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Dockets Management Branch
U.S. Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

**COMMENTS ON CITIZEN PETITION
Docket No. 2006P-0090**

The undersigned, on behalf of Xanodyne Pharmaceuticals, Inc. ("Xanodyne"), which markets Darvocet A500[®] (propoxyphene napsylate and acetaminophen), Darvocet-N[®] 50 (propoxyphene napsylate and acetaminophen), Darvocet-N[®] 100 (propoxyphene napsylate and acetaminophen), Darvon[®] (propoxyphene hydrochloride), and Darvon-N[®] (propoxyphene napsylate), submits these Comments to the February 28, 2006, Citizen Petition filed by Public Citizen.

For the reasons discussed below, the Petition should be denied.

I. OVERVIEW

Public Citizen's February 28, 2006, Citizen Petition requests that the United States Food and Drug Administration (FDA) immediately begin the phased removal of propoxyphene-containing drug products from the marketplace. Drug product approval may be removed only under specific circumstances as set forth in the Federal Food, Drug, and Cosmetic Act and its implementing regulations. The Secretary of the Department of Health and Human Services may withdraw approval of an application or abbreviated application for a new drug if he or she finds it presents an "imminent hazard" to the public health. In the alternative, FDA may remove approval after it determines that clinical or scientific data demonstrate the drug is unsafe under the conditions of use for which the product is approved and labeled or that there is a lack of substantial evidence from adequate and well-controlled studies that the drug will have the effect it purports to have under the conditions of use prescribed in its labeling.

In this case, Petitioner does not contend that propoxyphene represents an "imminent hazard." Therefore, these products may be removed by FDA only upon a determination that they are

2006P-0090

C 1

Dockets Management Branch

April 14, 2006

Page 2

unsafe or ineffective. Public Citizen's Petition fails to present credible scientific evidence that propoxyphene drugs are unsafe or ineffective when used according to approved labeling.¹

More than 25 years ago, Public Citizen similarly petitioned FDA to remove propoxyphene drugs from the market. The group has now repeated its removal request, supported with little more than the data it presented in its 1978 Citizen Petition, which was denied in 1979 by the Department of Health, Education, and Welfare (HEW) (the predecessor of the Department of Health and Human Services). Public Citizen's Petition does not raise any new safety or efficacy issues that have not already been considered by FDA. For nearly 50 years, FDA, along with other national governmental bodies tasked with regulating pharmaceutical products, have carefully watched over the use of propoxyphene drugs and have considered propoxyphene safe and effective when taken as directed. While all prescription and over-the-counter pharmaceutical products carry some risks, propoxyphene has a long history of safe use in the United States and is an essential option in the treatment of mild to moderate pain.

Pain, a condition that stems from many diverse disease processes and conditions, is highly subjective and varies based on its source and duration. Acute pain generally results from injury, surgery, or sudden illness, and typically resolves as the body heals, while chronic pain is often tied to disease or injury. Whether chronic or acute, pain can significantly affect functioning and reduce a patient's quality of life. The diversity and subjectivity of pain make it difficult to treat, thereby necessitating a wide variety of therapeutic options.

Propoxyphene has been one of the most widely prescribed treatments for mild to moderate pain since FDA first approved Darvon nearly 50 years ago. Propoxyphene was first approved in the 1950s based on its safety. Subsequently, pursuant to the Kefauver-Harris Drug Amendments of 1962, propoxyphene underwent a second, independent evaluation of the product's efficacy. This second evaluation found the drug efficacious in the treatment of mild to moderate pain. The product's safety and efficacy was reaffirmed each time a new propoxyphene drug product was reviewed and approved by FDA, including where sponsors requested new formulations, new strengths, and new combinations of the product with other active ingredients. As recently as 2003, FDA approved a Darvocet line extension, Darvocet A500 (propoxyphene napsylate and acetaminophen), and subsequently approved a generic version of that same product in 2006.

¹ In addition, Petitioner fails to acknowledge that other requirements must be satisfied before a product may be withdrawn from the market, including notice to all applicants and opportunity for a hearing. *See* 21 U.S.C. § 355(e); *see also* 21 C.F.R. § 314.150.

Dockets Management Branch

April 14, 2006

Page 3

As with all drugs, there are risks associated with propoxyphene use, including deaths associated with overdose and concomitant use with drugs and/or alcohol, and drug addiction. However, these risks have not prevented the safe use of propoxyphene in accordance with the approved prescribing information. The safe and appropriate use of propoxyphene is further safeguarded by its classification as a Schedule IV drug under the Controlled Substances Act. As a Schedule IV controlled substance, propoxyphene drugs are subject to specific registration, security, labeling and packaging, inventory and recordkeeping, import/export, and prescription requirements.²

Public Citizen's 1978 Petition requested a propoxyphene ban based on an alleged "imminent threat" the drug presented to the public health. After considering the 1978 Petition, HEW found there to be no imminent threat, declined to remove the drug from the market, and denied the Petition. As with the denied 1978 Petition, Public Citizen's 2006 Petition provides no credible scientific evidence to support an FDA withdrawal of the products.

Instead, Public Citizen approaches its 2006 Citizen Petition with inaccurate and misleading data and information to summarily suggest that propoxyphene drug products should be removed because the products are unsafe and not effective. Public Citizen provides no legitimate scientific or clinical evidence that propoxyphene products are not safe or effective when used according to the approved labeling. Rather, Public Citizen relies upon strained interpretations of the public literature and unpublished "personal communications," unsubstantiated claims regarding the effect of a propoxyphene metabolite, conclusory summaries of compilation data without true causal analyses, and largely irrelevant data from non-U.S. populations and dissimilar drug usage, bearing little correlation to the propoxyphene products utilized in the United States. Additionally, Public Citizen's reliance on the United Kingdom's (U.K.'s) experience with co-proxamol is misplaced and not relevant in the United States; as discussed below, in the U.K., the composition, use, and availability of propoxyphene-containing products is not compatible with the propoxyphene products in United States, where the drugs are regulated as controlled substances.

In failing to meet the necessary scientific and statutory evidentiary standard, Public Citizen's Petition should be denied.

² See 21 U.S.C. Chapter 13, 21 C.F.R. Part 1300 *et seq.*

II. PROPOXYPHENE-CONTAINING PRODUCTS ARE SAFE AND EFFECTIVE

A. The Petition does not raise new safety or efficacy concerns.

For nearly 50 years, propoxyphene drugs have been considered safe and effective when taken as directed. Physicians have long found propoxyphene products to be safe and useful drugs in the treatment of mild to moderate pain. As a result, propoxyphene has been, and continues to be, widely prescribed. Since its first approval nearly 50 years ago, it is estimated that more than 600 million prescriptions for propoxyphene drugs have been dispensed. In 2005, over 26 million prescriptions were filled, making it one of the twenty-five most commonly prescribed drugs. Propoxyphene drugs are also used throughout the world, including in South America, Europe, Africa, Australia, and Asia. In addition to the fact that propoxyphene has been used for nearly 50 years to safely and effectively treat many millions of patients with pain, the extensive regulatory history of these drugs offers further support for their continued availability.

