acetaminophen age and gender group. These rates, what you see is that the females have a much higher rate than males and this is true I think for the remainder of the slides. Then the mid-range age rates are very similar, but now we see a spike at the 30-34 year age group.

I should point out that there is also a much higher rate for the 65 and over. However, that is not totally a fair comparison because these ages are in age bands of 5-10, whereas this includes everything over 65 and there was a fair number in the 10-year age bands even in the 85-year old age range.

[Slide]

So then, looking at propoxyphene adverse eventsB- the previous two slides were for all cases and now we are

looking at those that are the subset with adverse events. Males and females have similar rates; the 18-20-year olds are almost comparable to the 30-34 and over 65.

[Slide]

Then, looking at the propoxyphene-acetaminophen rates, we again see that the females have a rate that is much higher than the males, more than double. Then, the younger age groups are very similar. The mid-range groups are very similar. But, again, we see that higher rate for the 30-34-year olds and, again, the 65 and over have a rate that is higher.

[Slide]

Then we looked at polydrug use for the adverse reactions. The yellow are for the ones where they only had one drug. The purple and the blue are for when they had polydrug use. You can see that for polydrug use it was much more common than it was for single drug use for all three drugs.

[Slide]

Then we looked at the polydrug use for the adverse reactions group that had cardiovascular involvement. It is a little bit more dramatic here in that it is predominantly one drug rather than two or three drugs.

[Slide]

So, some things that I didn't share in slides but I will tell you about them are that the proportion of propoxyphene-acetaminophen cases, all cases, compared to propoxyphene plus acetaminophen, propoxyphene so, in other words, the denominator is all cases of propoxyphene in relationship to the numerator being propoxyphene-acetaminophen, is about 84 percent. Then when you look at the subset of those adverse reactions where you have propoxyphene-acetaminophen on top compared to all propoxyphene cases, it is about 92 percent.

Then, we did look at the suicide cases but they were too small to analyze by the time you break them out by age, gender and other factors. We just didn't have enough. Finally, we did not see any deaths in the emergency department component.

[Slide]

Moving on to the mortality component, we collect data from medical examiners and coroners, and we do that in selected metropolitan areas and selected states. This is, again, a retrospective review of medical examiner files and we collect raw counts of drug-related deaths. This is not a statistical sample. We can't generalize to the nation. We

can't generalize to metropolitan areas if we have incomplete participation. These are where the drug was implicated in the death of the patient or decedent, I should say.

[Slide]

So, this is looking at the manner of death for deaths that occurred in 2007. This is from 168 participating jurisdictions. So, deaths that were classified by the medical examiner as an accident occurred in the majority of cases, followed by suicide. The CNBDs could not be determined. There were no homicides and very few were classified as natural deaths. These are the subset of those jurisdictions where we collected data, not all jurisdictions that we could have collected data from.

[Slide]

For deaths involving propoxyphene what we found is that there were very few that were related to the drugs of interest. Six percent out of 503 cases were propoxyphene only; one percent were the propoxyphene-acetaminophen combinations; and one percent were when there were two drugs, the propoxyphene and, as a separate drug, acetaminophen. In the medical examiner side it is insufficient, and it is true actually on the ED side as well-Bwe don't classify things based on the toxicology

alone. We do collect toxicology data but if that is the only data we have, then we can't use that data to determine whether the case is a DAWN case or not.

[Slide]

I know we say we shouldn't use things like this for trends because the number of jurisdictions participating change over time so it is not a fair comparison. But this slide was really intended to just show polydrug use or single-drug use for the decedent cases. You can see that single-drug use is very low.

[Slide]

This slide was put in here just to give a different comparator for propoxyphene--and this is all propoxyphene not just propoxyphene or propoxyphene and acetaminophenB-with oxycodone, hydrocodone and methadone. So, you can see that the propoxyphene deaths were much lower than these other opioids.

[Slide]

Then, this is again for a single year, 2007, and what it shows is the age distribution for propoxyphene, hydrocodone and oxycodone. You can see that the distributions are almost normal for all three of them and, again, there are fewer cases for propoxyphene in comparison

to hydrocodone and oxycodone.

[Slide]

So, in conclusion I wanted to go back and restate that propoxyphene-acetaminophen cases accounted for almost 92 percent of all ED drug-related visits for those visits where propoxyphene overall was involved.

Propoxyphene-acetaminophen had similar characteristics to those of codeine. There was a small number of cardiovascular events overall. The age distribution tended to be higher in older individuals, but with the caveat that this was not in the same year band as presented for other age groups, and that polydrug use was common whether we were talking about the emergency department or the medical examiner component.

I think that concludes it. Yes, that concludes my presentation.

DR. FARRAR: Thank you. Given that it is almost 12:30 and probably we all need a little bit of nourishment to be thinking straight about questions we may have, I think we will break for lunch.

I would like to remind people that the lunch for the committee is in the restaurant. It is a buffet and it is set up. There is a special area that is set aside for

us. I will also remind folks that we are not supposed to discuss the meeting during lunch and amongst ourselves, with the press or any member of the audience. When we come back we will start with the open public forum for a brief presentation. We have one person signed up for that. Then we will go into a question and answer period for the FDA, and extend it if we want to include the morning's presentations, with a focus on getting to a discussion amongst ourselves.

I would ask the committee, if you would take two seconds or two minutes maybe, to pull out the questions that are in your folder and have a look at them. You are not allowed to talk about them at lunch, but you certainly can think about them at lunch. I think we may go a lot faster in terms of the discussion if people have some idea about how they feel about those particular things. It may also focus the questions that we come to on questions that really will make a difference in how we might answer those particular questions as opposed to sort of general interest questions.

So, we will return at 1:30 and pick up where we left off.

[Whereupon, at 12:28 p.m., the proceedings were recessed for

lunch, to reconvene at 1:30 p.m.]

A F T E R N O O N P R O C E E D I N G S

Open Public Hearing

DR. FARRAR: Let's get started. As I said before lunch, we are going to start with the open public hearing.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision-making. To ensure such transparency at an open public hearing session of the advisory meeting, the FDA believes that it is important to understand the context of an individual's presentation.

For this reason, the 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 the sponsor, its product or, if known, its direct competitors. For example, this financial information might include the sponsor's payment of your travel, lodging or other expenses in connection with your attendance at this meeting.

Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such 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.

The FDA and this committee place great importance on the open public hearing process. The insights and comments provided can help the agency and this committee in consideration of the issues before them. That said, in may instances and for many topics there will be a variety of opinions. One of our goals today is for this open hearing to be conducted in a fair and open way where every participant is listening to careful and treated with dignity, courtesy and respect. Therefore, please speak only when recognized by the chair, and thank you for your cooperation.

The person who signed up for the open public hearing is Cynthia Reilly. Cynthia?

MS. REILLY: Good afternoon. I have no conflicts of interest to disclose.

My name is Cynthia Reilly, and I am the Director of the Practice Development Division at the American Society of Health System Pharmacists. ASHP represents pharmacists who practice in hospitals and health systems. The Society's more than 35,000 members practice in a variety of health system settings including inpatient, outpatient, home care and long-term care.

I appreciate the opportunity to present the views

of ASHP on appropriate regulatory action relating to propoxyphene-containing products. ASHP policy advocates Food and Drug Administration withdraw propoxyphene from the United States market based on the drug's poor effectiveness and safety profiles, and because more effective and safer alternatives are available to treat mild to moderate pain.

Propoxyphene has been used for treatment of mild to moderate pain but it is inadequate for managing severe pain. In 1997 BMJ published a meta-analysis of 26 randomized, controlled studies of more than 2,000 patients with postoperative arthritis and muscular sclerodermal pain to compare the effectiveness of acetaminophen plus propoxyphene, with acetaminophen alone, or placebo, and demonstrated that the addition of propoxyphene 100 mg to patients' pain regimen was no more effective than using acetaminophen alone.

Similarly, an evaluation of patients with moderate to severe postoperative pain found that propoxyphene-acetaminophen combination therapy had only similar effectiveness compared to tramadol 100 mg but was less effective than ibuprofen 400 mg at controlling pain for four to six hours.

While less than one percent of patients taking the

recommended dosage of propoxyphene experience adverse effects, some patient populations, such as the elderly and those with kidney and liver disease, are at increased risk. Use of propoxyphene in these patient populations represents the greatest potential for patient harm.

Propoxyphene has been listed among drugs and drug classes defined by the Beers criteria and Zahn criteria as potentially inappropriate medication for older adults because the drug offers few advantages over acetaminophen, while potentially causing adverse effects associated with opioid analgesics. Elderly patients taking propoxyphene who experience CNS effects may be prone to falls that result in bone fractures, including hip fractures, that can lead to significant morbidity and mortality.

Studies of heart failure demonstrated that propoxyphene is commonly prescribed for elderly patients, especially those living in nursing homes. An assessment of prescribing practices for more than 20,000 nursing home residents with persistent pain found that propoxyphene was prescribed for 18 percent of those patients. It should be noted that propoxyphene is not recommended for treatment of chronic or persistent pain, and that extended use of the drug places this already vulnerable patient population at

greater risk of harm.

Based on the Beers criteria, the National Committee on Quality Assurance included propoxyphene in a list of medications to avoid in the elderly in the 2006 Health Plan Employer Data and Information set. The avoidance of propoxyphene has also been recommended by the Agency for Healthcare Research and Quality, the Veterans Health Administration and many other health systems as a strategy to improve patient safety.

These efforts have resulted in moderate increases in healthcare professional awareness about the potential for patient harm. However, inappropriate prescribing of propoxyphene remains widespread and is unlikely to change in the absence of a requirement that drug manufacturers participate in enhanced surveillance activities and provide education to healthcare professionals and patients.

In summary, ASHP believes that the usefulness of propoxyphene to treat pain is limited and that the possible risks clearly outweigh any potential benefit. A number of alternative analgesic therapies have demonstrated superior effectiveness and safety for the treatment of mild to moderate pain. Prescribing patterns for propoxyphene also indicate that the drug is commonly inappropriately

prescribed for patients and indications for which it is not recommended that result in increasing the risk of patient harm.

Based on this evidence, the Society encourages complete withdrawal of propoxyphene from the United States market. Thank you for your time.

DR. FARRAR: Thank you very much. The open public hearing portion of this meeting is now concluded and we will no longer take comments from the audience. The committee will now turn its attention to addressing the task at hand, the careful consideration of the data before the committee as well as the public comments.

In terms of thinking about this afternoon, what we had talked about was proceeding with a period of time when we can ask questions. I think we should start with questions focused on the FDA's presentation for clarification, but since we will be moving into a discussion section I think it is reasonable to consider questions that are a little bit broader perhaps than I was allowing this morning.

Clearly, as the agenda states, we will move to a discussion of the formal questions that have been posed to us by the FDA and we will need to try and start that

certainly by 2:30 and maybe a little bit before that.

So, hopefully, you all had a good lunch and were thinking strenuously about what we are trying to do this afternoon, and have your thoughts all cogently prepared. Let's start with some questions for the FDA and then we can progress into questions that are broader and a bit more discussion. Dr. Crawford?

Questions to the Presenters

DR. CRAWFORD: Thank you. My question for the FDA is for Dr. Chen. Dr. Chen, as you are coming up, I am just going to make a comment. I did notice our speaker, Miss Reilly, just now, and the sponsor had differing conclusions about the report from the Veterans Administration about the use, avoidance and/or safety of propoxyphene. So, that is just a little confusing to me.

But, Dr. Chen, in your presentation, I was a little curious, there is something curious about the handwritten graphical comparisons in the original NDA submissions in 1971, on slides 11, 13 and 16. It appears that something was whited out for the treatment labels. Each time it appears something was whited out and either the word Darvon on slides 11 and 13 or Darvon-N on slide 16 was written in. Do you have any idea what might have been going

on with that?

DR. CHEN: Yes, I don't know. That is a good question. Something is erased or replaced. I don't want to hazard a guess even now.

DR. HERTZ: That is how we had the submission. Presumably that is how it came in.

DR. FARRAR: Dr. Ciraulo?

DR. CIRAULO: I apologize if this has been brought up, but I am confused by the DAWN data, particularly the slide that shows the percentage of suicides with propoxyphene at 20 percent. I am wondering if I just missed this, but do we have comparative data that is adjusted by the number of prescriptions for either oxycodone or hydrocodone? In other words, is this a higher risk, highly determined risk in suicide? This was a surprise to me, that the suicide involvement was so high. Has that been adjusted compared to similar agents, adjusted for prescriptions? Can we get an actual rate? So, the question is, is the rate of suicide or do people use this drug at a higher rate than the other drugs?

CAPT PONELEIT: In part, the question has to do with adjustment by the number of prescriptions, and we don't have the data for that. I know FDA presented information

but we don't useB-was it NOVA? I am sorry, somebody will have to help me out, but we don't have those data.

That also looks relatively high in relation to some of the others, like accident, but in part it may be because some jurisdictions only code for Acould not be determined@ when, in fact, it could have been accident, could have been something else. You know, it wasn't suicide so one of these other categories could actually grow.

DR. CIRAULO: If that was hydrocodone, would it be 50 percent suicide?

CAPT PONELEIT: That is a good question. Dr. Crane, of my staff, do you have a sense of that? I may have that information.

DR. CRANE: We do have that information but not with us.

DR. CIRAULO: Thank you.

DR. FARRAR: Dr. Gardner?

DR. GARDNER: I have a question for Dr. Mehta. I may be interpreting your slides incorrectly, but your slide 14 seems to show that the frequency of duration of use for people over 45, including the 65-year olds, was 0-7 only about a third of the time, maybe a little more than a third. Yet, your conclusion seemed to be that the most common

duration of use for all groups was 0-7. It seems to me that two-thirds is more than seven days for the elderly and for the middle-aged group. Am I interpreting that incorrectly?

DR. MEHTA: No, that is correct. For patients aged over 45 it was not significant. About 35 percent did have 0-7 days for 45-64 years and over 65 37 percent. For the other days, like 8-14, the percentage was low, maybe 10 percent and it just went on from there. But the most frequent was 0-7 days.

DR. GARDNER: So, am I interpreting correctly that for, say, the elderly group 63 percent are more than seven days prescribed?

DR. MEHTA: Yes, but I broke it down from, like, 0-7, 8-14, 15-21 and for everybody else the percentages were like 10 percent, 15 percent, adding up to 60 percent. Yes.

DR. FARRAR: But what was the number over 21 or 30?

DR. MEHTA: I don’t recall, but I believe it was 12 percent.

