DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

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Re: Docket No. FDA-2006-P-0270

Dear Dr. Wolfe, Mr. Suzman, and Drs. Jonasson:

This letter responds to your citizen petition (petition) dated February 28, 2006.[1] You request that the Food and Drug Administration (FDA or the Agency) begin the phased removal of all propoxyphene-containing products from the market including, but not limited to, Darvon and Darvocet, which are indicated for the relief of mild to moderate pain. You offer the following arguments in support of your request for removal of all propoxyphene-containing products from the market:

1. The products have a high level of cardiotoxicity.[2]
2. A substantial number of deaths, both accidental and intentional, are associated with use of the products.[3]
3. The products are over-prescribed in the elderly.[4]
4. The products have addiction-causing properties and a related potential for abuse.[5]

[1] This citizen petition was originally assigned docket number 2006P-0090/CP1. The number was changed to FDA-2006-P-0270 as a result of FDA's transition to its new docketing system (Regulations.gov) in January 2008.

[2] See Petition at 4-7.

[3] See Petition at 7-11.

[4] See Petition at 11-12.

[5] See Petition at 12-13.

5. The products are relatively ineffective as pain medications, the purpose for which they are indicated.[6]

FDA has carefully considered the information submitted in your petition and other relevant data obtained by the Agency, including the presentations made during, and other information submitted in connection with, the January 30, 2009, Joint Meeting of the Anesthetic and Life Support Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee. Based on our review of this information, and for the reasons described below, the relief that you request is denied. However, in light of the information presented to us, we have decided that other measures short of withdrawal are necessary — including initiating the process to require revisions to the product labeling, requiring a Medication Guide (MedGuide) as part of a Risk Evaluation and Minimization Strategy (REMS),[7] requiring a clinical trial to assess the potential for cardiotoxicity associated with propoxyphene use,[8] and issuing a Public Health Advisory to underscore safety issues that are highlighted in the product labeling.

I. BACKGROUND

Propoxyphene hydrochloride (HCl) is an opioid[9] that was originally approved and marketed in 1957 by Eli Lilly (Lilly), under new drug applications (NDAs) 10-996 and 10-997. Lilly marketed it both as a 32-milligram (mg) single-agent and as a combination drug consisting of 32 mg of propoxyphene HCl, aspirin, phenacetin, and caffeine. The single-agent product was trade-named Darvon (NDA 10-997), and the combination

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[6] See Petition at 3-4.

[7] A Medication Guide (MedGuide) is FDA-approved patient labeling that conforms to the specifications in 21 CFR part 208 and other applicable regulations. The Agency will require a manufacturer of a prescription drug product to develop a MedGuide for distribution by physicians to patients when we determine that the drug product poses a serious and significant public health concern and that patient labeling is needed to ensure the safe and effective use of the product (§ 208.1(a) and (b)). Under § 208.1(c), we will require a MedGuide when we determine that one or more of the following circumstances exist: The drug product is one for which patient labeling could help prevent serious adverse effects; the drug product is one that has serious risk(s) (relative to benefits) of which patients should be made aware because information concerning the risk(s) could affect patients' decision to use, or to continue to use, the product; the drug product is important to health and patient adherence to directions for use is crucial to the drug's effectiveness.

[8] Under section 505(o)(3) of the FDCA (21 U.S.C. 355(o)(3)), FDA has authority to require a clinical study or trial to identify an unexpected serious risk when available data indicate the potential for such a serious risk. In this case, we have made a determination that an analysis of spontaneous adverse event reports under section 505(k)(1) of the FDCA will not be sufficient. Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to identify this serious risk. Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to identify the serious risk of cardiovascular events, including life-threatening arrhythmias, that may occur in association with use of propoxyphene.

[9] An opioid is an analgesic that works by binding to opioid receptors.

product was trade-named Darvon-Compound (NDA 10-996). Shortly after the initial approval, a 65-mg single-agent product was also approved.

Following the passage of the Kefauver-Harris Amendments to the Federal Food, Drug, and Cosmetic Act (FDCA), Darvon and Darvon-Compound underwent a Drug Efficacy Study Implementation (DESI) review. In 1969, Darvon and Darvon-Compound were determined to be effective for the relief of pain.[10] In 1971, Darvon-N (propoxyphene napsylate) was approved in a 100-mg strength (the equivalent of 65 mg of propoxyphene HCl), and in 1972, Darvocet (propoxyphene acetaminophen) was also approved.

In 1973, propoxyphene was reviewed for scheduling under the Controlled Substances Act (CSA). In 1974, the issue was taken to an Advisory Committee. Consistent with the advice of the Advisory Committee, FDA did not recommend that propoxyphene be scheduled.

However, in 1976, the issues of propoxyphene abuse, dependence, and association with fatal overdose were revisited at an Advisory Committee meeting, culminating in revision of the propoxyphene products' labeling and control of propoxyphene products under Schedule IV of the CSA. The 1976 Advisory Committee focused on a study conducted by Dr. Brian Finkle, an epidemiologist at the University of Utah, which showed that the number of propoxyphene-related deaths increased sharply between 1972 and 1975, although most of those deaths involved ingestion of multiple drugs.

