Memorandum

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Subject: Scientific Issues and Regulatory Considerations concerning Propoxyphene[1]

Summary

Propoxyphene is approved for the treatment of mild to moderate pain. Like other opioids, with excessive dosaging this agent can cause dose-related respiratory depression and vascular collapse. However, in conjunction with opioid class-related overdosing effects there is ongoing concern that at pharmacologically equivalent doses propoxyphene may be uniquely associated with heightened risk for clinically life-threatening suppression of cardiac inotropy and/or induction of arrhythmias in susceptible individuals. Prompted by deliberations surrounding an Advisory Committee held in 2009, FDA has initiated plans for the performance of 1) thorough QT studies to test the EKG effects of maximally tolerated dosaging of propoxyphene in healthy subjects, and 2) new epidemiological studies using the Tennessee Medicaid, Medicare and HMO data bases to assess the risk for death, sudden death and life-threatening cardiac and hepatic events among propoxyphene users, including elderly patients. In this memorandum I discuss critical evidence which has been gathered over a span of four decades surrounding the cardiotoxic potential of propoxyphene and point out important gaps in our current knowledge. Accumulated data suggest that a subset of susceptible individuals may be prone to propoxyphene-induced cardiotoxicity when treated with recommended or near-recommended doses of this agent. Concern that there is wide inter-individual variability in the cardiotoxic threshold of propoxyphene is driven by 1) the published coroner studies that have identified a subset of lethal overdose cases (ascribed to propoxyphene alone) with measured post-mortem propoxyphene blood levels which overlap with Cmax levels observed in pK study volunteers using recommended doses of propoxyphene and 2) the relatively higher tissue penetration from the circulation of propoxyphene and its major norpropoxyphene compared with other opioids. It can be postulated that patients who may be especially vulnerable to propoxyphene-induced cardiotoxicity, even when receiving therapeutic doses, are those with 1) reduced clearance of the parent drug and its principal metabolite nor-propoxyphene caused by renal

[1] Invaluable input for this assessment has been provided by L. Steven Leshin, DVM, Ph D, pharmacologist, DAARP; A. Wasserman, Ph D, supervisory pharmacologist DAARP; J. Koerner, Ph D, senior pharmacologist, DCRP; and R. Ouellet-Hellstrom, Ph D, epidemiology team leader, DEPI.

insufficiency 2) underlying heart failure and/or ischemic disease or 3) pre-existing disturbances of cardiac conduction caused by changes in intra or extracellular ion concentrations, concomitantly administered arrhythmogenic drugs, or underlying dysregulation of ion channel function. Unfortunately, a comprehensive comparison of propoxyphene and norpropoxyphene, side-by-side with other opiates (e.g. tramadol, codeine, hydrocodone, etc.) and their principal active or toxic metabolites, measuring dose-related effects on human EKG profiles and concentration-related effects on in vitro and in vivo animal test systems for cardiac conduction and inotropy (in both therapeutic and supra-therapeutic ranges), has not been performed. In addition, there are likely to be practical barriers in the accurate identification and reliable reporting of patients who would develop propoxyphene-induced sudden death or other life-threatening cardiac-related events while treated with therapeutic or near-therapeutic doses of the drug. With this background, the merits and short-comings of three regulatory options are considered. These include 1) the deferral of a decision concerning the US marketing of propoxyphene, pending completion of new epidemiological studies, 2) the deferral of such a decision, pending characterization of propoxyphene's cardiotoxic profile compared to other opioids, with a set of in vitro, pre-clinical and clinical EKG studies, and 3) the initiation of a phased withdrawal of propoxyphene from marketing in the US, without waiting for the completion and review of new studies.

Background

Propoxyphene was initially approved by FDA in 1957. Since 1976 this agent, either as a single ingredient or in combination with acetaminophen has been marketed and regulated in the US as a Schedule IV agent. Beginning in 1978, a number of petitions seeking reclassification of this agent from a Schedule IV to a Schedule II substance or removal of propoxyphene products from the market have been submitted to FDA. In the latest petition filed by Public Citizen on February 28, 2006, a phased removal of all propoxyphene products was requested. The petition claims that 1) propoxyphene has weak analgesic effects, even in relief of mild to moderate pain (the indication of use), and that in propoxyphene/acetaminophen containing combination products much of the efficacy is driven by acetaminophen, 2) the product has a low margin of safety and is particularly cardiotoxic, 3) there are high numbers of completed suicides and accidental deaths associated with propoxyphene, 4) despite its weak analgesic effects, repeated use of propoxyphene is associated with dependency and a related potential for abuse and addiction, and 5) there is inappropriate over-prescription and misuse of propoxyphene in the elderly population. With reference to use of propoxyphene in the elderly, the petition argues that as a consequence of age-related alterations in PK and PD drug effects there is an unacceptable level of risk for heart and central nervous system related adverse events in a population that is especially susceptible to toxicity, even when therapeutic doses are used.

In developing a response to this petition, extensive reviews of available data that impact assessments of both risk and benefit of propoxyphene were undertaken by a number of expert analysts representing key regulatory units and pertinent core disciplines in CDER including DAARP (medical officers, pharmacologists and toxicologists), OCP (clinical pharmacologists), DCRP (cardio-toxicologists), OSE (epidemiologists and safety

evaluators). The most recent cycle of reviews culminated in a joint meeting of the Anesthetic and Life Support Drugs with the Drug Safety and Risk Management Advisory Committees on January 30, 2009 to consider data on both the efficacy of propoxyphene alone or in combination with acetaminophen as well as its cardiotoxic potential. After being asked about alternative and unintended risks associated with the substitution of propoxyphene with other pain products, the advisory committee voted by a narrow margin (14 to 12) against the continued marketing of propoxyphene products.

In considering the main issues raised by the petition, and taking into account the previously mentioned FDA reviews as well as input from the advisory committee, on July 7, 2009, the FDA publically responded to the petition with a statement that propoxyphene would not be removed from the market but rather a series of other regulatory measures would be undertaken. These included 1) institution of revisions to the product labeling, 2) development of a Medication Guide as part of the institution of a REMS, 3) issuance of a Public Health Advisory about the safety issues of concern and 4) requirement of a clinical trial to be performed by the sponsor to assess the potential of propoxyphene to disturb cardiac conduction through the measurement of dose effects of the drug on Q-T prolongation in normal volunteers undergoing EKG monitoring). Subsequently, on August 6, 2009, Public Citizen submitted a new petition asking FDA to reconsider the agency's decision not to ban propoxyphene. This new petition highlighted previous actions in the United Kingdom to remove propoxyphene and by EMEA on June 25, 2009 to recommend that member states withdraw propoxyphene from their markets.