1. FDA has approved propoxyphene as safe and effective.

The Petition does not present information or data that FDA has not already evaluated and considered. FDA first reviewed the safety of propoxyphene-containing drugs when Eli Lilly and Company (Lilly) submitted new drug applications (NDAs) for its Darvon products in the 1950s. Following FDA approval of the Darvon products, Lilly began marketing the drug as a single agent, containing a dose of either 32 mg or 65 mg propoxyphene hydrochloride, and in combination with aspirin, phenacetin, and caffeine.

After the Kefauver-Harris Drug Amendments of 1962, which in part required the effectiveness of a drug to be established prior to marketing, FDA commenced a Drug Efficacy Study to review drug products approved before 1962 on the basis of safety alone. The National Academy of Sciences/National Research Council (NAS/NRC) Drug Efficacy Study Group specifically evaluated studies related to the efficacy of propoxyphene drugs, and concluded they are effective for the relief of pain. Based on the panel's recommendations, FDA issued a Drug Efficacy Study Implementation ("DESI") notice, confirming the efficacy of Darvon products for the treatment of mild to moderate pain, and approving the continued marketing of 65-mg formulations.³ The

³ 34 Fed. Reg. 6264 (April 8, 1969).

Dockets Management Branch

April 14, 2006

Page 5

DESI notice permitted the 32-mg formulation to remain on the market for the purpose of treating patients for whom that dosage was shown to be effective.⁴

Subsequent to the DESI review, FDA periodically reviewed the safety and efficacy of modified propoxyphene formulations when Lilly submitted NDAs for drugs containing the napsylate salt of propoxyphene, either alone or in combination with acetaminophen. In 1972, after considering the differences between the dosing of the hydrochloride and napsylate salts of propoxyphene, FDA approved these products based on standards of safety and efficacy.⁵

2. FDA has re-examined the safety and efficacy of propoxyphene.

In addition to FDA's specific approval of a number of propoxyphene drugs, such as propoxyphene hydrochloride, propoxyphene napsylate, and propoxyphene/acetaminophen in combination, as both safe and effective, FDA and HEW have re-evaluated the safety and efficacy of propoxyphene-containing products. In November 1978, the Health Research Group of Public Citizen petitioned HEW to either: (1) immediately ban marketing of propoxyphene as an "imminent hazard" under 21 U.S.C. § 355(e) and make it available only as an investigational drug for treating narcotics addicts, or (2) reschedule it as a Schedule II narcotic under the Controlled Substances Act.⁶ In response to the 1978 Petition, FDA Commissioner Donald Kennedy and FDA's Bureau of Drugs evaluated the scientific and medical issues related to

⁴ 37 Fed. Reg. 26538 (Dec. 13, 1972).

⁵ For a discussion of the differences between the propoxyphene HCl and napsylate salts, see *infra* section IV.

⁶ Citizen Petition from Sidney M. Wolfe, M.D. and Public Citizen Health Research Group, to Joseph Califano, Secretary, Dept. of HEW (Nov. 21, 1978) (on file with FDA).

Dockets Management Branch
April 14, 2006
Page 6

propoxyphene.⁷ After reviewing FDA's evaluation, HEW Secretary Joseph Califano denied the Petition, finding that propoxyphene did not present an "imminent hazard" to public health.⁸

Before reaching their ultimate conclusion on the 1978 position, FDA and HEW evaluated many of the identical safety and efficacy concerns raised in the current Petition. The current Petition's safety and efficacy concerns previously addressed by FDA include the following:

- The 1978 Petition and the current Petition both argue that many of the deaths reported as attributed to propoxyphene are due to a so-called "cardiotoxic" effect of its major metabolite, norpropoxyphene.⁹ For example, the current Petition states, "Propoxyphene is implicated in a high proportion of accidental deaths each year, because the majority of the drug is converted into a metabolite [(norpropoxyphene)] that is even more toxic and has a longer half-life than its parent compound."¹⁰ However, in response to the 1978 Petition making similar allegations, HEW concluded there was little evidence that norpropoxyphene's effects were a "common factor in the deaths associated with propoxyphene."¹¹ The current Petition, in fact, provides no new data for this argument. Public Citizen merely restates the same unsubstantiated speculation that FDA considered and rejected more than 25 years ago.

⁷ See letter to the HEW Secretary, from Donald Kennedy, FDA Commissioner (Jan. 17, 1979) (on file with FDA), Memorandum from Director, Division of Neuropharmacological Drug Products, to Director, Bureau of Drugs (Jan. 15, 1979) (on file with FDA) [hereinafter 1979 FDA Recommendation].

⁸ Order of the Secretary Denying Petition, HEW (Feb. 15, 1979) [hereinafter Order Denying Petition].

⁹ Citizen Petition from Sidney M. Wolfe, M.D., Director, Public Citizen's Health Research Group, to Andrew von Eschenbach, M.D., Acting Commissioner, FDA 1 (Feb. 28, 2006) [hereinafter Petition].

¹⁰ *Id.* at 2.

¹¹ Order Denying Petition, *supra* note 8, at 13.

Dockets Management Branch

April 14, 2006

Page 7

- Petitioner repeatedly claims, in both the 1978 Petition and the current Petition, that even when taken as directed, propoxyphene drugs can cause accidental death. The current Petition states, for example, “Propoxyphene . . . can cause severe cardiovascular effects with overdose or *even when used as directed*” (emphasis added).¹² The Petition also repeatedly suggests that many of the reported propoxyphene-related deaths are accidental.¹³ However, in 1979, FDA’s Bureau of Drugs concluded: “there are *no well documented examples of deaths when the drug is taken under the approved conditions of labeling*” (emphasis added).¹⁴ Furthermore, in the Order denying Petitioner’s 1978 request, Secretary Califano stated: “there is no clear evidence to date demonstrating that the use of propoxyphene, *in the absence of tranquilizers or alcohol*, has caused accidental death” (emphasis added).¹⁵ The Secretary further remarked that “most identified propoxyphene-associated deaths appear to be the result of misuses of the drug” and referenced a report showing that some of the cases classified as “accidental” involved “such large quantities of propoxyphene that it is very likely that the drug was not being used for therapeutic purposes at the recommended dosage level.”¹⁶ The current Petition provides no examples of, or direct support for, the contention that propoxyphene causes accidental, unintended death when used as directed. Thus, just as in 1978, propoxyphene remains safe when used according to the approved conditions of labeling.
- Both Petitions argue that other analgesics, including acetaminophen or aspirin, are better alternatives to propoxyphene.¹⁷ However, in its 1979 analysis of propoxyphene, FDA appropriately noted that acetaminophen and aspirin are also toxic at high doses and may

¹² Petition, *supra* note 9, at 4.