DR. FARRAR: Ten or 12 percent?

DR. MEHTA: Yes.

DR. FARRAR: Dr. Zito?

DR. ZITO: I have an additional thought beyond what Dr. Gardner was just raising, which is to reflect on both

Dr. Mehta's and Dr. Lee's presentations together and to think how lucky we are to have a substantial amount of utilization information, at least outpatient, and a substantial amount of safety information from the AERS but, yet, they are not put together in any meaningful, measurable way that would help us to understand.

What I am specifically referring to is proportional reporting ratios that would gather all of the propoxyphene products versus all the codeine products versus all the morphine products, which would be really nice to understand because we don't really know. I don't meet a lot of people in an academic medical center who are prescribing these products for anything.

So, there have been big changes and, yet, here it seems to get lost in the forest. There are lots of details here but not good knowledge of long-term use in the elderly which is our biggest particular concern. And, I wonder if there is any published information with respect to this question of utilization patterns that have been published.

DR. FARRAR: Dr. Mehta, do you know if there are any published results related to the use of propoxyphene products in the elderly?

DR. ZITO: I know of Kamal and I can answer my own

question with one study that is included in the packet very nicely which used Medicare data, the Medicaid beneficiary data, to show that the institutionalized area is where the usage is twice as much as in the outpatient usage. So, that is why I am wondering a little about utilization data presented here, Verispan, and whether that really reflects institutional usage, which is where this main elderly thing is happening. So, it seems like we could be doing a little bit more work to zero in on the usage patterns for chronicity and in the elderly and, finally, in regard to multiple medication use.

That was really my question about is there anything published. Because concomitants grow with the age of the population. So, there is going to be lots and lots of medication in U.S. elders, both psychiatric drugs which are a problem here, and cardiac drugs which suggest the propensity for cardiac effects. So, we could be looking at a more persuasive set of data I think.

DR. FARRAR: Dr. Mehta?

DR. MEHTA: Well, once again, I just wanted to say this does not include institutional data. It is just strictly outpatient. And, I am not aware of any printed studies.

DR. ZITO: Thank you.

DR. FARRAR: Dr. Kramer?

DR. KRAMER: I have two questions for CAPT Poneleit. My first question is I wonder if you could clarify. I got a little confused this morning when I read the background packet and in listening to the sponsor presentation. The description of DAWN talked about mentions of propoxyphene that were basically just drugs that might have been, as somebody said, in a bottle, found at home and brought in. Yet, in Sidney's presentation he made an effort to point out that reporting physicians are trained to determine drugs that are related to that emergency room visit or death in reporting. So, could you clarify whether these are just incidental observations, mentions of drugs they think the patients are taking, or is there some determination, judgment of the physician as to whether they are, quote, related.

CAPT PONELEIT: Yes, the data that were presented earlier by Dr. are from the prior design, and there are distinctions now with the new design. Right now in the new design we collect data that are implicated or involved. In other words, if they were taking a prescription--and I was trying to think of a good example earlier. Let's say they

are taking an antibiotic but that was not related at all to the reason why they came into the emergency department, then that doesn't get recorded by reporters. It is based on what the doctor is making the determination for what was related. I mean, reporters, you know, they aren't making something up along the way. They are actually going by what is in the written record.

DR. CRANE: I just wanted to clarify a little bit what she said. Elizabeth Crane. I am a scientist with the Drug Abuse Warning Network at SAMHSA. Until 2002, it is true DAWN collected data just on drug abuse-related ED visits. Any drug that was reported in the chart or in the mortality data was included.

We redesigned DAWN in 2003, and after that point we specified, and trained our reporters that they should only record drugs that were indicated in the medical chart or death investigation record that were actually involved or contributed to the visit.

So, Amentions@ is old DAWN. In new DAWN we talk about the drug reports or the ED visits. Dr. Wolfe's presentation actually used the more current data where the drug was only listed if it was actually involved in the ED visit. But the presentation from the sponsor that used data

prior to 2002, that was when DAWN was using Amentions.@

DR. KRAMER: Could you clarify if in the new reporting this term of it is related implies that the physician has determined that they think that it is causally related?

DR. CRANE: Yes, it means that the drug was somehow implicated either directly or indirectly with the ED visit or death. So, it could have been the direct cause of the ED visit, like an overdose or a heart attack, or it could have been a contributory factor, such as if somebody is under the influence of drugs and alcohol, crashes their car and ends up in the emergency department because they have a brain injury and the drug is contributed to that.

DR. KRAMER: If I could ask my second question, it has to do with your statement that all the patients over age 65 were grouped together in many of these trials, and you warned us about interpreting that versus the deciles in the other age groups. I just wondered if you had a breakdown that you could show us of the differences between the elderly in ten-year increments, or anything like that, so we could get a sense of the distribution of adverse effects.

CAPT PONELEIT: I do, the question is can I find it rapidly. Yes, I did bring information like that with me

and, certainly, while other questions are being asked I can locate that.

DR. FARRAR: Why don't you do that and we will give you a chance to show it when you find it.

CAPT PONELEIT: Also, I wanted to address a little bit more about the earlier question with the high proportion of suicides. I do have information with me from our 2004 medical examiner report. I was looking at the various state data, and what it was showing is that the overall proportion from the drugs that were reported was showing anywhere from around 12 percent to about 17, 18 percent in the ones that I was looking through. In 2004 we had six states. So, the range for all drugs was somewhat comparable to what was specific to just the propoxyphene.

DR. FARRAR: Dr. Omoigui?

DR. OMOIGUI: From the slides that were shown in the comparison of the propoxyphene combination compared to acetaminophen alone, first of all, there was obviously very little difference between the two and, most importantly, there was no statistical analysis between the two.

I bring this to your attention because if it is equivalent in efficacy to the propoxyphene combination, acetaminophen is indicated for minor aches and pains,

whereas propoxyphene's current indication is for mild to moderate pain. So, is there any reason for jumping when all the studies show that they were equivalent in efficacy essentially and one is indicated for minor aches and pains and the other is indicated for mild to moderate pain?

DR. FARRAR: You are referring to the hand-drawn graphs?

DR. OMOIGUI: Yes, the hand-drawn graphs.

DR. FARRAR: I understand. I think we can answer that question in that the review for that was done in the mid-'70s. Maybe Sharon wants to comment as to why that was indicated that way.

DR. HERTZ: Actually, I can only partially answer it. But the minor aches and pains indication is an over-the-counter indication, which is currently used with over-the-counter products. I don't know that I have with me what the original Rx indication for acetaminophen was but that might speak a little bit to this. I don't know if we can find it right now. But the OTC indications, if you compare them to the Rx, they do tend to differ even for the NSAIDs. So, that is part of the difference.

DR. FARRAR: Dr. Hennessey?

DR. HENNESSEY: Thank you. We haven't heard any

presentations of controlled epidemiologic studies that have looked at adverse events associated with propoxyphene. From what I understand, there is at least one study looking at motor vehicle crashes. There is another study using Saskatchewan data to look at the association with hip fracture. That study did find an elevated relative risk for hip fracture, particularly in the first prescription period among new users. I was wondering if the agency had a review of the controlled epidemiologic studies that have been done today even though they seem to be few in number.

DR. FARRAR: I am not sure who from the agency wants to answer that question.

DR. BOUCHER: Is there anyone from Epi who can answer? We don't have any information on that.

DR. RAPPAPORT: Can you tell us what the comparator was in the study you just referred to?

DR. HENNESSEY: In the hip fracture study, to give you the reference, the first author's last name is S-h-o-r-r, first initials R.I. It was published in the Journal of Gerontology in 1992, and that was comparing users to non-users. They found elevated relative risks both for propoxyphene and for codeine, and they were similar. From the abstract that I am looking at now, it looks like they

lumped the two drugs when looking at a difference between the initial prescription period and later prescription period.

DR. RAPPAPORT: So, people on propoxyphene versus people on nothing?

DR. HENNESSEY: That is what I can tell by looking at the abstract right now.

DR. FARRAR: Dr. Tinetti?

DR. TINETTI: Let me comment a bit on Dr. Hennessey's question because I have actually been involved in a couple of epidemiologic studies looking at association between different classes of drugs and likelihood of falls and hip fractures. Actually, in those epidemiologic studies narcotics actually don't come out when you look across. It is actually the anticonvulsants, antidepressants that come out much more often. I am not aware of Darvon specifically, but it hasn't really shown up in most of the epidemiologic studies.

My question was for Dr. Chen, and I think it actually follows up on the previous question. What is really amazing is how little randomized, controlled trials there are in the literature at all looking at effectiveness. I mean, there are only a couple of thousand people in any

of these studies.

But I was curious, with the meta-analysis that was in the British Medical Journal, which I have here in front of me, and I was wondering if you could showB-there are only three studies that I saw that actually did the direct comparison between the propoxyphene and acetaminophen versus acetaminophen alone. Actually, all three of those studies favored the combination.

Although Po, which I think you summarized, does say that it wasn't significant and it included zero, but if you look at the tail it is a very small tail and clearly shows very close to statistical significance with very small numbers. I wondered if you had that if you could show people because it really is, as far as I can see, the only data in the literature that actually does a head-to-head comparison and I think for the group it would be helpful to have the actual data rather than just the summary statement.

DR. CHEN: Yes, I do have one slide to show this forest plot.

[Slide]

This one is the direct comparison. This is the three studies you mentioned. Right? Yes, during the presentation I was saying that one had a statistically low

difference between the combination and acetaminophen alone, but numerically it still somehow favors the combination here. If you take a look at the responder rater ratio, it was actually 1.09. That means no difference. This is a meta-analysis, you know, where it is mixed together, using a different method, accounting for the data in a different way and it may come out with different results.

[Slide]

That is why they also used another way to compare the data they collected, using placebo as a reference. So, they calculated the relative benefit, combination and placebo and acetaminophen and placebo. So, they did that comparison. They found the 95 percent confidence interval actually overlapped. So, that is why they came to the conclusion that acetaminophen basically is the primary contributor to the combination.

DR. FARRAR: Can you explain what the white and the black are there?

DR. CHEN: The meta-analysis was conducted by two different models, a random effect model and a fixed model. The white is the fixed model and the black is the random model. That is the most commonly used method to do a meta-analysis depending on heterogeneity. So, in this meta-

analysis they showed it was very consistent. So it is actually a very good signal also.

DR. FARRAR: Just to be clear, the two plots on top are paracetamol versus placebo alone. The two plots on the bottom are the propoxyphene and paracetamol versus placebo.

DR. CHEN: Yes.

DR. FARRAR: And you are saying that they showed similar effect sizes.

DR. CHEN: Yes.

DR. FARRAR: Does that get to your question?

DR. TINETTI: The previous one did.

DR. CHEN: Yes, this is really the question she asked because for the head-to-head comparison the data has to come from a three-arm study at least. So, very little data are available in the literature.

DR. FARRAR: Just to expand, the bottom one-Bhow are they defining response? Is that a 50 percent response?

DR. CHEN: Yes. They give 50 percent, the maximal response, and then percentage of patients in the control group and the active treatment group and the calculated ratio between response rates.

DR. FARRAR: Thank you. Dr. Maxwell?

DR. MAXWELL: I want to go back to DAWN just for a

minute because a lot of people get confused, but DAWN emergency department is a random sample nationally in which they can project the rates. We could go to the IMS data and look at the number of prescriptions versus the number of DAWN cases.

The emergency department data is not what it is cracked up to be because it is a voluntary reporting system of medical examiners who send it in. So, last year I had Dallas; this year I don't have Dallas. And, it is going to vary. You might get a metro area like San Francisco where two of the three counties report and the third one doesn't.

So, to try to calculate rates using IMS data you would have to go into, like, IMS for every county. And, people tend to--in fact, it was in one of the earlier documents--roll it all up, so this is the number of people who died. DAWN ME data does not give you the number of people who died, except the number of people who died in the county that reported. So, hopefully, we won't see anymore submissions like that. Thank you.

DR. FARRAR: Dr. Burlington?

DR. BURLINGTON: Sure, I have a question for the Office of Surveillance and Epidemiology. FDA has pioneered methods for looking at the AERS data. We look at the

comparative reporting rates by system organ class, looking for drugs that are for similar indications and seeing the relative differences. I was sort of surprised not to see that presented here. Have you done that analysis?

DR. BOUCHER: No, we haven't done that specific analysis. And, we discussed that internally in the run-up to the AC and the consensus was that the propoxyphene-containing products are a fairly heterogeneous group of products. They are in a different schedule than a lot of the other opioids or most of the other opioid pain relievers. The indications are somewhat different. The treatment population is different. The dosing schedule is different. And, it would be difficult to come up with meaningful data given all of the differences.

DR. BURLINGTON: Given the relatively low rate of events that were reported from the non-overdose cases, then one of the other concerns we might have is given an overdose what the fatality ratio is. Have you attempted to look at fatality ratios among overdoses or look at dose response and mortality by size of overdose, or other ways that would allow us to look more closely at whether in overdose is this a more toxic drug than some of the other analgesics?

DR. BOUCHER: There are too many limitations to the

AERS data that we get to have calculations along the lines which you are requesting. Most of the AERS reports show that in the death cases and the other serious adverse event cases the individuals are taking concomitant medications. That is one issue.

The other issue is that for the most part in the majority of the reports we don't have satisfactory dosing information at all. So, it is just difficult to make a determination about what the real exposure is.

DR. FARRAR: Dr. Nelson?

DR. NELSON: I have a question for Dr. Mehta. You know, I come from a big city and the amount of propoxyphene products that I see in my practice is fairly limited. I wonder if there is any macro or micro type of regional variation that you have seen in the prescription data that might explain that.

DR. MEHTA: We didn't specifically break down the use into different regions. So.

DR. FARRAR: Dr. Rosenberg?

DR. ROSENBERG: This is for Dr. Leshin and perhaps the sponsor if they know. In looking at your information, it seems to indicate that perhaps the models that we have been looking at for pain activity for this drug might be

different than the one in which it is active. I was wondering if there is any evidence in animals or man of neuropathic pain in neuropathic models.

DR. LESHIN: From the nonclinical viewpoint in terms of animal data, I am not aware of any efficacy type of studies that have used propoxyphene in the last 20, 30 years.

DR. FARRAR: I will let the sponsor also respond.

DR. JONES: Yes, I concur. I don't know of any clinical studies in which it has been evaluated either.

DR. FARRAR: MR. GOOZNER?