Scope of Current Memorandum

Much has been written and discussed about propoxyphene, both in the literature as well as by FDA analysts and advisory committee presenters who are expert in a variety of disciplines. The purpose of this memorandum is not to comprehensively evaluate such a large body of work, especially by a reviewer who has limited expertise in pain management and until now has had only a peripheral level of involvement in the propoxyphene question. Rather, it is to point to some critical features of the accumulated safety data sets that have been presented or published as well as gaps in information that may still exist which would inform an overall conclusion about benefit-risk of propoxyphene. With this as a framework, the merits and short-comings of a set of regulatory options are considered, including 1) the deferral of a decision concerning US marketing of propoxyphene, pending completion of new epidemiological studies, 2) the deferral of such a decision, pending characterization of propoxyphene's cardiotoxic profile compared to other opioids, with a set of in vitro, pre-clinical and clinical EKG studies, or 3) the initiation of a phased withdrawal of propoxyphene from marketing in the US, without waiting for the completion and review of new studies.

An expected consequence of removal of propoxyphene would be a shift of utilization to non-opioids and/or other opioids for the management of pain. Thus, consideration of relative access and comparable benefit/risk of these products is a necessary step in taking a regulatory stance on propoxyphene removal. Other drugs used to treat similar levels of

pain include non-opioids such as acetaminophen alone and NSAIDs, and opioids such as tramadol and codeine with/without acetaminophen. In addition, other opioids that are used to treat moderate forms of pain include hydrocodone with acetaminophen and oxycodone.

In weighing the merits of immediate removal vs further study of propoxyphene prior to the adoption of a definitive regulatory decision, the following questions should be considered:

1. Is propoxyphene more dangerous than other opioid analgesics in causing unintended life-threatening adverse events when used for pain control?
2. Among opioid analgesics currently used to treat mild to moderate pain does propoxyphene stand out with regards to efficacy, dependency and abuse potential or intrinsic toxicity?
3. If propoxyphene is removed from marketing are there alternative agents that are available with similar access which provide a better if not equal overall benefit/risk profile in the treatment of mild to moderate pain?

Framework for consideration of overall risk and benefit

Generally, opioids are all linked to a risk for misuse, dependency, and abuse. Moreover, all opioids have been linked to both intentional and accidental overdose associated with deaths. This class effect is exemplified by the robust AERS signals that reflect these effects for virtually all opioids. In an analysis of serious adverse events reported to AERS from marketing to February 2, 2005, there were 91 US deaths associated with Darvocet, the most commonly dispensed formulation of propoxyphene. Most of the reports identified opioid drug overdoses in individuals with profiles of drug dependency in which there was co-ingestion of multiple medications or in those attempting suicide. Similarly, an AERS review of tramadol in 2005 noted that drug overdoses, intentional overdose and completed suicides were among the top 30 adverse event terms associated with reports for this drug. Based on a number of OSE reviews the majority of tramadol overdose cases involved the use of one or more concomitant medications. When comparing AERS crude counts of completed suicide, overdose and death associated with tramadol, hydrocodone, propoxyphene and diclofenac the proportions of overdose and suicide were highest for hydrocodone and propoxyphene. Because of limitations intrinsic to AERS, a quantitative comparison of risk among products cannot be performed from this finding alone. Thus, it is not surprising that analyses of AERS reports have demonstrated that propoxyphene, hydrocodone and tramadol share safety profiles known to be associated with scheduled opioids.

As a class, many opioids have a relatively narrow therapeutic index and overdose can lead to respiratory depression and death, particularly in individuals who have not developed opioid tolerance. For example, after propoxyphene or tramadol overdosing, death can occur within just a few hours of dosing. In the case of propxyphene, death may result from dose-related respiratory depression, an opioid class effect, and/or from drug-related cardiotoxicity in susceptible individuals. As highlighted in a recent OSE review, an advisory in 2005 by the Committee on Safety of Medicines that propoxyphene should be

withdrawn from the UK market did lead to a substantial reduction in analgesic-related suicides in England and Wales in a two year frame after the announcement (Data based on death registrations obtained from the Office for National Statistics). In this period, a compensatory increase in the use of other analgesics in suicides did not occur, although outcomes over a longer follow-up were not reported. However, when accidental deaths from misuse and/or overdose with analgesics were combined with suicides in the trend analysis, the effect of the advisory in 2005 to reduce overall overdose deaths was less pronounced.

An important element in balancing the benefits of therapeutic opioid use as analgesics against risks for either accidental or intentional lethal overdose is that many of the marketed drugs in this class are highly effective in alleviating moderate and severe pain, for which there are few satisfactory alternatives among non-opioid agents. However, there are a few members of the opioid class, (e.g. propoxyphene and codeine) that are currently only approved for the treatment of mild to moderate pain. In this instance, benefits and risks must be especially carefully considered given the potential for life-threatening adverse events associated with excess dosing of these products. As will be discussed below, propoxyphene overdoses have been linked to deterioration of cardiac pump function as well as life-threatening rhythm disturbances. Based on separately published coroner's data that will also be summarized it is likely that there is significant inter-individual variability in the threshold blood and tissue levels of propoxyphene and norpropoxyphene which trigger these events. An important consideration in a comparative assessment of the benefits and risks of opioids approved for the treatment of mild to moderate pain is whether the therapeutic margins and inter-individual variabilities in threshold blood and tissue drug levels responsible for lethal or life-threatening events are substantially different between products.

Categorization of lethal overdose cases

In analyzing the spectrum of lethal overdose cases associated with excess administration of opioids, a distinction is often drawn by experts between accidental and intentional overdose. In evaluating the risk of opioids, which may have a relatively narrow therapeutic index, a third conceptually related but distinct 'excess dosing' category should also be considered. This would be a category of dose-related deaths that occur as a consequence of therapeutic misadventure, despite health care provider and patient adherence to dosing regimens which are more or less consistent with product labeling instructions, for the management of pain. That such events could often go unrecognized and may be occurring more frequently with propoxyphene than with other similarly marketed opioids used to treat mild to moderate pain in highly susceptible and often elderly individuals is one of the important concerns underlying the regulatory question at hand. The scientific basis and critical regulatory implications of such a possibility will be discussed below.

Epidemiological data on lethal overdoses

Characteristics of individuals prone to intentional vs accidental overdose must also be taken into account when considering the adoption of remedial public health and regulatory measures. Studies from the UK suggest that there may be important differences as well as overlapping characteristics in the profiles of individuals who fit into each of these categories of overdose. Coroner's data on deaths related to analgesic and cough suppressant-opioids in England and Wales (1996-2002) voluntarily supplied to the National Program on Substance Abuse exemplify some of the key profile characteristics of individuals with intentional and accidental overdoses. Among 2024 deaths that were analyzed, 910 occurred in addicts and 1114 in non-addicts. 70% of the non-addicts were 45 years and older and their deaths were often the result of intentional overdose, whereas 85% of the addicts in this series were younger than 45 years. Importantly, over 83% of the deaths in the addict group were deemed accidental, whereas at least 44% of the deaths in non-addicts were the result of suicide. Notably, use of propoxyphene-containing compounds was more frequently identified in deaths among non-addicts compared to the addicts (65.2% vs 18.1%), whereas the opposite trend was true in the case of codeine-containing products (non-addicts, 11.3% vs addicts, 48.0%). Concomitant use of substances in conjunction with propoxyphene, including opioids, psychoactive substances, hypnotics, anti-depressants, etc. was close to 90% in both groups. Overall, these data suggest that a significant percentage of older non-addicts use propoxyphene in attempted or completed suicides.