¹³ *E.g.*, *id.* at 4.

¹⁴ 1979 FDA Recommendation, *supra* note 7, at 2.

¹⁵ Order Denying Petition, *supra* note 8, at 13.

¹⁶ *See id.*, (citing Wright Baselt *et al.*, *Propoxyphene and Norpropoxyphene Tissue Concentrations in Fatalities Associated with Propoxyphene HCl and Propoxyphene Napsylate*, 34 ARCH. TOXICOL. 145-152. (1975)).

¹⁷ *See, e.g.*, Petition, *supra* note 9, at 3.

Dockets Management Branch
April 14, 2006
Page 8

not be safe options for some patients.¹⁸ Specifically, FDA stated: “they [acetaminophen and aspirin] are toxic at high doses and can produce adverse reactions in certain individuals including severe allergic reactions and, in the case of aspirin, gastrointestinal bleeding and peptic ulcer.”¹⁹

Just as FDA and HEW rejected Public Citizen’s 1978 Petition, the same result is warranted in response to the 2006 Petition, which does little more than restate the same arguments based on almost entirely the same information.

Although FDA’s and HEW’s conclusions regarding the 1978 Petition resulted in HEW’s denial of that Petition, due to concern over the use of propoxyphene in suicides and deaths resulting from the interaction of alcohol and/or other drugs with propoxyphene, HEW directed FDA to hold a public hearing on the continued marketing of propoxyphene. HEW also advised that it would forward any recommendations regarding the possible rescheduling of propoxyphene to the Department of Justice.²⁰

Following the public hearings, FDA again determined that propoxyphene drugs were safe and effective, and propoxyphene drugs remained on the market. Importantly, the public hearing brought into specific focus certain safety issues that could be adequately addressed through additional education of practitioners. In response, Lilly agreed to revise the labeling of its propoxyphene products to emphasize further the warnings applicable to the improper use of the products.²¹ Additionally, Lilly undertook an educational effort with doctors, pharmacists, and patients to provide and enhance warnings regarding the improper use of propoxyphene products.²² Today, the approved labeling for propoxyphene products contains strong warnings

¹⁸ Indeed, virtually all drugs are toxic when misused and taken in high doses.

¹⁹ 1979 FDA Recommendation, *supra* note 7, at 9.

²⁰ Order Denying Petition, *supra* note 8, at 20.

²¹ KEY DOCUMENTS AND STATEMENTS RELATING TO HEARINGS CONDUCTED BY THE SENATE SELECT COMMITTEE ON SMALL BUSINESS AND THE FOOD AND DRUG ADMINISTRATION AND TO MEETINGS OF THE FDA DRUG ABUSE ADVISORY COMMITTEE, JANUARY-JUNE, 1979, ELI LILLY AND COMPANY 7-9 (July 1979) (on file with Xanodyne).

²² *Id.*

and precautions regarding appropriate use of the products. More specifically, the full prescribing information for propoxyphene products bears a boxed warning highlighting issues related to suicide, overdose, addiction, and concomitant alcohol or drug abuse.²³ Additionally, the package insert contains extensive information on how to manage a suspected drug overdose.²⁴

3. Propoxyphene's addictive properties are well-characterized, and appropriately managed.

The Petition argues that the addictive properties of propoxyphene warrant removal of all propoxyphene containing drug products from the market. However, many drug products have addictive properties and nevertheless may be safely and effectively utilized in patient therapy. In the United States, over 200 substances used for medical treatment are scheduled as controlled substances due to their addictive or abuse potential.²⁵ The proper management of this class of drugs is not product removal, but rather, adequate controls derived from scheduling. In the case of propoxyphene, it is successfully managed as a Schedule IV controlled substance. The Drug Enforcement Administration (DEA) has not taken steps or expressed any perceived need to further restrict the availability of propoxyphene by changing its scheduling.

As Petitioner notes, the addictive nature of propoxyphene drugs is well-documented. Investigations into the addictive properties of propoxyphene date back to the mid-1950s. At a meeting in 1957, before the enactment of the Controlled Substances Act of 1970, the Committee on Drug Addiction and Narcotics of the National Research Council reviewed studies on propoxyphene and found that it did not have the same addiction producing or sustaining properties as morphine, but that it would be in the public interest to apply to such substances some "modified form of control."²⁶ Ultimately, in 1977, the DEA issued an order placing

²³ See, e.g., Package Insert, Darvocet-N[®] 50 and Darvocet-N[®] 100 (propoxyphene napsylate and acetaminophen tablets).

²⁴ See, e.g., *id.*

²⁵ U.S. DRUG ENFORCEMENT ADMINISTRATION, DRUG SCHEDULING, *available at* <http://www.dea.gov/pubs/scheduling.html> (last visited April 3, 2006).

²⁶ Letter from H.J. Anslinger, Commissioner of Narcotics, to Mr. T. P. Carney, Vice President, Eli Lilly and Company (Feb. 8, 1957) (on file with Xanodyne).

Dockets Management Branch
April 14, 2006
Page 10

propoxyphene products in Schedule IV of the Controlled Substances Act.²⁷ The DEA based its decision on the following findings:

1. Propoxyphene has “a low potential for abuse relative to the drugs or other substances currently listed in Schedule III.”
2. Propoxyphene has a “currently accepted medical use in treatment in the United States.”
3. Abuse of propoxyphene “may lead to limited physical dependence or psychological dependence relative to the drugs or other substances in Schedule III.”²⁸

Schedule IV classification subjected propoxyphene drugs to registration, security, labeling and packaging, inventory and recordkeeping, import/export, and prescription requirements.²⁹

Following the request of the 1978 Petition and another Petition filed by Dr. Edward Press, a public health officer for Oregon, to place propoxyphene into Schedule II, HEW conducted a scientific and medical evaluation of the drug. From that evaluation, HEW concluded there was insufficient evidence to justify reclassification.³⁰ In 1980, based on this assessment, the DEA announced in the Federal Register that propoxyphene would remain in Schedule IV.³¹

B. The Petition is Misleading in its Use of Data Regarding Propoxyphene-Related Deaths.

1. Petitioner’s use of DAWN data is misleading.

The Petitioner’s allegations rely heavily on its interpretation of data from the Drug Abuse Warning Network (DAWN). However, the Petition misrepresents the significance of data from

²⁷ 42 Fed. Reg. 8636 (Feb. 11, 1977).