MR. GOOZNER: I was interested in a statement actually from the public presenter that there was a survey that saw that about 18 percent of patients with chronic, persistent pain were taking the drug. I presume the allusion was to being off-label. Dr. Mehta, was there any information in the prescribing data that would suggest how much use of the drug could be categorized as off-label?

DR. MEHTA: No, the databases that we have don't break it down into what is being used for off-label.

DR. FARRAR: MR. GOOZNER, do you have a sense as to what off-label would be here?

MR. GOOZNER: Well, in that definition it would be

used, instead of mild to moderate pain, for chronic pain, I mean for persistent pain. I presume that means that you would be more at risk for taking extra pills because it wasn't doing its job, or something like that. Then, there could well, given its opioid effects, be other uses that people may be using it for even in a clinical setting.

DR. FARRAR: I think Dr. Mehta said before in response to an earlier question that in the survey data around 10-12 percent of the elderly were using it for more than three days. So, that would be the best that we would have in terms of chronic use I think, unless there is better data that I don't know about.

DR. HERTZ: Right; in terms of capturing the indication in which it is off-label, the way the indication was written for propoxyphene, which was very common at the time, it doesn't really state acute versus chronic pain. It really just states mild to moderate. So, even if the chronic use would necessarily be captured under a different indication, that wouldn't trigger it as being prescribed off-label. In modern times we look at that more specifically and include that in our indications.

DR. FARRAR: Dr. Gardner?

DR. GARDNER: I am still trying to chase down

utilization in the elderly and I have a simple question for the sponsor on your slide 11. Would you just remind me whether the IMS NPA, National Prescription Audit, data is strictly outpatient prescriptions, or does it include institutional coverage? Maybe it isn't slide 11; it is page 11 of your handout; I guess it is slide 11. Anyway, it is a simple question. I mean, I think you know the answer. Is the NPA outpatient alone or ambulatory?

DR. JONES: You are correct. It really is outpatient.

DR. GARDNER: So, in addition to the 30 percent that we see in 65 and older in the National Prescription Audit data, then we have this whole cadre of institutionalized elderly patients who also are receiving propoxyphene. Some large numbers I think were presented by ASHP. So, this is a severe under-representation, could be a severe under-representation of the usage in elderly. Thank you.

DR. FARRAR: Dr. Hiatt?

DR. HIATT: Thanks. My question originated about 15 minutes ago and a lot of it has been answered. But I am not a pain doc. Let me just summarize a couple of things from looking at the data, and correct me if I am wrong.

When we think about combination products versus the individual components, I think the Backgrounder Figure 1a clearly demonstrates that a single dose of this drug beats placebo; that 1b, acetaminophen beats placebo; that the combination beats placebo. But the combination does not cleanly beat the individual components. Am I right about that? I think, Mary, you were getting at the same kind of question.

DR. TINETTI: The way I interpreted it, it was borderline. There was borderline improvement with the combination versus acetaminophen alone.

DR. HIATT: Right, but not cleanly positive. So, the strongest evidence that I can see is that a single dose beats placebo. Then, my other comments were on dose response. Do we have any data on that? The studies were single dose. How does that compare to multiple doses over a short period of time? And, we have hit on this, how does that compare to chronic dosing? I mean, is the effect persistent or is there tachyphylaxis? The last question has also been hit on a bit. The pain models were post-op pain, postpartum pain. There are other kinds of pain such as neuropathic pain. I wonder how generalizable the response to a single dose in those models translates to a broader

context of its usage.

So, what I am trying to frame here to try to understand the efficacy is that the cleanest efficacy seems to be limited as a single dose in a single, limited pain model. When you go beyond that the data really cut us off significantly or they are just not existent.

DR. FARRAR: I am going to ask Sharon if she might just comment about the fact that this was done in the ‘70s. So, I think the answer to your question is we don’t have the data, but I don’t want to answer that.

DR. HIATT: I guess my question is did I summarize according to what we heard today?

DR. HERTZ: I think that is fairly consistent with our current understanding of the data. There is really very little available. When Dr. Chen did his review of the literature we tried to apply a standard of looking for studies that were reasonably well designed in terms of comparator arms and we really don’t have, between the NDA and the literature, any information that speaks to multiple dose, and certainly nothing substantial for chronic use. If you look at the reviews done by the U.K. and the review done by the VA, in general people conclude that there is little data on chronic use.

DR. FARRAR: Dr. Prough?

DR. PROUGH: There are a couple of comparisons between the number of events with propoxyphene and codeine and I didn't catch the number of annual prescriptions for codeine versus the number of annual prescriptions for propoxyphene.

CAPT PONELEIT: We don't adjust for the number of prescriptions. We can only tell you the number of ED visits. Is that what you are asking?

DR. PROUGH: No, I was trying to make the adjustment. I was trying to figure out whether there are a lot more or a lot fewer prescriptions for codeine.

CAPT PONELEIT: Someone at FDA would have to answer that question. In the meantime, I have data. I will answer the first question that I was asked in terms of the percent suicide for hydrocodone for the manner of death. Dr. Crane looked that up on my system that we have access to online, and that was 16 percent for suicide; 72 percent for accidental; 10 percent for could not be determined; and 2 percent for natural. Looking at oxycodone, it is 11 percent suicide; 2 percent natural; 74 percent accident; and 13 percent could not be determined. So, it did fall within what I had looked up in terms of the state data.

DR. CIRAULO: So, 11 percent and 20 percent.

CAPT PONELEIT: Yes, basically. Then, in terms of the question that was asked by Dr. Kramer, the quick calculations and, hopefully, this answers the question based on what I was looking at, for overall for both forms of propoxyphene for adverse reactions for 65-74 I have 7.9 percent. Again, that is for adverse reactions. For 75-84 13.1 percent for adverse reactions. Then for 85 and over 11.9 percent. I can tell you it went all the way up over 100.

PANEL MEMBER: Could you just remind us what the question is that you are answering?

CAPT PONELEIT: Sorry; the question was could I break it out further, beyond age 65. I had pointed out that 65-plus was a collapsed category so you are including anything from 65 to over 100.

PANEL MEMBER: What are these percents of?

CAPT PONELEIT: These are percents of the total number of adverse reactions for those particular age groups. In other words, of those that had the adverse reaction, what proportion were within the age 65-74, 75-84 and 85 and over. Then, to answer it a little bit more specifically with those who had cardiovascular events, those same types

of proportions were 15.7 percent for 65-75. It went up to 24.2 percent for 75-84. Then it dropped to 8.9 percent for 85-plus. That is a function, I think, simply in part because of the small numbers once you start breaking it out that finely by age group.

DR. FARRAR: Are people clear about what slide that was referring to? What she did was to break out the 65-plus slide and extend it out.

CAPT PONELEIT: I wanted to make it a little bit clearer that those are rates and what I just gave was the proportions. I don't have the rate data. But I felt the proportions are probably enough to give you a sense of what is going on.

DR. FARRAR: Thank you.

DR. KRAMER: The slide you put up was codeine? Those were propoxyphene numbers?

CAPT PONELEIT: It is best to look at the propoxyphene-acetaminophen since that group represented the majority of the data that I presented.

DR. FARRAR: Right, which is what we have here. MR. LEVIN?

MR. LEVIN: People have expressed some desire to have clarity on the VA update of 2006. So, during lunch I

brought it up and, with your permission, it is not very long, I will read the conclusion:

Although new data became available on the single-dose efficacy of propoxyphene and on safety concerns associated with the drug in abuse and accidental fatal overdoses, we found no substantive evidence to alter our previous conclusions about the efficacy and safety of propoxyphene relative to other opioids. Our recommendations on the use of propoxyphene in the Veterans Health Administration remain essentially the same as in the previous review.

In the majority of VA patients with mild to moderate acute pain, and who do not have certain characteristics associated with intentional or unintentional overdose, single dose or short-term therapy with DPP, plus or minus APAP, probably provides adequate analgesia with an acceptable safety profile.

The efficacy and safety of long-term therapy with DPP, plus or minus APAP, for treatment of choreic pain has not been adequately studied. In patients with certain characteristics associated with intentional or unintentional overdose the potential for DPP toxicity probably outweighs the drug's potential analgesic benefit.

Important safety issues that remain unclear are what are the frequency and risk of serious DPP toxicity among veterans with risk factors, and how does this risk compare with the risk associated with other opioids. Until these questions are answered it seems prudent to restrict the use of DPP, plus or minus APAP, to those veterans who do not have the particular characteristics associated with intentional or unintentional overdose, and in whom NSAIDs, extra strength or high dose APAP, and other opioids are inadequate, intolerable or contraindicated.

Based on single doses with similar analgesic efficacy in the treatment of postoperative pain, codeine or oxycodone and probably hydrocodone in combination with APAP are just as or more cost effective than DPP, plus or minus APAP, and are probably acceptable alternatives to DPP, plus or minus APAP. These alternative opioids seem to be slightly safe than DPP, plus or minus APAP, in intentional or unintentional overdoses. Tramadol products may also be considered alternatives but are the least cost effective and have been are associated with substantial toxicity in veterans. That is the conclusion. It is available on their website. October 23, 2006 was the final version.

DR. FARRAR: We have four people still on the list

for questions. It is 2:22 and I am going to hold it to that. When we get to the end of the four I will ask if there are any burning questions to give people one last chance. Then we will go into the consideration of the questions and the individual issues. So, Dr. Bickel?

DR. BICKEL: Actually, I was asking about the VA and that clarified it, except for one point. Perhaps my colleague here could help me with that. I was wondering is there any evidentiary base in the VA review other than that which we saw today. If there is, I would like to know what that database is.

MR. LEVIN: It is 79 pages so I didn't have time to go through it. It looks to me like they basically did a literature review to update their previous recommendations. So, unless they discovered literature that nobody else has discovered--

DR. HERTZ: Right. The review of the data is pretty much comparable to the literature that you have heard about that. They especially looked at the meta-analyses that were conducted. They did a pretty exhaustive search, looked at the individual studies. It doesn't sound so much like they kicked out studies based on design; they looked at them in toto.

They also did a look at AERS cases specifically among VA patients to look at the safety for their patient population. So, that is slightly different than what you heard from our general AERS review. They also did comparisons based on their demographics to some of the data that they found, just to sort of compare where they think they have something that can be compared.

For instance, the seven studies in the NDA, not that they mention them by name, but they were in postpartum pain so that is not a big problem in the VA population. You know, that kind of a comparison.

DR. FARRAR: Dr. Omoigui?

DR. OMOIGUI: First of all, I want to address an issue raised by one of the previous speakers regarding the single-agent drug. According to the study, on Dr. Chen's slide 14, the single agent was no better than placebo. Acetaminophen was more effective than the single agent, and the combination of propoxyphene with acetaminophen was essentially not statistically different from the use of acetaminophen alone. I just wanted to highlight that and be sure about that.

DR. HIATT: Sorry, let me just correct that. Figure 1a says that 65 mg of propoxyphene versus placebo as

a single oral dose beats it by a relative risk of 1.48 and a confidence interval of above 1. That is what I was referring to.

DR. OMOIGUI: Okay, but acetaminophen was more effective than the single-agent propoxyphene, acetaminophen alone, by itself.

DR. HIATT: Yes, it looks like Figure 1b says that that same number is 2.52. So, on a relative basis, not comparing head-to-head, it looks like acetaminophen beats placebo a little bit numerically more than propoxyphene but propoxyphene beats placebo, at least on this, greater than 50 percent experiencing pain relief measure.

DR. OMOIGUI: I think the sponsor had raised in their presentation that propoxyphene mentions in the DAWN data had dropped 50 percent over several years. I believe during that same period of time the amount of prescriptions for propoxyphene also dropped at least 20 percent. Has anybody compared the data in terms of the drop in the mentions with the drop in prescriptions to know what is absolute and what is relative there?

DR. WOODS: The short answer is no.

DR. FARRAR: Dr. Chen?

DR. CHEN: I just want to clarify your question.

You are talking about different things. Dr. Hiatt is talking about literature information. He is referring to NDA data. In the literature very few studies were designed full factorial. That means only two arms. Just three trials, as I showed you in the meta-analyses, can do acetaminophen alone. However, in the NDA data, which is full factorial design study, there are four arms, combination, acetaminophen, propoxyphene and placebo. So, that is the difference.

Also, the figure he referred to, the 3b, that is one of the studies that showed different results from the remaining five studies and 3a and 3b is different from the other five studies, just to make sure here that we are talking about the same thing. Thank you.

DR. FARRAR: Thank you. Dr. Eisenach?

DR. EISENACH: I think the reason we have this first question is that it is unclear whether the drug by itself is effective. That is why we are being asked the question. I certainly have seen data on both sides of that. It depends how you massage the data whether there is an extremely minor but statistically significant effect or not. For someone who has worked in the pain field for a long time, if there is an effect, it is of a pretty small

magnitude.

The question I had related to the pharmacokinetics of the drug. It is a question actually to Dr. Chen and the sponsor. We were presented with pharmacokinetic data suggesting that Cmax and half-life were considerably increased in the elderly. We don't have any dose-response data but if you assume the drug has an analgesic effect it would suggest to me the drug would be more effective in the elderly. Do we have any analgesic efficacy data in the elderly? I will tell you the answer is going to be no but I will ask the question.

DR. FARRAR: Dr. Chen?

DR. CHEN: Actually, there was a review article published in 2005 specifically on efficacy in the elderly. Unfortunately, there is no specific study in the elderly. The review article actually pulled out some data from other studies with a different age cutoff and had mixed results. You cannot see if it is better or worse.

Another question is the dose response. Very few studies in the literature actually showed dose response. I think that there was only one study, 130 mg compared with 65 mg propoxyphene, and 130 mg was slightly better. That is one study. I don't have any detail in terms of study design

and study conduction. So, very few studies in the literature. No data in the NDA.

DR. FARRAR: Dr. Kramer?

DR. KRAMER: This is still for Dr. Chen. I would just like to clarify one thing on the study by Po and Zhang that Dr. Tinetti raised. You were making the point that many of these studies aren't completely factorial so they don't have the four arms. In the three studies in the summary that kind of is almost statistically significant where it compares the combination of propoxyphene plus APAP to APAP alone, in those three studies was there a placebo arm or was it just the combination?

DR. CHEN: I believe they did have a placebo. Actually, we reviewed those three articles in detail and that is included in our background package.

DR. KRAMER: So, your sense is that that analysis, even though it isn't strictly statistically significant, is real?

DR. CHEN: Well, yes, that is on the individual studies.

DR. FARRAR: So, understanding that we don't have a lot of the data that we would like to have in order to answer the questions that are being posed for us, I would

like to move on to considering the questions, unless there is somebody that has a burning issue. Dr. Lesar?