Concern about a relatively higher risk for lethality connected to propoxyphene overdose is also raised by results of a study of overdose mortality in Scotland demonstrating a ten-fold higher rate of lethal propoxyphene-acetaminophen overdoses per million prescriptions (2000-2002), compared to mortality rates associated with codeine-acetaminophen and dihydrocodeine-acetaminophen combinations (Afshari et al., Br. J. Clin. Pharm., 2005). Unfortunately, such ecological data alone cannot be extrapolated to an exact quantitative comparison of lethality risk between these opioids when overdoses occur.

In alignment with findings in the UK, a number of information sources including DAWN and a 2007 report by the Florida Medical Examiners point to propoxyphene-related deaths in the US as mostly a result of suicides, accidental death due to drug overdose, multiple medications and interactions with alcohol. In these databases, when controlling for prescription availability, across multiple states there were more deaths associated with propoxyphene, compared with tramadol or hydrocodone. Moreover, among 66 propoxyphene-related deaths deemed as accidental by the Florida examiner in 2007, 17 implicated propoxyphene as the sole cause. This finding raises concern, since in these cases there was no readily identified footprint of substance abuse or evidence of polypharmacy.

Limitations in the interpretation of Epidemiological Data

Unfortunately, there are also likely both limitations and biases in the ascertainment and reporting of different categories of propoxyphene overdose cases in systems such as AERS, DAWN, state medical examiners, etc. For example, patients who would fit into the third opioid excess dose category described above (excess dosing in highly susceptible elderly

individuals adhering to product label instructions) may go unrecognized, since deaths may be ascribed by health care providers or coroners to natural causes. In addition, physicians may be reluctant to report them, even if they were to be recognized, because of liability concerns. Therefore, drawing definitive conclusions about the relative cardiotoxic risk of propoxyphene for patients in this third category from epidemiological data alone continues to be problematic.

With currently available information, a determination whether there is an acceptable margin of safety in the therapeutic dose range of propoxyphene relative to other opioids must also lean heavily on interpolating a large body of pharmacological, toxicological and physiological data that has been accumulated over 40 years. The central question to be addressed in this analysis is whether propoxyphene and its major metabolite, norpropoxyphene can reach tissue and/or blood levels which are cardiotoxic or lethal in some patients using therapeutic (or near therapeutic doses) of propoxyphene-napsylate (100 mg/dose every 4 hrs) or propoxyphene-hydrochloride (65 mg every 4 hrs), as instructed in product labels. Each of these doses is equivalent to approximately 175 μmol.

Pharmacological data

Pharmacokinetic findings
As described in product labels, peak plasma levels of propoxyphene (P) are reached quickly (2.0 - 2.5 hrs). The parent compound has a half-life of 6-12 hrs with extensive first-pass metabolism in liver and intestine. It is N-demethylated by CYP3A4 to norpropoxyphene (NP) and importantly this major metabolite which is devoid of opioid agonism, in conjunction with propoxyphene, is cardiotoxic at above threshold levels (see below). NP has a longer half-life (30-36 hrs) than P and is excreted by the kidneys.

In weighing whether some patients might be put at risk because toxic threshold levels of P and NP are exceeded in critically affected organs (brain, circulation and heart, see below) due to the PK effects of propxyphene, the following findings are especially relevant:

- At steady state with multiple doses of the parent drug as per product labeling, there is significant inter-individual variation of levels of P and NP plateau trough and Cmax levels that is driven by a set of patient characteristics. A number of highly cited studies in the literature point to these. In a study by Flanagan et al. (Br J Clin Pharm., 1989) PK of P and NP in 12 young (21-28 yrs) and 12 elderly (70-79 yrs) volunteers after single and multiple propoxyphene dosing was studied. With multiple dosing in the elderly study group, median Cmax levels of P and NP were 239 and 1100 ng/ml, respectively, compared to levels of 116 and 673 ng/ml in the young subjects, respectively. Of greater importance, even in this small study of normal volunteers, the range of measurements in the elderly individuals included outliers with Cmax levels of P and NP as high as 509 ng/ml and 1500 ng/ml, respectively. The range of measures in this relatively small test sample points to the likelihood of even more pronounced outliers in a larger exposure population of individuals similar in their health status to the normal volunteers that were tested.

A tendency to increased steady state levels of P and NP is accentuated in individuals with disease states leading to compromised renal clearance of these compounds. With increasing age, even in normal individuals, creatinine clearance diminishes. Thus, it is not surprising that NP half life was found to inversely correlate with creatinine clearance in the aforementioned study. This observation is salient since although under normal conditions P has a half-life of 6-12 hrs, NP which is also cardiotoxic at increased levels, has a half-life of 30-36 hrs. In another study of single-dose testing of anephric patients with propoxyphene, the Cmax and AUC of P in the first 12 hrs were both found to be approximately twice the levels measured in healthy test subjects (Gibson et al, Clin Pharmacol Ther, 1980). NP levels were also higher and longer lasting in the anephric patients, consistent both with decreased biotransformation of propoxyphene and decreased elimination of norpropoxyphene. As will be discussed below, toxicological studies of death cases associated with post-mortem drug screens that tested positive only for propoxyphene have measured a broad range of P blood levels. In these series, in a subset of post-mortem cases P blood levels were not much higher than, and in a small percentage of cases overlapping with, the high 'outlier' levels measured in the normal volunteer PK dosing study. Furthermore, although not measured directly, it would not be surprising if heighted steady state blood P and NP levels in patients with significant renal compromise would be overlapping with blood levels identified in a proportion of the propoxyphene-associated deaths.