²⁸ *Id.*

²⁹ *See id.*; *see also* 21 C.F.R. Part 1300 *et seq.*

³⁰ 45 Fed. Reg. 3923 (Jan. 21, 1980).

³¹ *Id.*

DAWN as it relates to deaths caused by propoxyphene. While FDA has used DAWN data to assess the abuse potential of prescription drugs,³² DAWN data are not intended to scientifically assess a product's safety and are not a sufficient basis for substantive regulatory action.

DAWN data on drug abuse deaths do not provide an accurate reflection of actual deaths caused by a specific drug; rather, they only show whether a particular drug was reported or "mentioned" by a medical examiner (ME) in a drug abuse death report submitted to DAWN.³³ This means the DAWN statistics repeated throughout the Petition involve any death where a ME found propoxyphene in the blood of a decedent. While the statistics Public Citizen relies upon suggest a temporal association between propoxyphene and death, causation is not proven through the DAWN data.

In fact, close examination of DAWN's 1999 ME data reveal the misleading nature of Petitioner's representations, such as, "from 1981 to 1999, DAWN reported 2,110 accidental propoxyphene-related deaths, or 38.6% of the total number of propoxyphene-related deaths."³⁴ In 1999, there were 466 mentions of propoxyphene out of a total of 11,651 reported drug abuse deaths.³⁵ Of these 466 propoxyphene mentions, only 6.7% (or 31) were cases where no other drugs were found.³⁶ In fact, propoxyphene was not the direct cause of death in the majority of even these cases. Only five (or 1.1%) of the 466 deaths were reported as being caused directly by propoxyphene alone; 29.2% of these 466 deaths were actually reported as being caused by "drug

³² DRUG ABUSE WARNING NETWORK, WHO USES DAWN?--FEDERAL AGENCIES, at <http://dawninfo.samhsa.gov/about/whousesdawn/federal.asp> (last visited April 3, 2006).

³³ See, e.g., Dept. of Health and Human Services, Substance Abuse and Mental Services Admin., Office of Applied Sciences, DRUG ABUSE WARNING NETWORK ANNUAL MEDICAL EXAMINER DATA 1999, 2-4 (Dec. 2000) [hereinafter 1999 DAWN ME DATA] (describing methodology used to collect data).

³⁴ Petition, *supra* note 9, at 2.

³⁵ 1999 DAWN ME DATA, *supra* note 33, at 39.

³⁶ *Id.* at 54.

and physiological condition,” “drug and external physical event,” “drug and medical disorder,” or “unknown.”³⁷

Furthermore, Petitioner neglects to examine DAWN statistics in light of the amount of propoxyphene ingested. DAWN data does not show drug quantities found by MEs, only whether a specific drug was present. The 1999 ME report shows that out of the 466 propoxyphene mentions, 69.7% represented multiple drugs being reported as the direct cause of death.³⁸ Given the wide use of propoxyphene for the treatment of pain, it would be expected that many of the propoxyphene DAWN mentions reporting more than one drug as the direct cause of death were actually situations in which the decedent was taking propoxyphene as pain treatment appropriately, and not abusing it.

Petitioner admits other drugs were found along with propoxyphene in nearly all of the cases reported by DAWN. However, the admission is buried among suggestions that there was a causal relationship between propoxyphene and these deaths. In fact, immediately following this acknowledgment, the Petition states: “toxicity makes causation [between propoxyphene consumption and deaths where propoxyphene was mentioned] likely.”³⁹ Petitioner’s unscientific, self-determined “likely” standard is completely inadequate to meet the scientific, evidence-based standard required to justify market removal of an important and widely-used medication like propoxyphene.

The Petition’s statements regarding “accidental” propoxyphene-related deaths are also misleading. For example, the Petition provides, “[propoxyphene’s] toxicity accounts for the finding that only 30-40% of propoxyphene-related deaths are attributed to suicidal overdoses; over 40% have been found to be accidental.”⁴⁰ Deaths reported by DAWN as “accidental/unexpected” are not necessarily directly attributable to an overdose or use of any specific drugs. Some of the cases reported included individuals who were taking propoxyphene as directed for therapeutic purposes, and abusing a different drug altogether. Other cases

³⁷ *Id.* at 47 & 51.

³⁸ *Id.*

³⁹ Petition, *supra* note 9, at 7.

⁴⁰ *Id.* at 4

reported included drug abuse, but an incident or physical trauma (such as an injury) actually caused the death.⁴¹ Therefore, Petitioner's correlation between propoxyphene's toxicity and the number of accidental deaths reported by DAWN is inaccurate and misleading.

Petitioner also improperly compares findings from different ME panels. DAWN draws comparisons between different years based on data from a "consistent panel" of MEs.⁴² DAWN specifically advises that "[f]indings from [one] consistent panel must not be compared with findings from earlier consistent panels" because the consistent panel changes for each period reported.⁴³ DAWN does examine trends over time using findings from a consistent panel; for example, DAWN provides trend tables for 1996 to 1999.⁴⁴ Petitioner, however, compares DAWN data from non-consistent panels of ME's: Figure 1 depicts trends from 1981-2002 and Petitioner directly states, "Whereas 227 deaths were reported in 1981, a high of 459 was reported in 2002."⁴⁵ Based on DAWN's own stated limitations, such comparisons are inaccurate because the panel from 1996-1999 was not consistent with panels from the other years quoted by Petitioner.

Furthermore, Petitioner's Figure 1, a graph showing DAWN reported propoxyphene-related deaths from 1981 to 2002, is blatantly misleading. Instead of showing deaths per year over this period in order to determine if the number of deaths are trending in a particular direction, Petitioner depicts cumulative deaths.⁴⁶ Not surprisingly, given that the number of deaths reported to DAWN have remained fairly constant over this time period,⁴⁷ Figure 1 shows a predictable increase of cumulative deaths over the years (as would any drug's cumulative

⁴¹ See 1999 DAWN ME DATA, *supra* note 33, at 51.

⁴² A "consistent panel" is composed of the subset of total ME facilities reporting data for at least 10 months of a contiguous number of years. *E.g., id.* at ix.

⁴³ See, e.g., *id.* at 5.

⁴⁴ *Id.* at 66-90.

⁴⁵ Petition, *supra* note 9, at 8.

⁴⁶ *Id.*

⁴⁷ *Id.*

deaths). However, if not examined carefully, this figure leads the casual observer to conclude that the number of deaths since 1981 has been sharply increasing. This is not the case.