DR. LESAR: I just want to mention something that has come up a few times. It has to do with potential for drug interactions with this drug. I think that is something that, again, there is little data on but if you look at some of the data there are some of the case studies, also the risk of this drug inhibiting metabolism of other drugs, as well as other drugs inhibiting its metabolism and being used in a population which is going to consume a lot of drugs that are 3A4 inhibitors or are metabolized by that route. I think that needs to be considered.

DR. FARRAR: So, moving to the questions--

DR. HERTZ: John, can I just mention one thing?

DR. FARRAR: Please.

DR. HERTZ: There is some attempt at looking for dose response that is reported in the VA analysis. They cite another analysis, which is the Bandolier Oxford League table of analgesic efficacy from 2006. So, based on that, they have listed quite a number of products and they do show that a number needed to treat for benefit, which I think is a 50 percent reduction in pain was 2.8 for dextropropoxyphene 130 mg compared to 4.4 for the

combination with 65 mg and 650 mg of the two products, and 65 mg alone of the dextropropoxyphene was the number to treat of 7.7.

So, there is a little bit but it is pieced together. The Bandolier Oxford League table of analgesic efficacy also pieced it together from numerous sources. If you have it, it is page seven of that review.

Discussion and Questions to the Committee

DR. FARRAR: We are going to move to consideration of the questions. There are four questions and only the last one is a voting question. We will come to that last for voting. We will use a new electronic voting system, sitting in front of you, called the microphone. It has a Ayes@ and Ano@ button and Aabstain@ button. When we get to it we will ask you to hit that button and in theory the votes will be tallied and we will be able to display them.

But prior to that, what the agency has asked us to do is to discuss these various issues in a concise way. What I would like to do is to literally go around the room and ask you to address the issues in number 1. Obviously, by the time it gets to me everything that needs to be said will have been said. But I would ask that if you agree with what has already been said that you simply state whether you

agree with that or not and provide some additional discussion if you think it is pertinent. The purpose of this is to provide the agency with our best information or best assessment of where we are with this, and the questions are very specifically written. So, we will start with Dr. Beardsley.

DR. BEARDSLEY: You want me to address the first question?

DR. FARRAR: Let's just start with the first question, both parts, please.

DR. BEARDSLEY: Right, I see that there is only marginal evidence that the monotherapy is efficacious, and I see very little evidence that propoxyphene itself contributes to the efficacy of the combination product.

DR. FARRAR: Thank you. I am reminded I should read the question into the record so I will do that:

Based on the data that have been presented regarding the efficacy of propoxyphene-containing products, (a), discuss whether you agree or disagree that there is evidence of efficacy for propoxyphene as monotherapy; (b), discuss whether you agree or disagree that there is evidence that propoxyphene contributes to the efficacy of propoxyphene and acetaminophen combination products. Dr.

Omoigui?

DR. OMOIGUI: My answer to question (a) is that the evidence is marginal, and my answer to question (b) is that the evidence is also marginal that propoxyphene contributes to the efficacy of the combination and that there is any efficacy of propoxyphene as monotherapy.

DR. TINETTI: I would say based on primarily the Cochrane systematic review and the Po review, although I agree that the evidence is modest at best, there is modest evidence but it is positive that there is benefit to the propoxyphene alone and to the combination of the propoxyphene plus acetaminophen versus acetaminophen alone.

DR. FARRAR: Thank you, Dr. Tinetti. You bring up a point which is that if you feel that there is support or not support and are willing to indicate where that support comes from, as you just did, I think that might be useful. Thank you. Dr. Lorenz?

DR. LORENZ: I also agree on the basis of those same findings that there is evidence of modest benefit, of somewhat ulceration clinical significance, for propoxyphene versus placebo, and that most of the effect of the propoxyphene-acetaminophen combination is likely due to the coBanalgesic. I also agree, as Dr. Hiatt was stressing

earlier in the discussion of pain in the elderly, that much of the relevance of that for clinical practice in which the drug is actually used in the United States is unknown.

DR. FARRAR: Dr. Rosenberg?

DR. ROSENBERG: I agree with the evidence of efficacy of propoxyphene as monotherapy. I also agree that the evidence of increased efficacy by adding propoxyphene to acetaminophen is modest, and that is in the models that are being tested.

DR. FARRAR: Thank you. Dr. Eisenach?

DR. EISENACH: I disagree. I think there is not convincing evidence for either of these. In several of the pivotal trials it apparently did not separate from placebo. We don't have statistical analysis to know what separated but I am not convinced that it separates at all. I am very convinced that it doesn't clinically meaningfully separate the single drug by itself from placebo. And, I am not convinced that the combination separates from Tylenol.

DR. FARRAR: Thank you. Dr. Zito?

DR. ZITO: I disagree that there is evidence for monotherapy or that the combination exceeds the effect of acetaminophen.

DR. FARRAR: Dr. Brull?

DR. BRULL: Yes, I also disagree that there is probably marginal evidence, at best, of its efficacy, especially when you consider that there is a 30 percent response rate in the placebo group, and we really have no data on the dose-response curves. The only study that has looked at this actually did not compare equivalent analgesic doses.

DR. FARRAR: Dr. Ciraulo?

DR. CIRAULO: I agree that there is very weak evidence to suggest that propoxyphene as monotherapy is efficacious. I think there is evidence that the combination is efficacious but it is unclear whether it is attributable to acetaminophen or to propoxyphene.

DR. FARRAR: Dr. Prough?

DR. PROUGH: I agree that there is some evidence for efficacy as monotherapy and some evidence for efficacy of the combination.

DR. FARRAR: Dr. Nussmeier?

DR. NUSSMEIER: I agree with other statements that there is extremely marginal positive data but really a kind of paucity of data that I have never seen because I have never looked back at the history of one of these drugs. So, it has been a really educational experience to look at the

past versus the present.

We really have no data demonstrating either additive or synergistic efficacy. I think current studies are really needed that have more sophisticated design and statistics. These studies that we have looked at I suppose were adequate for that era but they are very dated now and we need new efficacy studies both for the acute pain indication that was originally approved and efficacy studies for the chronic pain off-label use that seems to be rather common now.

DR. FARRAR: Dr. Kirsch?

DR. KIRSCH: I believe the data demonstrate that propoxyphene has no efficacy of itself and adds nothing to Tylenol when given in combination.

DR. FARRAR: I feel that the data shows that there is a marginal effect of propoxyphene, not in monotherapy but in combination therapy it is marginally better than acetaminophen in the few acute studies that we have seen. And, I am very concerned about the chronic use and the potential for loss of effect and/or increased risk in that population.

DR. WOODS: My opinion is that it has a marginal effect when viewed across experiments, and the effect size

is very small, if at all reliable, and acetaminophen looks very good. Simply from the point of view of teaching about narcotics, I am interested in how propoxyphene compares to codeine, and it seems to me that we haven't talked enough about comparisons of efficacy to codeine and codeine-like products. I would like to hear some more discussion of that if possible.

DR. FARRAR: Thank you, Dr. Woods. Did you have a particular question? I think that there is a great interest in the analysis across different products but I think the honest truth is we don't have data. So, I think that is what we are hearing.

DR. WOODS: I am not satisfied with ignorance any time, but I will go with it if that is the case.

DR. FARRAR: Dr. Lorenz?

DR. LORENZ: I was just going to note with regard to the specific question that the VA did review the efficacy of alternative combination products, and with regard to your specific comparison, they cite a review, which I can't reference off the top of my head but they do cite a review of this comparison and actually both combination products, codeine as well as that involving propoxyphene, were not different in their comparison to placebo. I guess the FDA

found them both similarly ineffective.

DR. FARRAR: Thank you, Dr. Lorenz. Dr. Crawford?

DR. CRAWFORD: Thank you, Mr. Chairman. I do agree that there is limited evidence, both from the studies as well as anecdotally, of efficacy, however you want to say it, weak or mild, for propoxyphene monotherapy. For 1(b), there appears, in my opinion, to be somewhat of an effect because there were studies that showed the combination product to be superior to the comparators, but the evidence does not appear to be terribly convincing.

DR. FARRAR: Miss Zavacky?

MS. ZAVACKY: Yes, I also agree that the monotherapy has marginal evidence and also in the combination I agree too that there is evidence of efficacy.

DR. FARRAR: Dr. Hennessey?

DR. HENNESSEY: I would say that there is equivocal evidence of therapeutic benefit of an analgesic effect of the monotherapy product and, again, that there is equivocal evidence of a small benefit of the combination over acetaminophen alone.

DR. FARRAR: Dr. Maxwell?

DR. MAXWELL: Modest, marginal benefit for the monotherapy and slightly more for the combination but, for

the record, I am really uncomfortable with even being asked that question based on how bad the data are, or the lack of data.

DR. FARRAR: Thank you. Dr. Lesar?

DR. LESAR: For individual component product I don't believe there is a really meaningful effect versus placebo. So, there might be effect but it doesn't mean anything. For the combination there is some suggestion that there is some additional benefit in some patients.

DR. FARRAR: Dr. Gardner?

DR. GARDNER: I would like to echo Dr. Hennessey's use of the word Aequivocal@ on both counts, equivocal evidence of some marginal safety, but I am also concerned about the discrepancy between the patients studied to achieve that marginal efficacy and the patients who seem to be getting the product now and whether there is any relationship whatsoever to those two groups.

DR. FARRAR: Dr. Kramer?

DR. KRAMER: I would like to introduce my comment with a statement that I actually am feeling quite a sense of the responsibility this committee is having in reviewing old data and applying it to the current world in which drugs are currently approved. I just want to caution us all to

remember that as we apply new criteria we need to be careful because I think it is only fair that that be done uniformly across all the agents, not just for one drug that happens to be petitioned.

Having said that, I think I would have to echo my interpretation of this question to what Dr. Tinetti said. I think that the meta-analyses are suggestive. Granted, it is marginal evidence but it does look like there is some efficacy of the individual product in the Po and Zhang analysis showing that the combination has really almost statistically significant improvement compared to paracetamol alone.

Also to the comment that people made about comparison with codeine, I was impressed with the number needed to treat analysis. I think it was from Collins in our background packet. I think it was page 15 of the 41-page document on efficacy where it looks like both propoxyphene alone and the combination requires many fewer patients than codeine 60 mg. Not that that is the ultimate truth, but I think that it just shows the variability of these studies and the paucity of data that we have.

DR. FARRAR: MR. GOOZNER?

MR. GOOZNER: Well, on 1(a) I would say that when

six of seven trials showed that there is no benefit as monotherapy, then you have to say that there is no benefit for monotherapy. On 1(b) it is five out of seven that show that there is no benefit. So, I guess one could say that is marginal at best.

DR. FARRAR: Dr. Nelson?

DR. NELSON: I think that the obviously suboptimal data does speak for itself. When you combine them into meta-analyses you sometimes are able to find statistical things that don't necessarily make clinical benefit in the big picture. So, in answer to the first question, I don't really think in summary that there is a benefit to propoxyphene as a single agent. For the combination I would think perhaps there is a marginal benefit but I think when you sum it up and apply some of what I have already said there is really no benefit.

DR. FARRAR: Dr. Day?

DR. DAY: I think there is marginal evidence at best for both, and overall it is quite underwhelming.

DR. FARRAR: MR. LEVIN?

MR. LEVIN: For 1(a), I disagree and for 1(b), I disagree for all the reasons stated.

DR. FARRAR: Dr. Bickel?

DR. BICKEL: I think science moves along and, as I look at this data I believe that we have insufficient data to draw any strong conclusions of any sort regarding both questions.

DR. FARRAR: Dr. Hiatt?

DR. HIATT: In terms of 1(a), the meta-analysis would suggest that propoxyphene beats placebo but the individual trials listed in Table 1 don't give a consistent signal. So, I don't think the totality of the evidence supports benefit, and I am less convinced about combination therapy.

I would like to make one other comment about efficacy. If I was trying to write a label based on what you see here and if you believe propoxyphene beats placebo the label has to reflect the trials where the data were generated. Therefore, the label would have to read you can get one dose of drug if you are postpartum or post-op, and that is the label. So, nothing else would be allowed, in my mind, if you believed that the drug was efficacious.

DR. LINCOFF: I agree there is a lot of unease regarding the limitations of the data but that was the standard at the time the drug was approved as a legacy. So, I think within the existing data set that for 1(a) it is

actually fairly clear, relative to placebo, that most of the studies showed benefit not relative to acetaminophen. But I think most of the studies, in particular the meta-analysis, show what appears to be a significant benefit within all constraints of just how narrow of a population and indication it has been tested.

I think for 1(b) most of the data would suggest there is not a benefit of adding propoxyphene to an acetaminophen combination beyond that obtained by the higher dose of acetaminophen.

DR. ZELTERMAN: I would agree with Dr. Lincoff. There is marginal benefit as a monotherapy looking at the meta-analysis. Again using the meta-analysis, it seems that there is no benefit in addition to acetaminophen.

DR. BURLINGTON: Casting my mind back to the early ‘70s, or what must have been going on in the early ‘70s, I haven’t seen any new information here that would cause me to disagree with the conclusions that were reached at that time, that is, that there is evidence that as monotherapy the drug is active and has an effect, and that in combination, at least in the two studies, it did seem positive and that is evidence of effectiveness as a combination product.

MS. BHATT: Dr. Tortella?

DR. TORTELLA: I agree, evidence both for the individual and the combination.

DR. LORENZ: I just wanted to correct a statement that I made and expand a little bit. I have found the quote in the review. It is just that combinations of codeine, oxycodone or tramadol plus acetaminophen are also not better than acetaminophen alone. That was from the Oxford League of analgesic efficacy.

DR. FARRAR: In summary, what I heard from the committee in general was that there was lack of enthusiasm for evidence with regards to monotherapy and lack of enthusiasm, varying from no evidence to not clinically important evidence, for the combination therapy, and that there was some variability in the results of studies that we looked at but there was certainly no convincing evidence on either of those.

Moving to number 2, what I would like to do for this one is we will start and go the other way around but, rather than providing an explanation for everything I would ask you to provide information about whether you think that the cardiotoxicity issue is an important one. I would ask, if we can, to try and move quickly so we can do what we need

to do. On the other hand, this is very, very important so I don't want to dissuade anybody from providing evidence that they think is important. Let's start with Dr. Zelterman.