- In contrast to many other opioids[2], the volume of distribution of propoxyphene is very large (16 L/kg). This implies that much of the drug and its metabolites are distributed into tissues as well as the circulation. Variability in this distribution may play a key role in determining patient characteristics which determine heightened susceptibility to propoxyphene toxicity. Since cardiotoxic effects of P and NP may closely correlate with local tissue levels, using P and NP blood level measurements alone to establish a precise threshold that will reliably predict onset of toxicity in all treated patients is problematic. In the rat, IV propoxyphene dosing was associated with measured concentrations in lung, heart, adrenal, kidney and brain tissue that are 10-20 fold greater than those in blood, demonstrating the high level of tissue uptake of the drug from the peripheral circulation (Emerson et al. Toxicol., Appl. Pharm., 1967). Oral administration of propoxyphene is followed by first-pass uptake by intestine and liver. Nonetheless, in the aforementioned rat study, 5 minutes after oral dosing, the highest tissue concentrations of P were found in liver, followed by lung and heart. (Emerson et al. Toxicol., Appl. Pharm., 1967). It is notable that P concentrations in heart (a potential target of P and NP toxicity, see below) somewhat exceeded that in the blood for up to 30 minutes after oral dosing. Of course, direct measurements of the distribution and levels of uptake into specific tissues in human test subjects cannot be performed, in vivo. Nonetheless, inter-individual variability in propoxyphene absorption and biotransformation kinetics observed after even a single oral dose in human test subjects has been

[2] Volume of distribution for other opioids as per product labels: tramadol, 2.6-2.9 L/kg; morphine, 1.0-4.7 L/kg; oxycodone, 2.6 L/kg; hydrocodone, 3.4 L/kg – 4.1 L/kg; codeine 3-6 L/kg; dihydrocodeine, 1.0-1.3L/kg.

observed (Verebely and Inturrisi, Clin Pharm Ther. 1973). It is likely that there is an added layer of variability of P and NP flux and distribution between the intravascular, extracellular and intracellular compartments, including those tissues listed above. It is notable that under normal circumstances, 80% of circulating propoxyphene is protein bound (Thus, dialysis is ineffective in the management of overdose). However, the circulating fractions of free vs bound forms of P and NP may fluctuate under certain physiologic conditions. For example, reductions in P/NP binding proteins or blood pH may cause an increase in the free fraction causing more flux of these compounds into tissues (Giacomini et al., Clin Pharm Therap, 1980). Since heart may be a key target of toxic effects mediated by P and NP in which functions of conduction as well as inotropy could be jeopardized (see below), it would be of interest to determine levels of these compounds in cardiac myocytes, Purkinje cells, fibrocytes, etc., as well as in the extracellular compartment using animal models to measure the cellular (or even sub-cellular) distribution of these compounds after oral administration of propoxyphene. Studies to address this level of detail have not been performed to date.

Pharmacodynamic concepts

In the spectrum of marketed opioids, propoxyphene has relatively low potency as an analgesic (see January 25, 2010 review by LS Leshin through A Wasserman). Like other therapeutic opioids, it is a centrally acting opioid which has Mu receptor agonist activity. It may also have analgesic effects via noncompetitive antagonism of NMDA receptors. In addition, it may have weak opioid-mediated effects in the periphery, affecting gastrointestinal motility. Of critical importance in the potential of P and NP to cause dose-related life-threatening toxicity, opioid antagonists such as naloxone are able to reverse centrally mediated respiratory depression caused by these compounds but have little or no impact in reversing their cardiotoxic effects (Giacomini et al., Clin Pharm Ther., 1980).

Toxicology of Propoxyphene

Effects on cardiac inotropy and conduction

With increasing levels, P and NP have been found to cause changes of 3 distinct cardiac functions. These are 1) inhibition of Purkinje fiber contractility and cardiac muscle inotropy, 2) inhibition of inward sodium current similar to Class IC anti-arrhythmics, and 3) perturbation of hERG currents (either facilitation or inhibition, depending on drug concentrations). A comprehensive FDA review of these has been recently performed by LS Leshin (see citation above). In the clinical arena, a sufficient deterioration of any of these functions, if caused by P and NP alone or through a dynamic interaction of these drugs with other patient risk factors would lead to substantial reduction in cardiac performance or life-threatening arrhythmias. Some salient findings in considering such scenarios are highlighted below:

- A retrospective review of 222 consecutive Danish patients admitted to ICU with acute propoxyphene poisoning in which propoxyphene was the only drug ingested

(44%) or was regarded as the main toxic substance in a background of use of either alcohol or other drugs (56%) included 17 with death as an outcome (Madsen et al. Acta Anaesthesiol Scand, 1984). In the elderly group (age over 50 yrs) of patients that died (11/17) cardiac failure predominated as the cause of death. In this review, blood levels of P and NP were not included.

- A pig model of IV propoxyphene-induced cardiac insufficiency and circulatory shock was tested to determine whether cardiac pacing would reverse the reductions in cardiac index and systemic arterial pressure. Lack of reversal of the circulatory failure by increasing the heart beats per minute alone highlights the profound negative inotropy caused by propoxyphene in this model (Strom et al., Clin. Toxicol., 1985). In a separate study using the pig model, circulatory failure was reversed by dopamine infusion and not naloxone, suggesting that propoxyphene suppression of cardiac inotropy, which occurs through a non-opioid receptor mediated mechanism, must be pharmacologically reversed to gain physiological improvement (Strom et al., Acta Anaesthesiol. Scand., 1985).
- 12 patients with cardiovascular failure caused by propoxyphene were treated with dopamine, an inotrope and chronotrope (Krantz et al., Acta Anaeshesiol. Scand., 1986). The patients responded with significant improvements in cardiac and circulatory performance.
- A variety of in vitro models have been used to test dose-dependent P and NP inotropic effects. These include in vitro studies of Purkinje fibers of dogs and guinea pig atria and isolated ventricular papillary muscle of cats. Across these models, P and NP have significant negative inotropic effects at concentrations of 10 μM (1.0 μg/ml). The effect of NP is slightly higher than P and there is an additive effect with both together. Isolated papillary muscle contractile responses to other opioids, including methadone, and pentazocine, meperidine, morphine, fentanyl and piritramide have also been studied by different investigators. With virtually all opioids, at high concentrations there are dose-dependent decreases in contractility. However, among most of the opioids that so far have been tested, suppressive effects on contractility either 1) occur at drug concentrations significantly higher than 10 μM and/or 2) are of little significance when standardized to relative analgesic potency (Cmax levels measured at steady state in therapeutically-dosed individuals would be far below the concentrations associated with suppression). Nonetheless, it should be emphasized that a comparative evaluation is primarily based on the interpolation of different studies, which have utilized different techniques tissue sources, etc. To date, a systematic head-to-head comparison of dose-related effects of similarly utilized opioids and their principal metabolites, including P, NP, codeine and tramadol, using a panel of validated in vitro models to comprehensively test 1) suppression of cardiac muscle contractility, and 2) perturbations of Na+ channel, and hERG channel functions has not been performed.
- Except for methadone, the opioids morphine, meperidine, fentanyl, petazocine and perhaps tramadol show negative inotropic effects on cardiac muscle at doses 10-1000-fold greater than average C-max values indicated in labels for these drugs (Rendig et al., J. Pharmacol. Exp. Ther., 1980). No Cmax PK information is provided for codeine. However, dose-response effects across the aforementioned in vitro inotropy models directly comparing P and N with other equivalent members of

the opioid class (in particular codeine, tramadol/M1 metabolite [O-desmethyl tramadol], hydrocodone, etc.) have not been systematically assessed.