Besides compiling medical examiner data, DAWN also reports on drug-related emergency department (ED) visits. In January 2003, DAWN published a report on Narcotic Analgesics, showing trends from 1994 to 2001. This report provides that during this time period, the estimated number of ED visits involving the entire class of narcotic analgesics increased 117% (41,687 in 1994 to 90,232 in 2001).⁴⁸ However, when examining data for the specific drugs involved, propoxyphene mentions actually decreased from 6,731 in 1994 to 5,361 in 2001.⁴⁹ Thus, ED mentions of propoxyphene are *steadily declining*, even though narcotic analgesic mentions are rising rapidly. Virtually every other narcotic analgesic drug increased during this time.⁵⁰

The Petition fails to acknowledge that removal of propoxyphene drugs from the market will result in patients being prescribed other painkillers as an alternative. So, instead of patients using a prescription drug such as propoxyphene with well-characterized safety concerns, patients may be prescribed other drugs in the class whose overall safety profile is less well-known and, in some instances, associated with greater risks. Thus, from a public health perspective, removing propoxyphene from the market may have the unintended effect of exposing patients to greater risk.

2. Petitioner's statements that propoxyphene drugs are unsafe and ineffective are scientifically unsupported and misleading.

Several of the Petition's statements regarding safety lack scientific substantiation. For example:

⁴⁸ Office of Applied Studies, Substance Abuse and Mental Health Service Admin., THE DAWN REPORT: NARCOTIC ANALGESICS, IN BRIEF 1 (Jan. 2003), *available at* <http://www.oas.samhsa.gov/2k3/pain/DAWNpain.pdf> (last visited March 31, 2006) [hereinafter NARCOTIC ANALGESICS].

⁴⁹ *Id.* at 3.

⁵⁰ *Id.*

- The study conducted by Verebely and Inturrisi relied upon in the Petition is cited to support the assertion that “[t]he fact that norpropoxyphene is cleared from the body more slowly than its parent compound and thus reaches considerably higher blood levels and is more cardiotoxic, explains the high risk of accidental overdose.”⁵¹ The study does not make this conclusion. Instead, the study merely measured plasma levels of propoxyphene and norpropoxyphene and found that “the plasma level of norpropoxyphene was more persistent” than that of propoxyphene.⁵² Verebely and Inturrisi did not show or suggest that drug persistence caused a cardiotoxic effect that “explained” a “high risk” of accidental overdose. In fact, the Petition refers to no studies that find a correlation between the cardiotoxic effects of norpropoxyphene and a high risk of accidental overdose when propoxyphene is taken as indicated. This statement is thus unfounded and unsupported.
- The Petition’s argument that “chronic users of propoxyphene are at high risk of accidental overdose”⁵³ also lacks support. The Petition relies mainly upon unpublished, “personal communications” from the 1970s to create Table 1 showing blood propoxyphene and norpropoxyphene levels in a handful of individual regular users of propoxyphene products.⁵⁴ This dated, unsubstantiated, anecdotal information is completely inadequate for causing a product to be withdrawn from the market.
- Petitioner provides no support for the statement “even where propoxyphene shown (sic) to be effective for this kind of pain [chronic, such as that from cancer], chronic usage increases the likelihood of adverse events due to the buildup of the cardiotoxic

⁵¹ *Id.*

⁵² Karl Verebely and Charles E. Inturrisi, *The Simultaneous Determination of Propoxyphene and Norpropoxyphene in Human Biofluids Using Gas-Liquid Chromatography*, 75 J. OF CHROMATOGRAPHY 195 (1973) .

⁵³ Petition, *supra* note 9, at 6.

⁵⁴ *See id.* at 5 (citing “Inturrisi CE. Personal communication to Dr. Sidney M. Wolfe. January 29, 1979” and “Gorodetsky C. Personal communication. February 8, 1979.”).

propoxyphene metabolite, norpropoxyphene.”⁵⁵ This proposition, in fact, has not been proven with any credible scientific data.

- The statement, “The dose of propoxyphene necessary for cardiac toxicity to occur overlaps significantly with the increased dose which a user dissatisfied with the analgesic effects and still in pain, may ingest”⁵⁶ is speculative and lacks scientific support. Propoxyphene drugs are dispensed only via prescription and have specific indications for use. Furthermore, propoxyphene drugs have been considered safe when taken as directed for nearly 50 years.

Petitioner, therefore, has not come forward with sufficient credible scientific evidence to support its contention that propoxyphene drugs are unsafe or ineffective. Rather, the Petitioner relies on unsubstantiated “personal communications” and draws scientifically unsupported conclusions from bits and pieces of information in the literature.

3. The Petition’s assertion that propoxyphene is inappropriate for the elderly lacks scientific support.

While the Petition correctly notes that the elderly account for a large proportion of propoxyphene use, the studies relied upon to support the argument that propoxyphene use is “inappropriate” in the elderly and that there is an increased “risk of adverse reactions” in this population⁵⁷ are both flawed and misrepresented.

The Petition claims that the publication by Beers *et al.*⁵⁸ “put propoxyphene among the drugs that are inappropriate for use in the elderly due to its lack of significant efficacy and high incidence of adverse effects.”⁵⁹ The Beers publication, however, is not a scientific study and is

⁵⁵ Petition, *supra* note 9, at 4.

⁵⁶ *Id.* at 6.

⁵⁷ Petition, *supra* note 9, at 11-12

⁵⁸ Mark H. Beers *et al.*, *Explicit Criteria for Determining Inappropriate Medication Use in Nursing Home Residents*, 151 ARCH. INTERN. MED. 1825 (Sept. 1991).

⁵⁹ Petition, *supra* note 9, at 2.

replete with methodological flaws and bias. Beers was nothing more than a survey of 13 “experts” to “reach consensus on explicit criteria defining the inappropriate use of medications in a nursing home population.”⁶⁰ These “experts” were personally selected by the study authors, rather than by scientific survey of the appropriate medical community. The qualifications of the “experts” were also not provided. Interestingly, one of the “experts” was Dr. Sidney Wolfe of Public Citizen, who submitted both the 1978 and current Petitions.⁶¹ In addition, the survey questions were phrased in an inconsistent, biased manner. For example, one statement was phrased: “Pentazocine (Talwin) is not the best narcotic to use when a narcotic is needed,” while the propoxyphene statement was: “Propoxyphene (Darvon, and as in Darvocet, Darvon Compound, Wygesic) should be avoided.”⁶² While both medications are narcotics and indicated for pain relief, the statement for propoxyphene was phrased such that it had no possible benefit, whereas the one for pentazocine was not. The selection of products in the survey also was biased, as only two analgesics (propoxyphene and pentazocine) were included, even though numerous other analgesics of varying efficacy and safety were available. No scientific evidence in the form of clinical studies, meta-analyses, or structured reviews was presented to support the opinions or the conclusions reached in the study.