I am sorry. Sorry, my fault. I need to read the question: Based on the data that have been presented regarding the nonclinical cardiac effects of propoxyphene and the postmarketing reports of deaths in which propoxyphene was identified, (a), discuss whether there is evidence that propoxyphene is cardiotoxic in the therapeutic range and (b), discuss whether additional data are needed to adequately assess the potential for cardiac effects and, if so, what data.

DR. ZELTERMAN: I didn't see a lot of evidence of cardiotoxicity in the data presented.

DR. FARRAR: Dr. Lincoff?

DR. LINCOFF: In the therapeutic range I didn't see any evidence that would suggest it, aside from the theoretical cell-based data and receptor-based data. We can infer from some of the toxicity data in overdoses that there may be in overdose settings and that that may contribute to the incidence of deaths prior to the patients coming to the hospital. But we don't really have evidence for that. Additional data would be needed I think, including studies

perhaps to test for QTc prolongation, etc.

DR. FARRAR: I apologize. I should have started with Dr. Tortella.

DR. TORTELLA: So far I see no evidence, and perhaps an EKG study going forward as a postmarketing opportunity would give us more data than there are.

DR. FARRAR: Dr. Burlington?

DR. BURLINGTON: I agree, no evidence that it is cardiotoxic in the therapeutic range. I would like to see additional data on individuals at high systemic exposure for both propoxyphene and norpropoxyphene.

DR. FARRAR: Dr. Hiatt?

DR. HIATT: I think that there are preclinical signals of concern, particularly its effects on potassium channels. In the therapeutic dose there wasn't anything obvious. In overdose there might be.

But my main comment is that the absence of evidence isn't evidence of absence. So, I think there is enough signal of concern here that I would recommend that if this drug were to continue to stay on the market that a thorough QT study be performed.

I also think that, particularly in the elderly patients where they have background comorbidities, the risk

of cardiovascular events goes way up and the background rate can be as high as five percent of people with stable atherosclerosis and ten percent in acute coronary syndromes. The challenge we have in drug safety is understanding when there is a signal above that background rate and the current reporting systems just can't pick that up.

Therefore, a way to do this postmarketingB-I mean, the best way to do this is randomized, controlled trials. The way to do it is postmarketing, and there are examples of that where you do observational studies and use propensity matching to match around decisions around treatment allocation. Then you can potentially compare rates of adverse events once you have controlled for that. You can do this in the real-world setting.

So, my minimal sort of criteria to establish safety at this point in time is a QTc and then a formal observational study with propensity matching to establish if there are any true signals of cardiac concern.

DR. FARRAR: Dr. Bickel?

DR. BICKEL: I agree that there is not evidence of cardiotoxic effects in the therapeutic range. I would like to see more information, as we just heard, particularly in the elderly.

DR. FARRAR: MR. LEVIN?

MR. LEVIN: I will pass on (a), but just to reinforce (b), if experts who know a lot more about this than I do believe there is a signal, we have a responsibility to follow-up on that signal if this drug remains on the market.

DR. FARRAR: Dr. Day?

DR. DAY: I think there are some potential signals but not in the therapeutic range at present, and I like what Dr. Hiatt said about studies to be done, especially with respect to the background rate in the elderly.

DR. FARRAR: Dr. Nelson?

DR. NELSON: I actually think the signal is very concerning for the presence of cardiotoxicity even at therapeutic doses. You know, overdose, with respect to this cardiotoxic effect, is largely exaggeration of what is seen at therapeutic doses. The only difference is that in therapeutic doses most people metabolize the drug and eliminate it rapidly and it is not a problem. But we learned with terfenadine and other drugs, there are subpopulations of people out there who have difficulty, either because of genetic predisposition to drug interactions or eliminating the drug properly, and these

people I think are going to be at significant risk.

The problem with finding them on an individual basis is post mortem, for example. The post mortem exam is often just a normal exam because these people who die rapidly and it would be very difficult to really make a link to the drug, other than perhaps having the drug level which may even be in the therapeutic or high therapeutic range.

So, I think that we do need clearly more studies, both at therapeutic doses which have to be epidemiologic in nature perhaps, and we need more specific individual studies, perhaps based on EKGs and QT studies.

DR. FARRAR: Thank you. MR. GOOZNER?

MR. GOOZNER: In the postmarketing context, I want to endorse what Dr. Hiatt said. He said it far better than I possibly could. Also, I have been really wrestling with this whole idea of the therapeutic range. It seems to me that this is the kind of drug where the therapeutic range is really defined by community practice and not what it is prescribed as and that is very difficult to manage, obviously, given a drug of this nature. So, I think that the signals definitely are there.

DR. FARRAR: Dr. Kramer?

DR. KRAMER: I think the greatest theoretical

concern, and I emphasize theoretical, is the similarity in the structure to methadone that alarmed me when I read the background packet and the effect on the potassium channel. However, I did not see evidence of that theoretical effect being translated into clinical evidence that it was cardiotoxic either in the therapeutic range or even really in overdose in terms of the data that we have.

That doesn't mean the absence of evidence proves that it doesn't cause a problem. So, I would say there is not evidence but that it would be wise if this stays on the market for a thorough QT study to be done.

DR. FARRAR: Dr. Gardner?

DR. GARDNER: I don't see evidence as stated here, but I don't know what to recommend for studies.

DR. FARRAR: Dr. Lesar?

DR. LESAR: I agree, there a a number of concerns related to this issue, basically in the preclinical data the reported effects in overdoses and the fact that therapeutic levels are often exceeded in a large number of these patients. It has a lot of drug interactions and, again, the issue related to methadone, and I believe the type of data in both preclinical, EKG studies, as well as some epidemiologic studies, similar to those that have been done

with methadone.

DR. FARRAR: Dr. Maxwell?

DR. MAXWELL: No and yes.

DR. FARRAR: Thank you. Dr. Hennessey?

DR. HENNESSEY: I know that everybody likes to think that IK blockade and QTc prolongation is a good marker for a drug's arrhythmogenicity. I don't know that that has been established. I don't know that there is a good relationship between those two things. Maybe there is and maybe there isn't. I am not sure that a thorough QT study will provide us much information. I think large epidemiologic studies will, particularly if they are randomized. Those would be expensive so we are probably going to be stuck with the non-randomized variety.

DR. FARRAR: Miss Zavacky?

MS. ZAVACKY: I also agree there is no new evidence in the therapeutic range and I would like to see more studies too.

DR. FARRAR: Dr. Crawford?

DR. CRAWFORD: I agree that I did not see evidence of cardiotoxicity in the therapeutic range. I also agree with comments espoused by many, starting with Dr. Hiatt, on the need for additional studies. Perhaps it might be more

feasible for the observational studies. I would be interested in looking at the dosage and duration because I am not quite sure if the therapeutic range means just dose or if it includes how long the therapy is. And, possibly the Arizona Center, among other researchers might be considered for the agency to contact if this drug is allowed on the market, or the sponsor, in terms of some postmarketing surveillance studies.

DR. FARRAR: Dr. Woods?

DR. WOODS: No to (a) and yes to (b). I think the evidence that we were presented, the preclinical evidence was very weak and could be improved markedly.

DR. FARRAR: From my perspective, I agree that there is no evidence in the current therapeutic dose but that there is a potential signal, and that large epidemiologic studies, using available databases to start and maybe some specific data that is collected, would be warranted to demonstrate that the signal that is potentially there with the QT prolongation, if it exists, actually carries forward into a risk.

I would like to add one other caution, which is that sudden death in the elderly is a relatively common event and it would be a little hard to know whether it was

caused or encouraged by the drugs that they are taking, given the extent of the drugs that they are taking. So, I want to suggest that it is going to be very hard to do these studies in a way that is going to give us a real answer.

DR. KIRSCH: No, and I would agree with postmarketing studies suggested.

DR. FARRAR: Dr. Nussmeier?

DR. NUSSMEIER: I agree that the data regarding cardiac risk is even weaker than the data regarding efficacy. In the absence of safety studies, which really haven't been done, I am particularly concerned about use in the elderly, as has been stated; use in patients with renal insufficiency; use in patients with hepatic insufficiency; use in patients with cardiovascular disease, particularly those taking maybe chronic beta blocker or calcium channel blocker drugs, all of the above, particularly in the setting of the very common chronic use that seems to be going on.

DR. FARRAR: Dr. Prough?

DR. PROUGH: No to the first question, and to the second question, I am awfully uncomfortable suggesting that additional studies need to be done to verify the presence of something for which the evidence is so weak.

DR. FARRAR: Dr. Ciraulo?

DR. CIRAULO: No, I don't think there is cardiotoxicity in the therapeutic range, but I agree that the therapeutic range may be difficult to maintain given the possibility of drug interactions and genetic polymorphisms. As far as the additional data, as a psychiatrist I will yield to the cardiologists to design those studies.

DR. FARRAR: Dr. Brull?

DR. BRULL: Yes, I don't think that there is evidence of cardiotoxicity. However, lack of evidence of cardiotoxicity is not proof of safety. So, as part (b), the answer is yes, we would probably need a whole new NDA.

DR. FARRAR: Dr. Zito?

DR. ZITO: Well, there is certainly theoretical pharmacologic evidence that was presented here that cardiotoxicity would be a problem, particularly in those over 44 years of age which we believe is the bulk of the usage now and considering the number of death reports or serious adverse events that showed that multiple drug use was a problem.

I am also very concerned about the feasibility of treatment-emergent information that would identify this drug as the cause, this pure search for causation that we are fixated on. So, I don't have a strong feeling that I should

expect that we keep using a drug with theoretical evidence and a profile of usage that suggests that there is likely to be trouble here, and several nations in Western Europe certainly have already signed onto that.

So, what sort of pharmacopeia? We certainly could get very quickly, within six months, some good information that would show you the extent to which it is being used in various populations, major populations that are being treated; what the duration of use is; what the average dose is; what the multi-drug combinations are. If you want to do a study, that would be the one.

DR. FARRAR: Dr. Eisenach?

DR. EISENACH: You could say given the committee's response to question 1 that this is an academic discussion. I would say for 2(a) the answer is no. For 2(b) the answer is you need a chronic safety study.

DR. FARRAR: Dr. Rosenberg?

DR. ROSENBERG: I say to 2(a) the answer is no, and for 2(b) I echo what everybody else has said. Extra data would be good.

DR. FARRAR: Dr. Lorenz?

DR. LORENZ: I concur that to (a) the answer is no and to part (b) the answer is yes. Again, I think

epidemiologic studies are not the only kinds of investigations that are needed. I actually think that because, again, efficacy data is needed in the population in which it is commonly used and in a way in which it was not originally studied, that is also a setting in which these kinds of endpoints need to be evaluated.

I would like to stress that I think that when a putative and realistic mechanism for harm exists and evidence of harm in the super-therapeutic range, and again we understand the constellation of these factors that might put patients at risk, some additional steps should be taken now to change prescribing habits if this drug is to remain on the market because, while it may take some time to understand that, I think this potential causality is quite worrisome.

DR. FARRAR: Dr. Tinetti?

DR. TINETTI: I would say no to (a) and to (b), if we are going to do and studies I would favor not doing surrogate markers such as QT interval but really addressing the clinical question. In the elderly population is there more benefit versus harm? And it is not just cardiac; there are also the neuropsychiatric complications. And, we need to also compare these to the drugs that people would be

taking otherwise, the other opioids and the anticonvulsants and nonsteroidals, which are the drugs that people will be going on. That is why I would hope that we didn't do a half-way thing and just go to small postmarketing QTs if we are going to address the question at all.

DR. FARRAR: Dr. Omoigui?

DR. OMOIGUI: I think there is evidence that the drug is cardiotoxic and in the toxic range. But the question is when the drug is taken as directed toxic levels can be attained. Definitely, additional data is required. If the drug is to be left on the market, I believe that there should be labeling changes, number one, in terms of use with caution in the elderly population. Number two, it should be specifically stated that it should be used only for short duration. The only studies we have of this drug for efficacy is for two hours. Also, finally, the labeling should be changed from mild to moderate to just mild pain. Thanks.

DR. FARRAR: Dr. Beardsley?

DR. BEARDSLEY: I didn't think there was clinical data available to really answer that question. I thought the nonclinical data supported concern that this drug certainly can modulate cardiac functionality sufficiently

enough to do additional studies, the studies that have already been mentioned.

DR. FARRAR: Dr. Rappaport?

DR. RAPPAPORT: With all due respect to Dr. Hennessey's comments about the value of QT studies, I think that they are fairly well accepted in the cardiology community and they are certainly the standard that we use at the agency for assessing that particular cardiotoxicity. So, I would be curious, from the people who recommended that we do both QT and epi studies or observational studies or some other type of epi study, what the value would be if we find that the QT study doesn't show prolongation. If a good QT study doesn't show any prolongation why would we want to do the other study? Now, I know there are other safety issues and we can talk about that separately.

DR. HIATT: I guess I would respond that if you try to look at the literature on QT as a biomarker for not just arrhythmias but death, the data aren't great. And, some of those data come from trials where they have people who have familial prolongation of the QT interval. Others come from other drug trials, other antiarrhythmics like sotalol. So, the relative risks go up. Certainly above 5 milliseconds there is clear association with risk.

But I am a little worried that that alone would convince me that if there is an absence of a QT effect that there wouldn't be, as Dr. Tinetti points out, a clinical concern, particularly because there are other potential hemodynamic effects of a drug that might lead to hypotension in the elderly.

I guess the other thing to comment on the QT is that it would be nice to compare that to drug levels or metabolites. It could in fact be that at normal dosing and normal drug levels, in the absence of renal insufficiency, etc., there may not be a QT effect and that there could be one relative to higher levels or overdose. I think that would be very important information for the agency to go forward because that would give you a way to interpret the clinical data.

But my strong recommendation would be not to stop with QT. I think it is an interesting biomarker. We use it a lot, particularly in drug development, but it wouldn't necessary trump a more rigorous observational study that would exclude a clinical concern.

DR. ROSEBRAUGH: I was going to point out that for QT studies, just so the panel members are aware, we usually do push the dose. We go several fold above what the dose

is.

DR. NELSON: If I can comment, one of the problems may not be just a dose-related problem and it may be a situational problem as well. You know, again, it is drug interactions, drug combinations, physiological abnormalities whether they are genetic or acquired. All of these things play into it. Again, you know, I could use the Seldane example as something that, you know, took years to find. I mean, I know we weren't looking the same way at QTs back then because it is such a very unique combination of drugs plus people to make that apparent. And, it is a very hard entity to find epidemiologically, as has been pointed out already, because these are people at risk of dying often anyway and the ability to find them postmortem is very difficult.