- NP and P are both inhibitors of sodium influx across the Na+ channel, with NP showing comparatively more activity. Both these agents show slow dissociation kinetics compared to another inhibitor, lidocaine. Widening of the QRS reflects this dose-related effect, may result in conduction delays at the AV node and Bundle of His, bradycardia, and if extreme – asystole. It is not inconceivable that synergistic or additive toxic effects with drugs that impair conduction, ion abnormalities or genomic variants associated with functional impairment could lead to clinically serious effects. Unfortunately, the potential for such interactions has not been adequately studied. Whether combined or even synergistic effects of hypokalemia or hyperkalemia with heightened NP and P levels disrupt normal cardiac conduction during acute kidney injury is of concern and requires elucidation.
- A study in Xenopus oocytes has revealed that 5μM concentrations of both P and NP facilitate hERG currents, whereas when the concentrations rise, an opposite slowing effect occurs (Ulens et al., Cardiovasc. Res., 1999). However, measurements using this test system are known to substantially underestimate concentrations of agents that cause hERG inhibition.
- The effects of P and NP on cardiac conduction in the presence of genomic variants of hERG associated with functional impairment, other drugs that disturb normal channel functions, or ion abnormalities that influence cell membrane depolarization or re-polarization are unknown. Risk for adverse effects with drugs that lengthen the Q-T interval in the presence of elevated P and NP levels may be significant.

Post-mortem toxicologic studies of propoxyphene overdose deaths

A number of studies have linked propoxyphene-associated deaths with post-mortem levels in blood and other tissues. The importance of such studies is that they may provide important insights concerning the margins between minimum lethal levels of P/NP for some individuals and upper the range of Cmax of these compounds measured under normal therapeutic circumstances.

- From a survey of medical examiners addressing propoxypene-related deaths (1972-1975) in a geographical region covering 21% of the US population, 1022 cases were analyzed (Finkle et al., J Forens. Sci., 1976). In the subset of cases which involved propoxyphene alone, 14 (9.8%) were found to have P levels of 1,000 ng/ml or less (5 cases reported P levels in the range of 200-500 ng/ml). Nonetheless, across the whole series in which many of the deaths not only involved propoxyphene but other drugs such as hypnotics and/or alcohol, most of the fatal P blood concentrations ranged from 1,000 to 4,000 ng/ml. As described above, in a few of the cases described in this series measured P levels appear to be close or even overlapping with those measured in multiple dose propoxyphene PK studies in some normal volunteers (see above). In a separate study of 117 accidental or intentional deaths (1976-1978) from propoxyphene only, the same authors (Finkle et al., J Forens. Sci, 1981) provided post-mortem blood concentrations of both P and NP. The measurements of these compounds varied widely, but in some of the

cases measures of P and/or NP were within the range of therapeutic levels measured in PK studies of volunteers described above (e.g. Flanagan et al, Br J Clin Pharm., 1989). From these findings, there does not appear to be an absolute universal lethal threshold and there was considerable overlap in P and NP concentrations in those that died with individuals who recover.

- In a study of 100 consecutive propoxyphene-related death cases recorded by the Chief Medical Examiner of North Carolina (Hudson et al., S. Med. J., 1977), among 51 that did not involve other drugs or alcohol in which blood P concentrations were obtained, the average concentration was 8000 ng/ml, ranging between 2000 ng/ml and 27,000 ng/ml, well above therapeutic levels in the PK studies that have been described.
- In a study of 19 propoxyphene-related death cases 6/19 had measured P blood levels of 1,000 ng/ml, whereas the other cases showed higher levels of this compound (Rejent et al., Clin, Toxicol., 1977).
- Although there are possible differences in the gas chromatographic and derivative ultraviolet spectrophotometric methods used to measure P and NP in the post-mortem studies described above, compared to the HPLC method used in PK studies, they are generally accurate and quantitatively reliable.
- Toxicity is a function of the combined effects of P and NP. NP was only measured in one of the post-mortem studies (see above) such that its contribution to the toxicologic profile of propoxyphene in deaths is less studied.
- Toxicity could most directly be related to tissue levels (i.e. brain, heart, etc.) of P and NP. In this regard, blood levels are indirect, though often reliable, predictors of toxicity. It is notable that distribution of P and NP between blood and tissue compartments has been observed to be highly variable in post-mortem studies, depending on whether propoxyphene was acutely or chronically dosed, the time after last dose, and other factors. The degree to which redistribution of propoxyphene and its metabolites may occur after death has not been fully studied as well as the conditions and time parameters that would underlie such an effect. These questions bear a need for further study. However, given the relatively higher tissue concentrations compared to blood after propoxyphene administration, it is unlikely that substantial net fluxing of P and NP from blood into tissue occurs post-mortem. Thus, the presence of low levels of P and NP in propoxyphene deaths in some of the autopsy studies that have been cited, which are overlapping or close to levels measured in PK studies of volunteers, is of continuing concern.
- Absence of a large published series of post-mortem P and NP measurements of autopsy specimens obtained from individuals with sudden death who were therapeutically treated with propoxyphene by itself may not be reassuring. For reasons listed above, such individuals deemed to have died from natural causes typically may not be referred for toxicological evaluation, post-mortem.
- With possible pre-disposing conditions that may compromise normal heart functions in some individuals, it is difficult to rule out whether the lowest tier of post-mortem blood concentrations of P and NP that have been measured (i.e. P $\leq$ 1,000 ng/ml) would match or exceed concentration thresholds for cardiotoxicity identified in pre-clinical studies (P~10 μM), either to suppress inotropy or disturb conduction. As discussed above, other opioids, such as meperidine and morphine

suppress inotropy, but only at substantially higher concentrations. Moreover, a series of propoxyphene overdose cases cited above (Madsen et al., Acta Anaesthesiol Scand, 1984) showed that a high percentage of the propoxyphene-related deaths that occurred in older patients were caused by heart failure. In addition, in some individuals, conduction disturbances, QRS widening, bradycardia, asystole and other cardiac arrhythmias were observed. Unfortunately, this series did not provide data on P or NP blood levels, so that a toxico-pharmacologic correlation was not possible.