Beers *et al.* updated their publication in 1997.⁶³ The 1997 publication used a similar “methodology” to the 1991 publication, but draws “consensus” from a panel of 6, rather than 13. Unlike the 1991 criteria, which stated that propoxyphene should be avoided, the criteria established for propoxyphene use in the 1997 study was slightly less biased. Panelists were asked if they agreed with the statement “Propoxyphene should generally be avoided in the elderly. It offers few analgesic advantages over acetaminophen, yet has the side effects of other narcotic drugs.”⁶⁴ In addition, if the panelist believed the statement to be true, he was asked to

⁶⁰ Beers, *supra* note 58, at 1825.

⁶¹ *Id.* at 1830.

⁶² *Id.* at 1826.

⁶³ Mark H. Beers, *et al.*, *Explicit Criteria for Determining Inappropriate Medication by the Elderly*, 157 ARCH. INTERN. MED. 1531 (Sept. 1997).

⁶⁴ *Id.* at 1533. The statistics for this study used a 90% confidence interval based on n=6, causing the results to have virtually no statistical validity. *Id.*

rate the severity of any problems that might arise because of use of the medication as stated.⁶⁵ “Severity” was defined conceptually as a combination of the likelihood that an adverse outcome would occur and the clinical significance should that outcome occur.⁶⁶ The study respondents opined that propoxyphene use, as described, was not “severe” based on this conceptual definition.⁶⁷

Beers *et al.*'s publication was updated once again in 2003, this time by Fick *et al.*⁶⁸ The 2003 publication used a similar “methodology” as the 1997 Beers publication and also assigned it a “low” severity rating.⁶⁹ The Petition, however, makes no reference to either the 1997 or 2003 follow-up studies.

Petitioner also cites R.J. Flanagan *et al.* for the statement: “With repeated dosing, at the recommended doses,” the elderly are “exposed to a much higher dose of the drug for longer periods of time, increasing their risk of adverse reactions.”⁷⁰ However, this study conducted by R.J. Flanagan does not state that repeated dosing increases the risk of adverse reactions in the elderly. While Flanagan reported that propoxyphene and norpropoxyphene “often have prolonged half-lives in the elderly” and found that the results of their study “clearly demonstrate accumulation of [norpropoxyphene] and, to a lesser extent, [propoxyphene] itself in both young and elderly subjects,” it concluded that “*the implications of this finding for therapy remain unclear since no side effects were reported in this study*” (emphasis added).⁷¹

⁶⁵ *Id.* at 1532.

⁶⁶ *Id.*

⁶⁷ *Id.*

⁶⁸ Donna M. Fick *et al.*, *Updating the Beers Criteria for Potentially Inappropriate Medication Use in Older Adults*, 163 ARCH. INTERN. MED. 2716 (Dec. 2003).

⁶⁹ *Id.*

⁷⁰ Petition, *supra* note 9, at 11.

⁷¹ R.J. Flanagan *et al.*, *Pharmacokinetics of dextropropoxyphene and nordextropropoxyphene in young and elderly volunteers after single and multiple dextropropoxyphene dosage*, 28 BR. J. CLIN. PHARMAC. 463, 468 (1989).

The Petition also states that “the central nervous system-related adverse effects of propoxyphene use may increase the likelihood of falls and hence fall-related fractures in the elderly.”⁷² However, no correlative, much less causative, evidence regarding this alleged link between propoxyphene use and falls is provided by Petitioner.

More importantly, propoxyphene products are labeled with a precaution for usage in the elderly, noting that an increased dosing interval should be considered in patients where the rate of propoxyphene metabolism may be reduced.⁷³ This precaution recognizes and warns that there may be a longer half-life of propoxyphene in some elderly patients, but provides for the safe management of the drug’s use in these patients. Thus, FDA has specifically considered the issue of propoxyphene safety in the elderly and correctly determined that the risks raised by Petitioner are appropriately addressed through a precautionary statement in the product’s label.

III. PROPOXYPHENE IS IMPORTANT THERAPY IN PAIN MANAGEMENT

A. Pain is diverse, debilitating, and prevalent.

Public Citizen’s Petition is devoid of any discussion or even any acknowledgement of the real effects of pain on patients’ lives. Each year, 25 million Americans experience acute (short-term) pain caused by injury or surgery.⁷⁴ Approximately 24% of Americans, or approximately 48 million people, suffer from chronic pain.⁷⁵ Pain greatly impacts those who suffer from it: two in five pain sufferers cannot work and three in five are unable to engage in daily activities.⁷⁶

⁷² Petition, *supra* note 9, at 12.

⁷³ Package Insert, Darvocet-N® 50 and Darvocet-N® 100 (propoxyphene napsylate and acetaminophen tablets).

⁷⁴ American Academy of Pain Management, PAIN ISSUES: PAIN IS AN EPIDEMIC, available at <http://www.aapainmanage.org/literature/Articles/PainAnEpidemic.pdf> (last visited April 3, 2006).

⁷⁵ 1999 NATIONAL PAIN SURVEY, at http://www.chiro.org/LINKS/FULL/1999_National_Pain_Survey.html (last visited March 14, 2006).

⁷⁶ *Id.*

Unfortunately, pain is often inadequately treated, resulting in needless suffering, lost productivity, and excessive health care expenditures. In the United States, the total annual cost of pain, including healthcare expenses, compensation for lost work, and litigation, is estimated to be \$100 billion.⁷⁷

Pain is derived from many diverse disease processes and conditions. Some common causes of pain include migraines, headaches, medical procedures, burns, labor and delivery, surgery, back injuries, sickle cell disease, arthritis, neuropathic conditions, and cancer. As a result of the diverse nature of pain, managing patients with pain poses a significant challenge for healthcare professionals.

B. Effective pain management requires the availability of numerous therapeutic options.

The diverse nature of pain and the difficulty in appropriately treating it underlies the need to have a wide variety of treatment options, including propoxyphene, available to physicians. Indeed, some drugs are not viable options for patients. For example, Petitioner, relying upon a review article, states that ibuprofen is more effective than propoxyphene/acetaminophen and than propoxyphene alone. However, non-steroidal anti-inflammatory drugs (NSAIDs), which include ibuprofen and naproxen, may cause stomach bleeding, especially for individuals over 60, people who have had stomach ulcers or bleeding problems, and those who take anticoagulants or steroids, blood thinning or steroid drugs, other drugs containing an NSAID, have three or more alcoholic drinks per day while using the NSAID, or who take the NSAID for a longer duration than directed.⁷⁸ Additionally, long term, continuous use of NSAIDs have been associated with heart attack and stroke.⁷⁹ In fact, FDA's concern over the potential adverse effects of NSAIDs

⁷⁷ BA Coda and JJ Bonica, *General Considerations of Acute Pain*, BONICA'S MANAGEMENT OF PAIN, 2001, at 222-40, M. Glajchen, Chronic pain: treatment barriers and strategies for clinical practice, 14 J. AM. BOARD FAM. PRACT. 178-83 (2001).

⁷⁸ See, e.g., Drug Facts for Advil® (ibuprofen) products.