So, the signal being found on a thorough QT study would be great but its absence, I am not sure, would necessarily mean that all things are well just because when you put a drug out into practice many things happen. You know, we have known about atypical antipsychotics being PQ-prolonging drugs for a long time. There are still many studies out there looking, and there was one just published I believe last month looking at the clinical outcomes of

people on atypical antipsychotics and the controversy of whether or not there is, in fact, an increased death rate in that population.

So, these things are iterative and they just go on but, you know, this is a drug that has, in my mind, a fairly strong signal for cardiotoxicity and it is going to be something we might be able to prove with some sort of assessment of QT, but it may not necessarily be easy to prove unless we look at large populations.

DR. RAPPAPORT: Well, I think there are two different issues. One is if you have a QT signal what is the clinical relevance of it. So, that is the time when you want to look at the community and how it interacts in patients on other drugs and their own physiologies. But if there is no QT prolongation, if the drug does not prolong the QT, then it doesn't matter what the patient is already on or whether they have prolonged QT syndrome.

DR. NELSON: Yes, I would just take the position though that you are going to do several permutations of an experiment to find QT prolongation but, until you put it back in the real world where people start using it in their own self-acquired permutations, it may not necessarily become apparent.

I mean, the signal is there. I mean, we don't know that in human beings in a QT study but we know in animal studies that there are QT-prolonging drugs. We know at least on its structural basis and its relationship to methadone that it is going to have a fairly strong risk of having QT prolongation.

I think we know, perhaps based on some overdose data, that it has the potential to prolong the QT but it is hard to imagine that a thorough QT study won't show it. I mean, I guess it may not but if it doesn't I would argue that we didn't do a thorough QT study thoroughly enough.

DR. FARRAR: Dr. Kramer?

DR. KRAMER: Yes, on this same discussion, I am just not sure about the unequivocal statements that we definitely have a signal here. I am fairly familiar with the University of Arizona's approach on these things and I am really struck that they don't have it even in their suspected category. They are usually very inclusive as they list them. They are the group that discovered or identified the methadone relationship. So, I think we need to be careful here.

The other thing is if you use Seldane as an example and you do an epidemiologic study you are not going

to find something that rare that only shows up with the right drug combination. I mean, what was it? Fifteen cases in a million, or something. We have to be realistic about what we can truly find in a real-world epidemiologic study as well, and a negative epidemiologic study doesn't assure you that there is no problem either. So, at least enriching it by looking at dose and higher doses and its effect on QT, like you and Dr. Lincoff say, but I think it is a standard approach in cardiology.

DR. FARRAR: Dr. Hennessey?

DR. HENNESSEY: A thorough QT study can also provide false reassurance. Pfizer study 054 found no or at most small QT prolongation for haloperidol, yet, William Rays' study, published a couple of weeks ago, shows a clear dose-related relationship to sudden cardiac death in the elderly.

DR. FARRAR: What I am clearly hearing is that there was a consensus of the committee that at therapeutic doses there was no signal for increased cardiotoxicity, but that in a variety of forms people suggested that additional studies on potential cardiotoxicity were important, with some disagreement on whether QT would be reassuring if it were negative or damning if it were positive, and at least a

plurality of opinion that some types of epidemiologic studies should be conducted either in databases or perhaps in prospectively collected data.

In addition, I heard a couple of people speak to the fact that there is enough concern about use of the drug in the elderly and chronically that some change in label to make that more apparent, or in some way to reduce that potential risk, would be worth considering. Dr. Gardner?

DR. GARDNER: In going forward, could I just pause and ask our clinician colleagues on the panel who prescribe pain medications if there is a niche that we are missing for this? Is there a need that we haven't talked about? If there is a group of people that if we blew past this product, they would be severely under-served by a decision like that?

DR. FARRAR: Dr. Tinetti?

DR. TINETTI: Well, as a geriatrician, my point is that every drug you look at is bad. I mean, we can say this about every other drug. There is nothing terribly unique about this. This just happens to be the drug that got brought forward. Again, I think the issue that I see is in elderly patients who have pain which is a greater concern to them often than other diseases. Every drug that you are

talking about that is going to deal with pain has complications associated. Every opiate has difficulty. All the nonsteroidals have difficulty. The anticonvulsants which get used for pain have difficulty.

I will tell you I have never prescribed this drug in my life, but I am not the primary provider for people with pain. But, yes, I think there is the potential that there will be people in whom, although this is not an ideal drug, it may be less problematic than alternatives. That is how I would look upon it. So, I think there is the possibility that the drugs that would take its place might cause at least as much harm in some people.

DR. FARRAR: That actually is a very nice lead-in. Let me say that in thinking about what was just discussed, the whole issue of what would be used instead and what sort of approaches would need to be taken, I think we can usefully move into the consideration of that question. Dr. Omoigui?

DR. OMOIGUI: Actually, I wanted to respond to the prior speaker. I am a pain specialist. My real focus is inflammation and pain. With respect to the question of whether I prescribe Darvon or Darvocet, I think in the last 15 years I have probably prescribed it once or twice. I

found it to be very ineffective from a clinical point of view.

So, if there are any patients that are going to require this medication that can't be served with acetaminophen, I think there are going to be few. That is just from my own clinical experience and also from the clinical experience of some of my colleagues that I have talked to.

So, I think everything is a risk/benefit analysis. The question is what is the benefit of the drug and what is the risk associated with it, and how many people are really being helped as opposed to people who could be helped with Tylenol. The combination of propoxyphene with acetaminophen is the most common modality of the drug being prescribed now and,if there is no real analysis that shows that the combination is better than acetaminophen, then the options are pretty clear. And, I think the VA study also showed some of the other medications can easily take its place.

DR. FARRAR: Can I ask you to hold that conversation for the next question which is about the other drugs. Dr. Lorenz, will that fit with your need?

DR. LORENZ: Sure. I was just going to say that as a palliative medicine physician I feel like this medication

has no special place, which doesn't mean it would never be useful but, again, given the wide range or products, particularly in cancer where most of the evidence in the field of advanced illness care, if you will, lies, there is no reason to reserve this medication for any particular population since we have so many effective drugs to call upon.

I think the caution about drugs that might take its place is a very important one, especially with regard to certain medications that we commonly see as problematic in the elderly such as nonsteroidals which seem to be comparable, perhaps superior, but certainly comparable to this kind of drug in terms of when it might be used.

DR. FARRAR: So, I think that leads us to the next question, which is that propoxyphene-containing products are the second most frequently prescribed opioid in the United States. Discuss the potential risk associated with the replacement of propoxyphene-containing products by alternative products listed below should propoxyphene-containing products be removed from the market.

I am going to ask Dr. Kirsch to start that conversation. MR. LEVIN?

MR. LEVIN: I would just like clarification from

the agency. What potential risks are we talking about? I mean, does this mean the risk profiles of drugs that would be used instead? Does this mean risk to patients in terms of having to endure more pain or less pain? I mean, it is not written in a way that makes it clear what the risk is that we are supposed to discuss, and we haven't discussed the risk profiles of these other products.

DR. HERTZ: So, yes, in planning out the day there is only so much we can go through and we were sort of hoping and assuming that some of the risks associated with the alternatives will be reasonably well-known to most of the individuals here.

The risks that we are talking about here, it is everything involved in the risk of taking a drug. So, it is the risk of all of the known adverse events or potential adverse events. It is, to some extent, the risk of untreated pain but we are not saying the alternative is nothing. We are trying to say it is likely something will fill the void.

So, when we look at the overall risk/benefit balance, that risk is the bigger picture of risk. So, it is everything that we know about NSAIDs. It is everything we know about opioids. We have gone into the specifics of

propoxyphene and there is a question that you have just given us input on in terms of whether there is a special risk there with regard to the cardiac toxicity, and we have heard you.

So, given what we know about the efficacy; given what we can understand about safety; and given what we know about the available alternatives, what does that say to you?

MR. LEVIN: I mean, am I the only one uncomfortable with being asked to answer this question? It is a macro, macro question; it is impossible.

DR. FARRAR: I agree to a certain extent. I guess from my discussion with the agency, what they are interested in knowing is how to think about the risk/benefit. Let's suppose that the drug has a small but clear risk of cardiac arrhythmiaB-just make that assumption, how are we going to make a decision, how is the agency going to make a decision about the relative risk of forcing all of those people into taking hydrocodone and the potential risks of that, or something? The issue is how to make that decision. It is not really to sort of think comprehensively about the risks involved. I think they just want some guidance about how to think about those things moving forward. Dr. Kramer?

DR. KRAMER: I would just like to say that if this

question is too big for us, what does that say about what the practicing physician in the community is going to be faced with if we take it off the market and they have to deal with this? So, I think it is reasonable for an expert group to deal with the same question.

MR. LEVIN: I mean, for example, this kind of issue was raised in Vioxx, and the suggestion was that we needed, you know, a study to look at the comparative risks and benefits of all of the NSAIDs. We weren't asked to answer that question there and I think it is an impossible question to be answered. I don't even know how to address advice on what the process is other than that you study these things head-to-head.

DR. RAPPAPORT: That was a very specific situation where you are looking at the cardiotoxicity of a class of drugs and the individual components in that class. We are not asking you to do quantitative analysis here. We are asking you as clinicians, as experts, as physicians who know a lot about opioids, who know a lot about NSAIDs and the risks associated with them, what is going to happen if we remove propoxyphene from the market and everybody goes onto those other drugs. I don't think it is that difficult of a question.

DR. FARRAR: So, there is a difference of opinion about the question. I actually have Dr. Crawford and Dr. Gardner but then I would like to get to Dr. Kirsch, if I could.

DR. CRAWFORD: Thank you. I share some of the concerns as my colleague, MR. LEVIN, but in terms of the question, the Chairman has stated what I think is really the issue but it is not what the question is. The question is discuss potential risks, to which I say name your poison. Just as Dr. Tinetti and Dr. Lorenz said, every alternative product is going to have risks, GI bleeding and altered liver function and cardiovascular problems, nausea and vomiting, and the list goes on.

But the bigger question to me is not really number 3. We know all the products have their own unique and shared risks and it is risk/benefit. But that is not this question. That is question 4.

DR. FARRAR: Dr. Gardner, did you want to same something?

DR. GARDNER: No.

DR. FARRAR: So, Dr. Kirsch, do want to try and address the question as you understand it?

DR. KIRSCH: Sure; what the heck! So, I think that

the drug doesn't have an effect beyond placebo so I think the risk from therapy is quite small in taking the product off the market. As somebody just said a few minutes ago, I think that there is going to be a problem for the pain provider who probably thinks in their head, well, I can give them this drug. It doesn't have a lot of negative effects; it doesn't have a lot of positive effects. If a patient comes to my office and wants something to treat pain, I will give them this because I think it is not going to hurt them though I know it is not going to help them either.

So, I think the risk of taking if off the market really is going to be some uncomfortable situations for pain providers, but I don't think it would substantially impair patient care, with the exception that the pain provider may choose to give a drug that actually does have a worse risk profile.

DR. FARRAR: Thank you. Dr. Nussmeier?

DR. NUSSMEIER: Well, from the little that was presented today and from what I know, the alternative drugs seem to have similar overall risk profiles. Possibly the alternative drugs have more benefit but we really don't have adequate comparative data to state that definitively.

DR. FARRAR: Dr. Prough?

DR. PROUGH: Well, I think it puts the folks who are writing 21 million prescriptions a year in somewhat of a bind. If, in fact, the idea were readily accepted that you could simply stop giving propoxyphene and just give acetaminophen it would be simple and, presumably, it would beB-well, it wouldn't be a lot safer but it might be a little safer. Unfortunately, I think the vast majority of the people prescribing propoxyphene are going to substitute something else, and most everything that they might substitute for the propoxyphene is at least as hazardous as is propoxyphene.

DR. FARRAR: Dr. Ciraulo?

DR. CIRAULO: Yes, I think you will have a huge nightmare on your hands. First of all, even if you believe the drug has no efficacy, no one here is saying it doesn't have pharmacological activity. It is active at the mu and delta receptors, active at the nicotinic receptors. It is active at the MDM pain receptor. And, the psychological reliance on a product is another component that is going to be very difficult for patients and providers to handle.

I feel very uncomfortable, and I may be getting ahead of myself with this, but I feel very uncomfortable at this point, not having clear evidence of efficacy and

without having any proof that it is not efficacious, to say it should come off the market. I think it would be a mistake.

So, I would say the risks of removing it from the market outweigh the effect on patients. I think it would be very detrimental, especially to those folks who could develop withdrawal syndromes that have depressions associated with it. And, we know that the opioids have a strong effect on mood and withdrawal from hydrocodone, and other opiates are associated with very severe depressions and mood lability in treatment with some of the opioids or antidepressants. And, I think to do this in a cavalier fashion-BI don't think it is feasible at this point to do that.

DR. FARRAR: So, just to make the point that we are not talking about how it gets taken off, I am assuming that if it gets taken off it would be in a graded fashion, decreased over a number of years. But I think your point is, though, that you would argue that, with regards to potential other drugs that are there, taking it off the market without evidence of some marked problem with it would be something you would not recommend.

DR. CIRAULO: Absolutely, because other products

all have their own problems.

DR. FARRAR: Dr. Brull?

DR. BRULL: Thank you. Yes, I don't want to get into the debate whether this is an easy or difficult question and I think that it really depends on what our comparator is. I agree it would be a nightmare to take it off the market whether it is over one year or five.

You know, we looked at statistics and we can make them say anything we want. If you look at the data that looked at the number of patients who actually committed suicide of the ones who were exposed to propoxyphene, it is 20 percent, and they compared that to the data of those patients who were exposed to oxycodone, only 11 percent of them, and you would say, well, it would be better to just take it off the market and switch everybody to oxycodone but we know that that is probably not the answer. So, I don't think that we know the answer.

DR. FARRAR: Dr. Zito?

DR. ZITO: Well, I am having difficulty understanding how we should keep it on the market because it would be difficult to reeducate healthcare providers and to continue to spend dollars, particularly in populations where risks really do outweigh the benefits. So, I think we can

adjust over a reasonably slow process to adapt to other things and I am confident that the drug development people will be right there, helping us find new and safer products.

DR. FARRAR: We seem to have morphed into answering the last question, which we are going to vote on. I am not opposed to having a discussion on that and expressing your opinion but I think I would like to hear a little bit more about whether you think the other drugs that would be substituted are of equal risk in some way, or to provide some guidance on that briefly.

DR. ZITO: Right. Well, there are adverse event profiles for all drugs but they are not equivalent. When we work one-on-one with individual people we find specific medication which will work well.