Synthesis of current concern and gaps in data

When all these data are taken together, excess dosing of propoxyphene can lead to rapid death from centrally-mediated respiratory depression, circulatory failure and/or direct cardiac toxicity. The narrow therapeutic index of propoxyphene and risk of death from intentional or accidental overdosing is a feature shared with other opioids. However, the profile of cardiac toxicity caused by both P and NP appears to likely distinguish propoxyphene from most other opioids. It is also notable that post-mortem blood levels of P from a small percentage of propoxyphene death cases appear to be close or even overlapping with upper bound measurements of P measured in multiple dose PK studies in 'outlier' elderly normal test volunteers. Although the proportion of this subset of propoxyphene lethal overdose cases referred to coroners for investigation is small, therapeutic misadventures in highly susceptible individuals who were adhering to product label dosing instructions (a third category of excess dosing to be considered in conjunction with suicide and accidental overdose) may be under-represented. It is not inconceivable that deaths, if they occur in this category, might be ascribed by health care providers to natural causes and not further evaluated.

In therapeutic settings concern about a potential for propoxyphene to exceed toxic threshold levels in susceptible individuals, without intentional or accidental overdose, is further accentuated by 1) the observed reduction in clearance of P and NP that takes place in the presence of reduced renal function, 2) the frequent presence of underlying cardiac conditions and/or ion concentration abnormalities in older patients which might predispose them to develop cardiac failure and/or life-threatening arrhythmias, even when P and NP levels are not exceedingly high, and 3) the very high volume of distribution of P compared to other opioids, reflected by higher concentrations of P and NP in target organs of toxicity (e.g. heart) compared to blood. Concern about differential cardiac toxicity associated with propoxyphene compared to other opioids is also fueled by the prediction that overall redistribution of drug into tissues of similarly utilized opioids is substantially lower than the transfer observed with P and NP.

Given the measured effects that P and NP have on both Na+ and K+ ion fluxes across cardiac cell plasma membranes during phases of depolarization and repolarization, the degree that individual susceptibility factors would play a role to potentiate propoxyphene-induced life-threatening arrhythmias and/or sudden cardiac death is unknown. In general, these risk factors could include structural heart disease, ischemic heart disease, coronary

anomalies, myocarditis, cardiomyopathies, Wolf-Parkinson-White Syndrome and the emerging family of genetically determined K+ and Na+ Channelopathies (Long-QT syndromes and Brugada syndrome).

Unsettled issues in regards to comparative toxicity of propoxyphene with other opioids
Serious ongoing concerns about benefit/risk of propoxyphene are tempered by the observation that different opioids can have distinct toxicity profiles other than class-wide effects such as respiratory depression, reduced vascular tone, drug withdrawal, etc., that bear consideration. For example, tramadol may precipitate seizures. In addition, in concert with its inhibition of reuptake of norepinephrine and serotonin this agent alone or with the concomitant use of serotonergic drugs can induce serotonin syndrome.

As described above, the dose-related effects of P and NP on cardiac inotropy, Na+ channels and hERG channels can be measured using a number of currently available in vitro cellular and isolated muscle models, in conjunction with pre-clinical animal models. It is important to note that in vitro studies of some other opioids have also shown suppressive effects on cardiac muscle contractility. However, 1) the suppression occurs at comparatively higher concentrations than those of P and N which cause the effect and/or 2) because of higher analgesic potencies compared to propoxyphene, concentrations linked to these in vitro effects are substantially higher than therapeutic blood levels measured in PK studies. Nonetheless, a systematic head-to-head comparison of dose-related effects of N and P with the other opioids (and their major metabolites) that are currently used to manage mild to moderate pain (e.g. codeine, tramadol, etc.) is currently lacking. In particular, a comprehensive comparative dose ranging study on drug-induced 1) suppression of contractility, as well as 2) perturbations of Na+ channel and hERG channel functions, using a panel of currently applied in vitro models has not been performed.

Predicting whether the risk for developing toxic drug blood levels in the presence of renal insufficiency is worse for propoxyphene than other opioids is problematic. Since P and NP are cleared by the kidneys, it is not a surprise that the circulating half-lives of these compounds increase as renal function diminishes. Moreover, after a single dose of propoxyphene, the Cmax of P doubles in anephric individuals (see above). Unfortunately, pK information provided for other product labels is not comprehensive. Although the codeine product labels indicate that the drug is 90% renally excreted, information about the relationship of reduction in drug clearance or effects on Cmax with changes in creatinine clearance is not provided. Although 30% of a dose of tramadol is eliminated unchanged by the kidneys, according to the product label no consistent trend has been observed for systemic exposure to this drug, even in patients with moderate renal impairment. In contrast, exposure to M1, a principal tramadol metabolite increases with renal insufficiency, leading to a recommendation that tramadol should not be used in patients with severe renal impairment. In the acetaminophen-hydrocodone product label (Vicodin) there is little information provided on the impact of renal function changes on hydrocodone blood levels or clearance, other than the assertion that hydrocodone is substantially secreted by the kidney with an instruction that care be taken in dose selection in individuals with decreased renal function, such as the elderly. Without quantitative information on therapeutic indices of these drugs and defined blood levels that depress respiration, it is

difficult to predict a quantitative relationship between creatinine clearance reductions and toxic outcomes.

Pending studies

Planned Thorough QT studies by Propoxyphene sponsor in Normal Volunteers
After the January 30, 2009 Advisory Committee meeting FDA issued a letter on August 8, 2009 to Xanodyne, the sponsor of Darvon and Darvocet products requesting the performance of a clinical trial to assess the risk of QT prolongation with propoxyphene. Subsequently, draft protocols were submitted by the sponsor and reviewed by FDA that culminated in the development of 2 clinical trial protocols. The first protocol (XP20C-101) has the objective of determining the daily 'supratherapeutic' maximum tolerated dose of propoxyphene napsylate in *healthy subjects* (18-49 years of age) as a prelude to the performance of a separate thorough QTc study. In the first study, 6 cohorts of 8 subjects will be treated with a specified dose of propoxyphene or placebo for 10 days. The daily propoxyphene doses that will be tested range between 600 mg up to 2400 mg. Dose escalation in successive cohorts will not proceed to the next dose level if there is evidence of a reduction in general safety and/or tolerability. Patients will be assessed clinically and with ECG and Holter monitoring, lab tests, etc. In addition they will undergo sample collection for PK analysis of P and NP. The highest dose level in the aforementioned range of doses that is found to be both safe and tolerable will then be applied to a second planned study (XP20C-102). This study will be a 3 arm, 12 day exposure study of *healthy volunteers* (18-49 years of age; 48 subjects per treatment arm) receiving the maximum recommended dose of propoxyphene (600 mg/day), the 'supratherapeutic' maximum tolerated dose, or a control agent [Q-Tc lengthening control drug (moxifloxacin, 400 mg) cross-over to/from placebo]. Volunteers with abnormal baseline EKGs, underlying conditions (including significant cardiovascular disease), or treatments which may put them at risk will be excluded from the study. It is evident that individuals who may be predisposed to pronounced cardiotoxic effects associated with borderline elevations of P and NP (e.g. elderly, cardiac and/or renal disease, etc.) will be excluded from these studies.