⁷⁹ *Id.*

Dockets Management Branch
April 14, 2006
Page 21

prompted the Agency to request sponsors of such drugs to make labeling changes to their products.⁸⁰

Petitioner also states that “propoxyphene alone has been shown to be no more effective than two aspirin for relief of most kinds of pain.”⁸¹ However, aspirin also can cause gastrointestinal bleeding.⁸² Allergies are also a concern with both NSAIDs and aspirin.⁸³

Petitioner also compares propoxyphene with other narcotic drugs. Petitioner, for example, states that codeine/acetaminophen is more effective than propoxyphene/acetaminophen, “although the difference is not statistically significant.”⁸⁴ Codeine, however, is not always well tolerated, and can cause nausea and constipation.⁸⁵ Furthermore, Petitioner highlights the addictive properties of propoxyphene,⁸⁶ but codeine is considered more addictive, as evidenced by it being listed under Schedule II (codeine alone) or Schedule III (codeine combination products) under the Controlled Substances Act.⁸⁷ In contrast to these alternatives, propoxyphene has been associated with few side effects when taken as directed, as noted in its labeling: “In a survey conducted in

⁸⁰ See Food and Drug Admin., COX-2 SELECTIVE (INCLUDES BEXTRA, CELEBREX, AND VIOXX) AND NON-SELECTIVE NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS), at <http://www.fda.gov/cder/drug/infopage/COX2/default.htm> (last visited March 30, 2006).

⁸¹ Petition, *supra* note 9, at 3.

⁸² See, e.g., Package Insert for Bayer® Aspirin products.

⁸³ See, e.g., Package Inserts for Advil® ibuprofen products and Bayer® Aspirin products.

⁸⁴ Petition, *supra* note 9, at 3.

⁸⁵ See, e.g., prescribing information for Tylenol® with Codeine (acetaminophen and codeine phosphate tablets).

⁸⁶ See Petition, *supra* note 9, at 12-13.

⁸⁷ 21 C.F.R. §§ 1308.12 & 1308.13.

hospitalized patients, less than 1% of patients taking propoxyphene hydrochloride at recommended doses experienced side effects.”⁸⁸

All drugs have risks, as demonstrated by the risks enumerated above for NSAIDs and aspirin. However, the degree of risks associated with a particular drug exposure will vary among patients being treated for mild to moderate pain. It is important to have all these analgesic products available to treat pain due to the individualized needs of patients. Prescribing pain medication is a decision best left to the prescribing physician based on a number of factors. The Petition offers no credible medical or scientific justification for removing propoxyphene from the doctor’s arsenal of tools over any other analgesic products.

C. The risks of propoxyphene are well-characterized and should not prevent its proper use.

Like all prescription medications, propoxyphene has risks. However, as a result of propoxyphene’s use for nearly 50 years, practitioners are well-aware of these risks. Propoxyphene remains a widely-prescribed treatment option for pain. Physicians need the option of prescribing propoxyphene products to the appropriate patients who may benefit from it. Pain sufferers should not be deprived of an alternative that may relieve their pain because some patients may be inclined to abuse it. The potential for propoxyphene abuse is why it is subject to certain controls under the Controlled Substances Act.⁸⁹ The risks associated with propoxyphene use are adequately disclosed and described in the FDA-approved labeling of propoxyphene drugs.⁹⁰

While petitioner suggests that removing propoxyphene products from the market will eliminate or reduce suicides, this contention does not flow naturally simply from a product removal. What is more likely is that removal of propoxyphene products from the market would only displace suicide. Petitioner inaccurately implies that restricting drugs typically involved with suicide

⁸⁸ Package Insert, Darvocet-N® 50 and Darvocet-N® 100 (propoxyphene napsylate and acetaminophen tablets).

⁸⁹ See 21 C.F.R. Part 1300 *et seq.*

⁹⁰ Package Insert, Darvocet-N® 50 and Darvocet-N® 100 (propoxyphene napsylate and acetaminophen tablets).

greatly reduces suicide and that individuals intent on suicide will not move to another drug to attempt the act. Petitioner does this by showing a decline in the number of barbiturate and total drug suicides from 1968 to 1976 and suggesting the decline is due to the imposition of scheduling restrictions on barbiturates.⁹¹

Providing the number of barbiturate and total drug suicides from the late 1960s to the mid-1970s to show how “restricting the availability of barbiturates by imposing Schedule II controls had a marked positive effect on reducing the number of barbiturate suicides,” and then conjecturing that removing propoxyphene from the market rather than merely restricting its use would result in a decline total suicides,⁹² is inaccurate and based on flawed logic. Petitioner neglects to consider the fact that suicides would occur even if no drugs were available and provides no information regarding total suicides. The majority of suicides, in fact, do not occur with drugs, but with firearms.⁹³ Removing propoxyphene drugs from the market will likely lead suicidal persons to move to another method of suicide, whether drug or some other means.

IV. THE U.K.’S EXPERIENCE WITH CO-PROXAMOL IS DISTINGUISHABLE FROM THE USE AND AVAILABILITY OF PROPOXYPHENE-CONTAINING PRODUCTS IN THE UNITED STATES

The Petition notes that the U.K. ordered the phased withdrawal of co-proxamol from the market in January 2005. Indeed, the British Medicines and Healthcare Products Regulatory Agency (MHRA) withdrew co-proxamol from the market because it did not believe the benefits outweighed the risks, reporting that there are around “300-400 self-poisoning deaths [in the U.K.] each year, of which around a fifth are accidental” involving the product.⁹⁴ The situation in the U.K., however, is very different from that in the United States.

⁹¹ Petition, *supra* note 9, at 10-11.

⁹² *Id.* at 10.

⁹³ *See e.g.*, Centers for Disease Control and Prevention, *Deaths, Injuries, 2002*, NATIONAL VITAL STATISTICS REPORT, Jan. 31, 2006, at 10 (stating that in 2002, firearm suicide accounted for 54.1 percent of suicides).

⁹⁴ Medicines and Healthcare Products Regulatory Agency, QUESTION AND ANSWER DOCUMENT: CO-PROXAMOL: OUTCOME OF THE REVIEW OF RISKS AND BENEFITS (Jan. 31, 2005),
(continued...)

Co-proxamol cannot be compared to products on the market in the United States. Co-proxamol is a fixed combination product containing 32.5 mg propoxyphene hydrochloride and 325 mg acetaminophen.⁹⁵ In the United States, products such as Darvon contain 65 mg propoxyphene hydrochloride, twice the amount of propoxyphene as in co-proxamol.⁹⁶ The lower quantity of propoxyphene found in co-proxamol likely resulted in the U.K.'s conclusion that "[t]here is no robust evidence that efficacy of this combination product is superior to full strength paracetamol alone in either acute or chronic use."⁹⁷ FDA has recognized that propoxyphene may not be effective at nearly the same level as the amount contained in co-proxamol. As described above, in its DESI review of propoxyphene products, FDA found that the efficacy of the 32 mg dose of propoxyphene hydrochloride was limited.⁹⁸ Today, a 32 mg dose of propoxyphene is not even available in the United States. Thus, the risk-benefit ratio in the United States is entirely different than in the U.K.