I would also like to reflect on the perceived benefit of a medication which is a huge issue, going way back to the 1970s when people worked very hard, people who believed that this drug was not safe and effective and worked with academic detailing and other methods. Even in the current Goodman and Gillman, the reviewer, the expert reviewer, tells us that there is still an ongoingB-the popularity of this drug is not really based on science; it is really based on the perception perhaps that it is a

safer, non-opioid alternative, none of which is true but that is the reality.

DR. FARRAR: Dr. Eisenach?

DR. EISENACH: So, I think we have been presented with no data suggesting there are patients who fail all other therapy that need this drug. We have been presented with data that it separates possibly, but maybe not at all, from Tylenol. So, if this went off the market and people had to take Tylenol without the additional risks of this drug I think you would have a net risk reduction. You could say potential risk to patients might be that they would be getting better analgesia because we don't know the other products, we don't have a head-to-head comparison.

DR. FARRAR: Dr. Rosenberg?

DR. ROSENBERG: I come at this from a couple of different perspectives, one of which is as a pain specialist. For opioid-sensitive patients this seems to be one of the few analgesics they can actually tolerate. I have had many of my patients tell me that, and I too have been through the medical school teaching that this is not a better drug than Tylenol. But the clinical experience has taught me otherwise. So, it is a drug that I use. We use it at the end of the other things.

But the other perspective that I have of this drug is as an opioid-sensitive individual who gets kidney stones, and this is the one medication I can tolerate without having severe nausea that will help me get through a mild kidney stone attack. That is, you know, coming from me as a scientist, I have tried the other ones. They tried to put me on other ones and, you know, there is a medication that actually will get me through it.

So, my perspective has been that we are not really looking at this drug hard enough because it seems to do something and I don't see myself as a scientist in that regard. But the other drugs on this list all have substantial side effects. So, I would prefer that this drug not disappear but perhaps be more restricted in how we look at it.

DR. FARRAR: Dr. Lorenz, briefly, whether you think the risks of some of the other replacements are in the same league or not with this drug.

DR. LORENZ: Yes, it is hard to be specific about it because we don't know enough about the risk of this particular product. But I would say that we certainly know that some of the risks of the alternatives on this list are substantial.

DR. FARRAR: Thank you. In the interest of all of our travel, if we can try and keep it brief but succinct. Dr. Tinetti?

DR. TINETTI: I would say basically there is the unintended potential that there would be more harm by taking this off the market. First of all, I think that this common wisdom that it is not effective is really borne out from the evidence that we have today that there is really no evidence. It hasn't been looked at. Number one.

Number two, I mean, a billion people have used this drug and even if signals are hard to detect I think we would detect them more than we have. Clearly, the other drugs have adverse events. So, I would be concerned there would be more harm to taking if off the market.

DR. FARRAR: Dr. Omoigui?

DR. OMOIGUI: Yes, I think we already have studies about what can replace the combination of propoxyphene with acetaminophen, and the replacement is acetaminophen and the effects are the same. Of course, if we have a drug that doesn't have any effect, then you are not going to get side effects either.

I think that we have a lot of other opioid alternatives that can replace this drug if propoxyphene is

withdrawn. It is put as a Schedule IV drug because it really doesn't have a strong effect on the mu receptor. So, I don't think there should be any fear about patients going through withdrawal with a phased removal of this drug. This drug has been removed in Europe and I think the FDA can refer to the experience in Europe in terms of what happened when the drug was withdrawn from the market.

In conclusion, I believe that should the drug not be withdrawn the labeling should be changed to ensure that physicians understand that the indication should be mild pain, not mild to moderate. It should be for a short duration. They should also be informed that there is really no statistical significance of efficacy over acetaminophen, and it should be used with caution in the elderly.

DR. FARRAR: Thank you. Dr. Beardsley?

DR. BEARDSLEY: Given the data that I have seen and the testimony that I have heard, I think the risks outweigh the benefits of this compound. I don't really see a large patient population that would go unserved if this drug was removed from the marketplace. Someone had mentioned the possibility of withdrawal effects and I think that might be true for some patients, but there is any number of opioid products, opioid combination products, that I think would

alleviate those withdrawal effects if the patient was transferred onto them.

DR. FARRAR: Dr. Tortella?

DR. TORTELLA: Net increase in risk; more NSAIDs; more Schedule III; more Schedule II.

DR. FARRAR: Thank you. Dr. Burlington?

DR. BURLINGTON: Since this drug is predominantly prescribed as a fixed-dose combination I would guess that the prescribers would look at other fixed-dose combination narcotics, and most of those have worse GI tolerance and significant side effect profiles that switched patients would be exposed to.

DR. FARRAR: Dr. Zelterman?

DR. ZELTERMAN: To answer this question you really need to know more information than was presented today. That is the first point. The second point, if you just used the information that was presented today everyone on this drug should be receiving a high-dose placebo.

DR. FARRAR: Dr. Lincoff?

DR. LINCOFF: I think that most of the replacements would be drugs of equivalent or perhaps even lower risk. I don’t think there is any evidence, despite what was thought to be a safety profile of this drug, that it is, in fact,

safer than other narcotics. There may be better GI tolerance but in terms of major risk I think most of the replacements would be of similar risk.

I am not talking about the process of getting to those replacements, but in an equilibrium where one is replaced I think that the drugs that are available are similar or, perhaps if patients could be convinced that Tylenol high dose is in fact as effective, even lower risk.

DR. FARRAR: Dr. Hiatt?

DR. HIATT: So, I would take this on its own merits. If the safety is uncertain and the benefit is not well shown, then removing an ineffective drug would really not have a lot of clinical downside. I do think that there is a real psychological risk to taking this off the market in terms of patients' perceived benefit from the drug.

DR. FARRAR: MR. LEVIN, do you have anything to add?

MR. LEVIN: No.

DR. FARRAR: Dr. Day?

DR. DAY: We seem to have been melding comments about question 3 and question 4.

DR. FARRAR: Which is fine.

DR. DAY: That is fine. I would say little B, big

R for this drug, little benefit, minimal, and lots of risks, and that is very unsettling. Of course, all the others have an unfavorable risk profile. There are many of us in this room who have served on multiple advisory committees for all kinds of pain medications over the last couple of years. In my own case, we have considered about 8 to 10 to 12 different drugs for the relief of pain across the map of NSAIDs, COX-2, APAP, aspirin, fentanyl, oxycodone, and the fact that all of thee others have side effects and various adverse events as well is not a complete enough argument. It has to be how big is the benefit and how big is the risk.

DR. FARRAR: Dr. Nelson?

DR. NELSON: I am faced all the time in my clinical practice with prescribing low potency, kind of low efficacy opioids as well. I think part of the problem is that patients are not satisfied with getting just acetaminophen or a nonsteroidal. They have this sense that these drugs are much better. I think I have come to the conclusion that they are not but sometimes I have to bow to pressure and give out something a little bit Astronger.@

I don't think though that this drug or any of the other fixed combination products or acetaminophen would be any less effective, probably more effective, and I certainly

don't think they carry any greater risk if used appropriately. So, I don't think there would be any risk. Of course, unanticipated complicating consequences are unknown but I don't see why, at first blush, this should be an issue.

DR. FARRAR: MR. GOOZNER?

MR. GOOZNER: I wrestle a lot with this idea that this drug causes dependency and, you know, NSAIDs are available to do the exact same thing and perhaps even better. And, I think dependency is its own problem. So, for that reason I think that there are other things that are available and ought to be prescribed.

DR. FARRAR: Dr. Kramer?

DR. KRAMER: To just address question 3, I think many of the alternatives have potentially higher potential for dependency and I think the assumption that patients will accept Tylenol alone as an alternative is incorrect. So, I think that there would be some serious problems if we had to consider these alternatives. Is this the time to comment on 4?

DR. FARRAR: Yes.

DR. KRAMER: Well, I would just like to say that one thing that hasn't been said that always bothers me when

we have these sorts of deliberations is that, you know, we have gotten to the stage of evidence-based medicine and, yet, we really must keep in mind that clinical trials are studies of populations and average effects.

I have to say, as I was listening to Dr. Sacks' presentation and as I was imagining myself when I was in the rural mountains of North Carolina trying to take care of primary care patients, that the art of medicine is trying to find the right agent for an individual patient that takes into account all of these factors, the psychological factors, the expectations, the risk of dependency, the side effects. A lot of people can't take NSAIDs. Tylenol truly may not be effective.

So, I think we need to seriously think about whether we have identified enough real risk in terms of the petition that has been put forward. I mean, as we went around the table I didn't hear that there is a definite cardiac risk identified. So, I would just like to say that I think there may be individual patients. There is a lot we don't know. There is so much we don't know about the individual subsets, whether they be genetic effects or other determinants of why individual patients may benefit. The anecdote that Dr. Rosenberg gave us is a great example of

that. I will stop there but just say I do think there is a place for individualization of treatment and having this available as a tool.

DR. DAY: Just a brief comment. I would like to express disappointment in the questions. We are not asked to address overall risk. We are to address overall efficacy and for risk only cardiotoxicity. So, that is why I think that the discussion is not balanced enough when we come to number 4. And, I wish we had an opportunity to comment on dependency and everything else taken together as risk. So, I am a little disappointed about that.

DR. FARRAR: Dr. Gardner, feel free to comment on total risk.

DR. GARDNER: Gosh, thanks! I am going to skip to number 4 and assume that if a vote is taken that supports continuation that we really give consideration to labeling and education because 50 percent of the prescriptions for this drug, as we have seen today, are by family practitioners, internal medicine docs, not pain people and we really have to do a lot of work, even if this were withdrawn over time, to help people understand why and what they should go to next rather than just take it off.

DR. FARRAR: Dr. Lesar?

DR. LESAR: I will try 3 and 4 here together, which is when one considers that there are eight million patients receiving 20 million prescriptions every year, it is likely that on a public health basis there should be a reduction in risk. However, there are those individual patients, for all the reasons discussed, who will, indeed, have some adverse effects.

So, I echo Dr. Kramer's point of view about the individualization. But when one thinks about 20 million prescriptions one thinks that, obviously, this drug is overused and that that puts the population at risk. So, certainly there need to be some changes in the way it is used or it should not be on the market.

DR. FARRAR: Dr. Maxwell?

DR. MAXWELL: Okay, I am going to put on a different hat. Normally, I track trends in drug use, both illicit and licit. And, when I read 3 I had a heart attack because I realized that in terms of misuse of prescription drugs propoxyphene is very low. I have six times as many deaths in Texas from hydrocodone products as I do for propoxyphene.

So, in that sense of withdrawing it from the market and sending people to hydrocodone and oxycodone there

is a huge risk, which I hadn't really thought about until I looked at this question. I mean, it is not a good drug; I am not happy with it. I am not happy with the data we don't have. But one of the risks definitely will be that you will drive people to other drugs that are much more likely to be abused and the data reflects that.

DR. CIRAULO: The TADS data supports you.

DR. FARRAR: Dr. Hennessey?

DR. HENNESSEY: So, propoxyphene looks like it offers placebo benefit with opioid risks. Acetaminophen has acetaminophen benefits with acetaminophen risks. Other opioids have opioid benefits with opioid risks. The NSAIDs have NSAID benefits with NSAID risks. So, I think that is the overall comparison of the risks of the other drugs. I don't think that the U.K. has something that the North Atlantic [sic] since they withdrew the drug there.

DR. FARRAR: Miss Zavacky?

MS. ZAVACKY: I think the risk to remove it is problematic.

DR. FARRAR: Dr. Crawford?

DR. CRAWFORD: I have already commented on question 3 and I will wait for question 4.

DR. FARRAR: Dr. Woods?

DR. WOODS: I don't have anything to add.

DR. FARRAR: Dr. Rappaport, and then I will summarize and we will vote.

DR. RAPPAPORT: Well, I don't want to stay here any longer than anybody else wants to stay here, but question 4 was not meant to just be a vote where, you know, press your button and we will go home. As Dr. Day asked, we do want some discussion over the overall risk compared to the overall benefit. If you have something to say about that, we would like to hear it. So, I would prefer not to just end it now and vote, if possible.

DR. FARRAR: Dr. Lorenz?

DR. LORENZ: Sure, I would just like to stress again that I think the risks are unproven but very worrisome. So, I do think that this is a drug that has a place in the clinical armamentarium that exceeds the evidence for its efficacy and doesn't reflect the degree or risk that may exist. So, I am not sure what tools are at your disposal but I do feel that efforts should be made to change the use of this drug in clinical practice. I mean, you know, it is just not a feature of the environment that I work in, thank goodness.

DR. FARRAR: Dr. Eisenach?

DR. EISENACH: Well, I thought the FDA has something to do with safety and efficacy of drugs that are on our market. It seems to me we have not been presented with a lot of efficacy data, at least to my knowledge. I haven't seen anything that is convincing me that there is any efficacy here. And, there are concerns regarding risk.

To have a theoretical discussion of what might happen if we remove the drug, which we don't know is safe and is unlikely to be effective, seems to me to be going against the FDA's charter.

DR. FARRAR: Dr. Ciraulo?

DR. CIRAULO: I want to go back and address the efficacy. First of all, I don't think any of us would agree that the studies done were decent, or just because they did not show efficacy does not mean the drug is not effective. You know, as we pointed out, there are many different conditions that are being treated, many different models of pain, and there are 21 million prescriptions and I can't believe it is just doctors being stupid prescribing it.

The other issue is the dependence. I really want to emphasize the point that Jane made about the dependence potential of this drug. It actually is lower and there are studies, single-dose studies showing preference and that it

has a low abuse potential compared to other opiates. The TADS data has actually shown a decline and it is lowest. And, you see oxycodone up there, you see hydrocodone up there, and Tramadol. I am involved with physicians who are addicted. Tramadol is one of the major drugs that physicians get addicted to even though it is unscheduled. So, I think you cannot under-emphasize the dependence factor here.

DR. FARRAR: Dr. Kramer?

DR. KRAMER: I would just like to make the request when panel members, like when Dr. Lorenz said he was really concerned about these serious risks, if you could identify which risks you are concerned about so we all are talking about the same thing, it would be helpful.

DR. LORENZ: The fact that we don't really understand the fundamental pharmacokinetics and clinical efficacy of chronic dosing, especially in elderly patients with comorbid illness. And, yes, along with other risks that are common to NSAIDs, the falls that were cited and, you know, dependency and so forth, the issue of cardiotoxicity which I think is very suggestive, if not established.

DR. KRAMER: But on the issue of chronicity, we

have no data on chronic efficacy.