Planned New Epidemiological Studies
To gain more epidemiological data to assess the risk for death and life-threatening outcomes among users of propoxyphene including the elderly patients (65 years and older), the following medical claims based databases and outcomes will be investigated[3]:

- Tennessee Medicaid database – Sudden Death (1994-2008)
- Medicare database (2006 2009) – Death
- Medicaid database (2000 -2009) – Death
- Other HMOs - cardiac arrhythmias, liver failure, heart failure, and death

Utilizing social security patient identifiers, the Medicare and Medicaid databases capture medical and pharmacy encounters in the outpatient, inpatient (pharmacy) and skilled

[3] Dr. Rita Ouellet-Hellstrom, Ph. D., Epidemiologist Team Leader in the Division of Epidemiology provided valuable information for this section.

nursing facilities including nursing home. Deaths and sudden death codes will be linked with propoxyphene exposure and compared to codeine, hydrocodone and tramadol exposures. Stratification based on prior history of CV disease, CHF, liver impairment and renal deficiency, etc. will also be possible in some databases.

The Tennessee Medicaid database study (but not the Medicare database) can be linked to Medical Records and Death certificates, enabling an algorithmic analysis in which suicides and drug abuse cases can be excluded. A start date of April 1, 2010 has been planned for this study. It will be conducted over a number of phases, with a 2nd phase scheduled to begin in 2011.

The HMO study will attempt to estimate the incidence of cardiac arrhythmias (ventricular fibrillation/flutter), death, heart failure, and liver failure in new users of propoxyphene compared to new users of comparator opioids tramadol, codeine, and hydrocodone. Because of the availability of medical records (including electronic), EKGs, and laboratory results, this study also proposes to develop claims- and electronic medical record-based algorithms to identify cardiac dysrhythmias that may be associated with weak opioid use, and to validate cardiac outcomes using medical record encounter data that include EKGs and laboratory data. This study will also attempt to determine whether pre-existing cardiovascular disease or risk factors, hepatic impairment, and renal impairment affect the risk of adverse cardiac effects in propoxyphene by comparing new users of propoxyphene to new users of comparator opioids, tramadol, codeine, and hydrocodone with and without these co-morbidities.

In all databases reviewed to date, approximately 70% of propoxyphene and comparator exposure is ascribed to single prescription use.

Other databases in which feasibility studies for propoxyphene associated sudden deaths can be performed include VA and DOD.

All of these epidemiological studies present the following challenges:

- The actual doses will not be consistently ascertained for propoxyphene and comparators
- The sub-categories of propoxyphene- and comparator-related deaths (suicide, accidental overdose with drug abuse, excess dosing within therapeutic range in susceptible patients, natural causes, etc.) may not be consistently ascertained
- The P and NP blood levels will not be ascertained
- The sudden death cases in health care systems may not be consistently ascertained or coded although there is no reason to believe that the imbalance would favor one treatment (propoxyphene) over the comparators (codeine, tramadol or hydrocodone)
- The coding of causes of death (e.g. heart failure, arrhythmia, respiratory depression, etc.) may not be uniformly captured and documented in the medical records or death certificates although there is no reason to believe that the imbalance would favor one treatment (propoxyphene) over the comparators (codeine, tramadol or hydrocodone)

- The EKGs and lab data surrounding sudden deaths will often be absent in the Medicare and Medicaid databases although these data would be available in the HMO study
- There is no plan to apply propensity scoring as a statistical method for matching similar patients using propoxyphene vs the comparators. Thus, it will be difficult to definitively eliminate treatment biases, channeling, etc.

With these short-comings, it may be difficult to draw definitive conclusions about the relative cardiotoxic risk of therapeutic or near therapeutic doses of propoxyphene for sudden death in patients including the elderly, compared to drugs such as tramadol and codeine. In addition, the expected time required to obtain results from this wave of studies will be at a minimum a few years. However, as a natural experiment, these studies might provide insight on the burden of mortality for an exposed population, where direct QT studies are not possible.

A Path forward: Options to Consider

For a number of years, the benefit/risk of propoxyphene in the management of mild to moderate pain has been called into question. Although an evaluation of the cumulative data supporting the effectiveness of propoxyphene as an analgesic, either alone or in combination with acetaminophen is outside of the scope of this review, it is evident that this agent has relatively weak analgesic activity compared with many opioids. Either alone or in combination with acetaminophen, propoxyphene has not been convincingly shown to be superior to other non-opioid analgesics. With the high rates of fatality in drug overdose cases, the CHMP concluded on June 25, 2009 that the benefit-risk balance of propoxyphene is negative and that it should be withdrawn from EMEA member states. This follows a similar conclusion made by regulatory authorities in the UK in January 2005 that led to its final withdrawal on December 31, 2007. In the US, positions taken by the American Society of Health-System Pharmacists (December 5, 2008) and Public Citizen (February 28, 2006) have also advocated withdrawal of propoxyphene. With FDA's decision in 2009 to deny Public Citizen's petition for withdrawal of propoxyphene from the US market, ongoing analysis of issues surrounding the request continues. At this time, from this reviewer's perspective, 3 options are available to consider.

Option 1: *Defer reconsideration of the status of propoxyphene marketing until new epidemiological studies are completed and reviewed.*

With a possibility of increased use of other opioids or analgesics that could be substituted for propoxyphene products if they are withdrawn from marketing, in the aggregate, it is conceivable that the levels of drug-related suicide and accidental deaths may not substantially change. In addition, the potential of replacing risk associated with propoxyphene with a new set of risks associated with either non-opioids (e.g. acetaminophen and NSAIDs) or other opioids (codeine, tramadol, hydrocodeine, etc.) may create unintended consequences. [However, predicting the impact on overdose deaths in

the US must be approached cautiously. As discussed above, after a steep reduction in prescribing levels of propoxyphene products that took place after 2005 in the UK, offset use of other analgesics to preserve the same level of suicides in a time series analysis was not observed].