Additionally, propoxyphene hydrochloride products constitute only a fraction, less than 4%, of total propoxyphene drug prescriptions in the United States.⁹⁹ Instead, the vast majority of propoxyphene prescriptions in the United States are for propoxyphene napsylate products.

available at <http://www.mhra.gov.uk/home/groups/pl-a/documents/drugsafetymessage/con019462.pdf> (last visited March 31, 2006).

⁹⁵ *Id.*

⁹⁶ Package Insert, Darvocet-N® 50 and Darvocet-N® 100 (propoxyphene napsylate and acetaminophen tablets).

⁹⁷ Medicines and Healthcare Products Regulatory Agency, WITHDRAWAL OF CO-PROXAMOL PRODUCTS AND INTERIM UPDATED PRESCRIBING INFORMATION (Jan. 31, 2005), *available at* <http://www.mhra.gov.uk/home/groups/pl-a/documents/drugsafetymessage/con019461.pdf> (last visited March 23, 2006).

⁹⁸ 37 Fed. Reg. 26538 (Dec. 13, 1972).

⁹⁹ *See* IMS National Prescription Audit.

Propoxyphene napsylate is considerably less soluble than propoxyphene hydrochloride.¹⁰⁰ Due to this lower solubility, the absorption rate of the napsylate salt, including very large doses, is significantly slower than that of equimolar doses of the hydrochloride.¹⁰¹ This faster absorption rate of the hydrochloride salt increases the toxic effects of the product when taken at higher doses than indicated.¹⁰² This would explain the higher incidences of deaths related to co-proxamol in the U.K., which consisted of propoxyphene hydrochloride, while the United States population primarily uses the napsylate formulation.

Moreover, propoxyphene products are not subject to the same controls and warning requirements in the U.K. as they are in the United States. First, propoxyphene is not considered a “controlled substance” in the U.K. as it is in the United States.¹⁰³ Additionally, the labeling of co-proxamol in the U.K. is quite different from the FDA-required labeling of propoxyphene products in the United States. In sharp contrast to the extensive warnings required in the labeling of propoxyphene products in the United States, key information provided in co-proxamol labeling in the U.K. is not uniform: of the 18 products licensed in the U.K., 17 advised avoiding alcohol and the other mentioned that co-ingestion of alcohol with excessive doses of the product was a major cause of drug-related deaths; all warned of the risk of concomitant use of central nervous system depressants, but to varying degrees; and only 10 of the 18 licensed products contained a warning against use in patients who are suicidal or addiction prone, while five others gave precautions against use in patients with a psychological or personality disorder.¹⁰⁴

Furthermore, Petitioner improperly attempts to extrapolate U.K. data related to drug overdose involving co-proxamol in England and Wales to the United States (“in those two countries alone, with a population of 53 million people, approximately 18% of the size of the United States, there

¹⁰⁰ Package Insert, Darvocet-N® 50 and Darvocet-N® 100 (propoxyphene napsylate and acetaminophen tablets).

¹⁰¹ *Id.*

¹⁰² *Id.*

¹⁰³ See Committee on Safety of Medicines, Subcommittee on Pharmacovigilance, RISK: BENEFIT OF CO-PROXAMOL PRODUCTS (April 15, 2004) (on file with Xanodyne).

¹⁰⁴ *Id.*

Dockets Management Branch
April 14, 2006
Page 26

were an estimated 60 to 80 accidental deaths a year from co-proxamol¹⁰⁵) and uses studies examining propoxyphene overdose deaths in the U.K. and Sweden to show the “dangers” of “poisoning from propoxyphene” and argue that it should be removed from the market in the United States.¹⁰⁶

Among these different countries, these drug products differ in composition, as well as how they are controlled and labeled, and how physicians prescribe them. Additionally, a multitude of factors contribute to drug abuse and suicide rates, some of which are societal, making drug abuse and suicide data from foreign countries not particularly relevant in the United States. In fact, according to one of the studies cited by Petitioner, 18% of all drug-related deaths from 1977 to 1999 were due to poisoning alone and co-proxamol was the “second most common prescribed drug used for suicides,” after tricyclic antidepressants.¹⁰⁷ Thus, co-proxamol appears to be one of the “suicide drugs of choice” in the U.K. That is not the case in the United States.

The differences among countries has been recognized by the U.K. In its report on the risks and benefits of co-proxamol products, the U.K.’s Committee on Safety of Medicines Subcommittee on Pharmacovigilance cited the same studies by Jonasson as Petitioner discusses, but subject to the following qualification:

Swedish data cannot be extrapolated to other countries. National prescribing patterns for analgesics and CNS depressants, the prevalence of drug abuse and alcohol consumption and differing population structures will produce major international variations in patterns of DXP [propoxyphene]-related deaths. [Additionally,] . . . in Sweden DXP is used for detoxification of opiate addicts and is frequently a drug of abuse.¹⁰⁸

¹⁰⁵ Petition, *supra* note 9, at 1.

¹⁰⁶ *Id.* at 6-7.

¹⁰⁷ Keith Hawton *et al.*, *Co-proxamol and suicide: a study of national mortality statistics and local non-fatal self-poisoning*, 326 *BMJ* 1006 (May 10, 2003).

¹⁰⁸ RISK: BENEFIT OF CO-PROXAMOL PRODUCTS, *supra* note 103.

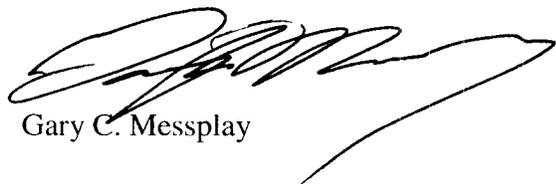
Dockets Management Branch
April 14, 2006
Page 27

V. CONCLUSION

Propoxyphene products have a long history of safe and effective use as labeled, having been approved nearly 50 years ago and continually used in multiple strengths, dosage forms, and combinations since then. The Petition does not present any credible scientific evidence that propoxyphene drugs present an imminent hazard to public health or that propoxyphene drugs are unsafe and ineffective when used according to approved labeling. Nor does the Petition raise any new safety or efficacy concerns that have not previously been considered and rejected by FDA.

For all the foregoing reasons, the Petition should be denied.

Respectfully submitted,



Gary C. Messplay

cc: Daniel L. O'Korn, Esquire
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