DR. LORENZ: That is right.

DR. KRAMER: That is a lack of evidence of efficacy as opposed to identified risk, wouldn't you say?

DR. LORENZ: It is, but especially given the lack of efficacy the risk is more concerning, knowing how widespread it is in use. I mean, you know, we just don't. The confidence intervals for the risk/benefit ratio are enormous I think, until we have more data. So, caution is appropriate.

DR. FARRAR: They are not enormous; they are not known.

DR. LORENZ: Okay, but there is just a big universe they could lie in. That is all I mean.

DR. FARRAR: Are there other comments about the general risks, benefits? Dr. Day?

DR. DAY: I would like to hear what the panelists think about accidental deaths, the magnitude of that risk.

DR. FARRAR: Dr. Tinetti?

DR. TINETTI: From the data we have, it looks like it is relative to the frequency with which it is used, very, very low likelihood.

I wanted to comment about risk. We keep talking

about Tylenol and acetaminophen as being the alternative, and I have to remind you that in an elderly population in which liver is a problem, increased use of Tylenol, if it was effective, is not without risk. I think we are sort of talking here like Tylenol is a completely safe drug and in an elderly population it is not a completely safe drug. I think that is important to bear in mind.

The second thing in terms of the risk and the benefit is that, again, we keep saying that there is no effectiveness. I think what we have seen today is that there is no evidence one way or another. So, when we make our decision here I would like us not to make the assumption that it is an ineffective drug. I think it is based on the fact that there is no data one way or another really.

DR. FARRAR: Dr. Rappaport?

DR. RAPPAPORT: Yes, I would like to just note that that is the case here. If you look back at a lot of drugs that were approved back in the ‘70s or before you are going to see similarly poor quality data. So, there may be an absence here but that is what the basis was at that time. Remembering what Dr. Crawford said earlier, you know, about sort of a level playing field, keep that in mind as well when you are thinking about whether this is something that

we should be considering with all products that were approved at a different time with a different science.

DR. HIATT: Could I comment on that?

DR. OMOIGUI: Let me make a comment on that.

DR. FARRAR: Dr. Omoigui.

DR. OMOIGUI: Yes, Dr. Tinetti made a statement that Tylenol is not without risk. The issue here is this; a patient who is already on combination therapy is already on Tylenol. So, we are talking about apples and apples. They are already on Tylenol. The question is removing a component of the combination that is not adding to the effect.

I would like to comment on accidental deaths. There is a risk with a drug that is not effective. The patients can end up taking more and more and more of the drugs whereby they end up getting to a toxic level without any therapeutic benefit. So, that is also a major risk of a drug that does not have any proven efficacy.

DR. HIATT: I was going to say that if the absence of benefit has been there for 30-plus years and we are having this conversation today, if this were a cardiovascular drug that took 20,000 patients to prove that it saves lives I could see where you might be challenged.

Forgive me, but I don't do pain clinical trials, but how hard is it to re-randomize patients with different forms of pain, short term and long term, and understand the efficacy cleanly as a single and a combination product, using proper factorial design trials? Because if you were to come back to this committee in 12 months and say here is some newer evidence; here is a TQT that doesn't show any clear safety risks and the observational data don't clearly show a major safety concern yet, I would feel very differently about the drug today.

But the absence of evidence just makes any decision-making so impossible. And, my question is why are we sitting here today having this conversation?

DR. ROSEBRAUGH: Let me just kind of add a couple of things to focus us a little bit. Why we sit here today is because we are always faced with tough questions and so we try to get advice from people to help us think through these things.

As Bob said, that was quite a different era back then, kind of like, I suppose, if you tried to compare a 1962 Buick to a 2009 Buick. It is a much different car and they handle a lot better, and all that kind of stuff. The agency as a whole does not go back and revisit these things.

So there was a question earlier about, well, if somebody comes in and they get a new drug approved do you re-look at efficacy. No, we don't. We accept the fact we said that there was enough efficacy to get it approved back when it happened, and we move forward. We don't keep going back and revisiting because the standards keep changing. It would be a never-ending process.

I think as Bob said also, I suspect that if we went back and reviewed most of the drugs that were approved at that time we might see less evidence than this has. So, we are asking you folks to try to help us sort through this because we have a petition that says that we have these new, well, maybe not new but we think we have these safety things and is that enough that it should now come off the market. So, we are kind of asking you and we are presenting this is what we got; this is what we have to make our decision on and we are not making it in 12 months, we have to make it now.

The other thing I did just want to mention because I have heard this several times about a gradual withdrawal from the market. I am not sure what folks mean when they say gradual withdrawal. That is really not how it would happen. So, we have a couple of mechanisms available to us.

I won't bore you with all the details and I also don't want to show that I am a policy wonk because I think you would lose your sense of humor if you know too much about the policy at FDA.

But what it amounts to is that we would have to have a notice of a public hearing, and we would go through this legislative activity but, at the end of the day if we decided it ought to come off the market, it would come off the market the next day.

DR. RAPPAPORT: I also want to add a couple of points. One, to get the studies you are talking about, even if we thought that that was the appropriate thing to do, requires us to somehow either have enough safety evidence to use our authority to require the studies, or negotiate getting a sponsor to do the studies. We don't do the studies. We don't have the money to do the studies.

The other point is that analgesic clinical trials are notoriously difficult to show as effective. Certainly, Dr. Farrar can speak too as to why we are in the process of trying to figure out why and how to do better trials in this area. But they are difficult. So, the fact that they didn't find an effect in the trials back in those days doesn't surprise me at all. We do trials today where we

don’t see an effect with oxycodone. It is the way it is.

DR. ROSEBRAUGH: Let me just add something quickly, not to belabor any of this, but we do have new authorities but those authorities do not cover us requiring efficacy studies. So, we can do safety studies. We can do stuff with labeling. We can do stuff with trying to change populations. We can do all that with our new authorities but we can’t require efficacy studies.

DR. FARRAR: Dr. Hennessey?

DR. HENNESSEY: I just want to make two brief points. One, the concerns about lack of efficacy and adverse effects of this drug were not just sprung on the sponsor. People have been discussing this for decades.

The second point I would make is that it would not surprise me if we were viewing a subset of the clinical trials that have been done and, in particular, a subset that makes the drug look more favorable than the subset that we are not seeing.

DR. FARRAR: There are three more people that wanted to speak and then I think we will try and get to the vote if we have answered the questions. Dr. Kramer?

DR. KRAMER: I forget what I was going to ask.

DR. FARRAR: All right. Dr. Zito?

DR. ZITO: I have three points. The limited generalizability of trial information in relation to chronic pain management and the great subjectivity of people's response to pain makes it, for me, a little different than cardiovascular issues.

Secondly, the safety data, really we could have much better safety analysis than was presented here today. Someone from FDA, and forgive me, I don't know who it was, made the point that we couldn't really do safety comparisons. But, in fact, FDA themselves, safety officers, have published some really excellent work on statins and rhabdomyolysis by doing comparison across specific safety issues in relation to specific statins. So, I think much more could be done.

Finally, safety information that we know about is recognized association of drug with adverse event. We know that from the AERS data maybe we are getting one percent, sometimes they say ten percent, of reporting. So, this vast under-reporting means you are perhaps looking at the tip of an iceberg.

DR. FARRAR: We are about to lose half or our committee and I think we have to have a vote. So, we are going to go there and then we are going to come back, if

people have the time and would like to add some comments because I think it is useful. Is that all right?

Number 4, based on the data presented, does the balance of risk and benefit support continued marketing of propoxyphene-containing products for the management of mild to moderate pain?

Just to be very clear, a vote of yes means continuing it on the market and a vote of no means taking it off. All right? Are we ready for the vote? Just to be clear, the bottom of your screen is now flashing and you pick yes, no or abstain. Remember, yes is keep it on the market; no is take it off the market.

[Electronic voting]

So, we will record into the minutes that there were 12 yes votes and 14 no votes, with zero abstaining. I want to take a minute to thank everyone for coming so far for this committee meeting.

There are several people who had additional comments. There are additional questions here. We have addressed some of those. Some of you have had a chance to address them, but I would like to offer others of you a chance to address them now. MR. GOOZNER?

MR. GOOZNER: I just wanted to underscore something

that the gentleman from the FDA said. I believe this is a generic drug and this is a generic sponsor of this drug, and it is very untypical that one would ask a generic company, I suppose, to do these kinds of trials. It is not expected, except that in this case, this is a very widely used drug and there must be a lot sales associated with it.

So, it seems to me that the two questions that you addressed before, that the policy wonking could be addressed in this case, which is that if your tendency, based on the advice of this committee, were to maybe withdraw this drug, pending, of course, the offer to the company to go out there and over the next year design a trial to bring in the information that would justify some continued marketing of it and perhaps change your mind. It seems to me that, you know, without having to change the law this may be an opportunity to maybe break some new ground in that regard.

DR. HIATT: Yes, I would just echo that. I appreciate I think your concerns and, as a committee member, I am trying to wrestle over those with you. I feel the same way. If the only thing you can do is just keep drug on or keep drug off, and you are not really in sort of the phase of an NDA that is going to get a postmarketing commitment to approve it, you are in a different situation here.

But faced with these concerns and the complete absence of so much critical data, if I were the sponsor and got a message that we might keep you on the market if you make certain commitments would be conversation you think you could have. But today I don't see how you have enough evidence to keep marketing this drug.

DR. FARRAR: Dr. Nussmeier and then Dr. Kramer.

DR. NUSSMEIER: I was one of the yes votes. Considering the alternatives and remembering the era in which this drug was approved, I really couldn't favor summarily removing it from the market. But I do favor strengthening the labeling. I mean, that is something apparently that can be done immediately if it is not removed from the market, again, particularly with respect to the elderly, concomitant use of alcohol, benzodiazepines, opioids, everything we have talked about today really.

I wanted to ask if we could require the sponsor to work to develop risk evaluation and mitigation strategies, as we have with some of the other pain therapies.

I also wanted to ask if consideration could be given to a change in the schedule or if that is a reasonable middle ground, perhaps to a Schedule III.

I certainly agree with all the comments regarding

clinical trials, the need for clinical trials.

DR. FARRAR: Dr. Kramer?

DR. KRAMER: I would just like to comment. I think we really need to think aboutB-I did vote yes, but with the majority no voteB-what this means for other drugs in this category and whether or not we need to revisit the efficacy of all drugs that were approved in this earlier era when the requirements were less, especially when you look at some of the comparative numbers needed to treat to benefit in the meta-analyses.

I would also like to say that, you know, the petition was arguing that this really needed to be removed from the market because of the risk and the minimal or marginal efficacy. But I am not sure that we, as Ruth said, really fully talked about all of the risk. I don't think we identified any documentation of real clinical cardiac risk. And, one thing that concerned me as I was reading the background packet and today is that we didn't talk at all or see any evidence about CNS side effects, and are there data about the risk of falls in the elderly? I didn't see that. I think if I had to explain to somebody why the majority of people voted no and what those risks were, I couldn't answer that question. Maybe somebody could clarify for me what

risk it was that made us vote a majority no on this question.

DR. FARRAR: I would comment that Dr. Hennessey actually presented briefly a paper that showed that propoxyphene had the same risk of fall versus codeine. But, obviously, other studies would have to be looked at. I mean, I am not trying to answer the question for you. I am simply saying I think there is additional data out there that probably should be considered in this.

DR. KRAMER: But what was our basis? What was this committee's basis to say the risk was enough that we should take it off the market? Could someone clarify that for me?

DR. HENNESSEY: I can only speak for my vote. It was because in the absence of a demonstrated benefit there is no acceptable risk.

DR. HIATT: I would also like to comment on risk. When you typically look at least at new drugs that are for symptomatic indications, it is the exclusion of risk that you are trying to define. It is not trying to define the point estimate of risk. It is what is the upper end of the confidence interval or risk that I can exclude. That uncertainty I think is a major issue, particularly with symptomatic therapies.

If a therapy is designed for a morbid, mortal indication you have enough events to know that you are either causing harm or not causing harm. But when you get drugs approved with a few hundred patients treated with one dose on a short course of the therapy, by definition you never know the true safety of that drug.

That is why, at least in the cardiorenal environment, we talk a lot about defining risk for symptomatic therapies as understanding how many events you have on drug and placebo, and the number of events drives the upper boundary of the confidence interval around that risk estimate. It is the uncertainty of that upper boundary that drives my understanding of risk. What I am reacting to here is no data and, therefore, I don't know what the risk is.

DR. FARRAR: Dr. Day?

DR. DAY: I would like to express concern that the entire label is not provided with the background materials, either by sponsor or by FDA. We did get the excerpt of the warnings, which was helpful. I went and printed out the whole thing and found a lot of things that could be strengthened. I would take every single risk that is in there and see if others need to be in. But are they in the

right location or do they need to be elevated up, say, from precautions to something else, something a little stronger? Even within the warnings, there are three warnings. The first is do not prescribe for certain patients who are suicidal, etc. The next one is prescribe it with caution. Does that need to be strengthened to do not or to some kind of qualification? Prescribe with caution, if at all? So, to start thinking perhaps about this being a second-line drug for some people.

So, there are a lot of things like that. I would go through every single risk and see if it is located correctly and is the language appropriate. Then I would look at that patient information sheet, which is woefully inadequate. It doesn't say anything about elderly, etc.

DR. FARRAR: Dr. Crawford?

DR. CRAWFORD: I voted yes because at present, to me, there was not sufficient evidence to support market removal. I just wanted to say into the record that I very much appreciate the efforts of the petitioner and other supporters of the petition bringing forth the issue again because, clearly, there appear to be signals problem in the use of the drug and perhaps marginal benefit on average. So, I do hope and encourage the agency to use its new

regulatory authority in requiring some type of postmarketing safety studies and enhanced labeling.

DR. FARRAR: Anybody else with something they can add to this conversation?

DR. ZITO: I just have one fast comment about increasing warnings. It is my experience over 25 years, 30 years of healthcare that you can put anything you want in the label and very, very little of the practice will necessarily change unless you are doing contraindications or restricted population, or something really severe. So, I mean, the warnings are there and they are probably on the bottle every time the patients get them. But I am not sure what the impact would be. So, impact would be valuable.

DR. FARRAR: Let me thank all of those of you who are still here again. Bob, did you want to say something?

DR. RAPPAPORT: Yes, I just want to add my thanks. I appreciate everybody staying and giving us your input. It was an interesting discussion.

DR. FARRAR: Thank you.

[Whereupon, at 4:21 p.m., the proceedings were adjourned]