Despite continuing concern, studies to date have not directly identified a significantly sized cohort of elderly patients who have inadvertently developed life-threatening propoxyphene associated cardiotoxicity while taking therapeutic or near therapeutic doses of this product. Lack of identification of such individuals is difficult to interpret since it may reflect inherent limitations in the recognition of such events when they occur, especially in an outpatient setting. Although post-mortem P/NP levels in propoxyphene over-dose deaths are partially overlapping with Cmax levels measured in some elderly volunteers in multiple dose pK studies, virtually all the overdose deaths identified in coroner-based studies appear to have been attributable either to suicide or accidental overdose, and not therapeutic misadventures in the elderly. Completion of the planned US epidemiological studies in the next few years may point to or exclude this latter category as having an overall impact in propoxyphene-related deaths. However, as discussed above, there are important limitations to consider on the overall impact they may have on regulatory decision making. First, lingering concerns about the ascertainment of propoxyphene-related deaths will be based on linkages between prescription databases and ICD-9 outcomes, with in some instances verification by linkage to death certificate information. For a variety of reasons, at a case level, with information that will be available, complete and/or accurate capture of all propoxyphene overdose deaths will be difficult to unequivocally validate. Second, and more importantly, uncertainty about attribution of cause of death in the elderly prescribed propoxyphene (i.e. deaths caused by the drug versus unrelated natural causes, background diseases not exacerbated by propoxyphene, etc.) may persist. Third, the planning, feasibility testing, execution, analysis and integration steps for such a composite of complex epidemiological studies will take at a minimum 1-2 years. Such a 'wait and see' time frame would only be justified if it is expected that major uncertainties surrounding propoxyphene-associated risk will be addressed by these studies.

Given the inevitable clinical circumstances and data capture limitations that have been discussed, attribution of cause of death in individual 'natural cause' cases will be plagued with significant uncertainties. With such limitations in the planned epidemiological studies, absence of unequivocal findings of significant hazard for unintentional propoxyphene-induced deaths is unlikely to put the issue to rest. Thus, although they will have an important role to play in the analysis of US patterns of drug utilization, patient characteristics, etc., these studies alone may not provide results that will be a primary driver of regulatory decision-making. For this reason, if results of studies described in Option 2 are convincing (see below) a phased withdrawal of propoxyphene would be justified, even in the absence of new epidemiological data.

Option 2: *Defer reconsideration of the status of propoxyphene marketing until the completion and review of a battery of comprehensive dose-ranging studies that will measure the effects of propoxyphene and norproxyphene on cardiac inotropy and conduction, side-by-side with other opioids (e.g. tramadol, codeine, hydrocodone,*

morphine, etc.). These studies will utilize in vitro and in vivo animal test systems that are currently available to assess concentration-dependent pharmaco-toxicologic effects on cardiac conduction and inotropy, typically with reference controls. Dr. John Koerner, Ph.D., a senior pharmacologist in DCRP, provided invaluable input for the development of this option.

FDA would request the propoxyphene sponsor and/or neutral party experts who could be contracted to perform comprehensive dose ranging comparative studies using assays they have established to measure the cardiac effects of propoxyphene and norproxyphene, *side-by-side* with other opioids, including tramadol, codeine, hydrocodone, morphine, etc. An analysis of measured dose-response effects should take into account previously performed pK measurements in human study subjects as well as re-distribution of tested drugs and their key metabolites into cardiac tissue.

Studies should include but not be limited to the following:

- In vitro voltage clamp studies on cardiac ionic currents (cloned cardiac channels in mammalian cell lines). Channels that would be tested include INa, ICaL, hERG, other K channels. One goal of testing of INa is to determine whether P and NP act as 1A, 1B or 1C antiarrhythmic agents, since the result may have implications as to the proarrhythmic potential of propoxyphene and its metabolite.

- In vitro studies of cardiac contractile force/tension in isolated cardiac tissues (e.g. guinea pig papillary muscle).

- In vivo studies of cardiac contractility in healthy animals. Measurements of left ventricular dP/dt and heart rates as well as BP and ECG measurements (PR, QRS, Q-T intervals, etc.) would be performed.

- In vivo measurements of myocardial vs plasma drug levels in healthy animals after oral and IV administration of drugs.

- In vivo precipitation of worsening disease states in animal disease models. Administration of drugs to animal models prone to CHF or arrhythmias. Measurements and characterization of cardiac performance and arrhythmias, as well as sudden death would be performed.

- Post-mortem redistribution of drug and metabolites between tissues and plasma in an animal model(s).

It is likely that the planning, performance, analysis and review of most of the in vitro and in vivo tests in animal models as described above could be performed relatively expeditiously. These would probably be finalized before results of the aforementioned epidemiological studies would become available. If findings of these in vitro and animal studies point to an interpretation that P and NP have a significant disruptive impact either on cardiac ionic currents and/or inotropy at tissue or plasma levels that are equivalent to those that occur at

therapeutic doses in patients, while other tested agents do not, a regulatory conclusion for market withdrawal would likely be justified. This is especially the case if physiologically relevant EKG changes induced by propoxyphene (e.g. Q-T, P-R, and/or QRS interval lengthening) are also observed in volunteers enrolled by Xanodyne in Studies XP20C-101 and XP20C-102 (see Pending Studies).

Option 3: *Initiate a phased withdrawal of propoxyphene based on current information.*

There is an ongoing concern about 1) the narrow therapeutic index of propoxyphene, 2) the observed high relative frequency of death after suicidal or accidental overdose, 3) the partial overlap of post-mortem P and NP blood levels in death cases with pK measurements in volunteers, 4) the relatively high distribution of P and NP from blood to cardiac and other tissues and 5) the plausibility of life-threatening cardiotoxicity associated with therapeutic or near therapeutic doses of propoxyphene in patients with susceptibility risk factors. However, there remain important gaps and uncertainties in assessing risk of this product relative to other opioid analgesics. In addition to questions surrounding the reliability of post-mortem measurements of P and NP blood levels, it has been difficult to directly identify patients who experienced sudden death as a consequence of a therapeutic misadventure, while using recommended or close to recommended doses of propoxyphene. There is a paucity of side-by-side cardiotoxicity testing and analysis of drug concentration effects with in vitro and animal models among members of the opioid class. Furthermore, propoxyphene dose-associated effects on EKG parameters in human volunteers will only now be formally studied. Finally, a prediction that propoxyphene withdrawal will lead to a reduction of opioid-related suicides (as observed in the UK) and accidental deaths in the US is speculative.

Nonetheless, a conclusion that a phased propoxyphene withdrawal should be taken by FDA without waiting for results from additional studies has merit. It would be supported by 1) the suggestion from DAWN and US medical examiner data (when controlling for prescription availability) that lethality is higher with propoxyphene than with tramadol or hydrocodone, 2) the prediction that such an action may have a salutary public health effect on aggregate suicides and accidental deaths in the US associated with opioids, 3) the narrow therapeutic index of the drug and its worrisome potential for cardiotoxicity in individuals susceptible to a ‘therapeutic misadventure’ when P and NP blood levels are close to those measured with therapeutic doses, 4) the modest if not low analgesic effectiveness of propoxyphene compared with other analgesics, and 5) the availability of other opioid and non-opioid agents to manage mild to moderate pain.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-10997	ORIG-1	XANODYNE PHARMACEUTICS INC	DARVON (PROPOXYPHENE HYDROCHLROIDE) CAPS

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARK I AVIGAN
06/10/2010

GERALD J DALPAN
06/13/2010
I will address Dr. Avigan's points in a follow-up memorandum.