In November 1978, the Health Research Group (HRG) petitioned the Department of Health and Human Services (HHS) (then known as the Department of Health, Education, and Welfare (HEW)) to remove propoxyphene products from the market as an "imminent hazard" or, alternatively, to reclassify propoxyphene as a Schedule II substance. As in the instant petition by Public Citizen, HRG argued that propoxyphene should be removed from the market based on lack of efficacy and the number of deaths associated with its use.

After an extensive review of the safety and efficacy of propoxyphene, HRG's petition was denied. However, in connection with HRG's petition, issues relating to propoxyphene were taken to another Advisory Committee in 1979.[11] The 1979 Advisory Committee recommended that propoxyphene should remain on the market under Schedule IV, with the caveat that Lilly, propoxyphene's manufacturer, would commence an educational program targeting prescribers. The educational program was supposed to

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[10] See 34 FR 6264, April 8, 1969.

[11] The Committee discussed many issues related to propoxyphene, but voted on the following: (1) Whether propoxyphene should remain in Schedule IV; (2) whether propoxyphene has a low potential for abuse relative to the substances listed in Schedule III; (3) whether propoxyphene abuse may lead to limited psychological dependence relative to substances in Schedule III; and (4) whether the Patient Information Sheet should be in larger print. A large majority of the Committee voted "yes" on each of these questions, 11 to 2, 9 to 2, 12 to 1, and 12 to 1, respectively. See HEW, Drug Abuse Advisory Committee Transcript, April 17, 1979, at 255-282.

emphasize the Black Box Warning (boxed warning), which advised prescribers not to prescribe propoxyphene products to suicidal or addiction-prone patients; to prescribe propoxyphene products with caution for patients taking tranquilizers or antidepressants or patients who use alcohol to excess; and to warn patients not to exceed the recommended dosage and to limit their consumption of alcohol.

On February 28, 2006, Public Citizen filed the instant petition. In the petition, Public Citizen requests the phased removal of all propoxyphene products from the market on grounds that they have a low margin of safety[12] and are less effective than other products on the market with the same indication.[13] Based on the information in the petition and information about ongoing regulatory action on propoxyphene taking place in the European Union (E.U.), FDA decided to discuss issues presented in Public Citizen's petition at a public Advisory Committee meeting.

On January 30, 2009, the Anesthetic and Life Support Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee met jointly to consider information from a variety of sources concerning the safety and efficacy of propoxyphene products. A presentation was made by Dr. Sidney Wolfe on behalf of the petitioner, Public Citizen.[14] As in the instant petition, Dr. Wolfe requested that the Committees recommend the phased withdrawal of all propoxyphene containing products from the market. In support of this request, Dr. Wolfe discussed Drug Abuse Warning Network (DAWN) data[15], medical examiner data from Florida,[16] FDA's original efficacy review for propoxyphene,[17] data from the European Union (including data from a hospital in Denmark, and the action on propoxyphene in the United Kingdom),[18] and possible treatment alternatives to propoxyphene including acetaminophen, aspirin, and hydrocodone.[19] Dr. Wolfe also presented a statement by Dr. Steven Karch, an assistant medical examiner in San Francisco, asserting that propoxyphene should be withdrawn from the market because attempted suicide with propoxyphene is difficult to treat.[20]

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[12] See Petition at 4-13.

[13] See Petition at 3-4.

[14] See Transcript of the Joint Meeting of the Anesthetic and Life Support Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee, Food and Drug Administration, Center for Drug Evaluation and Research, January 30, 2009 (2009 Advisory Committee meeting), at 17-46.

[15] See Transcript of the 2009 Advisory Committee meeting, at 20-21

[16] See Transcript of the 2009 Advisory Committee meeting, at 21-23.

[17] See Transcript of the 2009 Advisory Committee meeting, at 24-25.

[18] See Transcript of the 2009 Advisory Committee meeting, at 32-38.

[19] See Transcript of the 2009 Advisory Committee meeting, at 45.

[20] See Transcript of the 2009 Advisory Committee meeting, at 25-32.

Presentations were made by four people on behalf of Xanodyne Pharmaceuticals (Xanodyne) and other sponsors of propoxyphene products. These presentations discussed the prevalence of pain and its need for treatment,[21] the lack of evidence of propoxyphene's cardiotoxicity,[22] the lack of safer alternatives to propoxyphene,[23] the history of propoxyphene's approval and the data supporting its approval,[24] several reasons why the U.K. experience with, and decisions concerning, propoxyphene products are not applicable to the United States,[25] the data on propoxyphene products from the National Poison Data System (NPDS) (formerly know as the Toxic Exposure Surveillance System (TESS)),[26] and the utility of propoxyphene as a pain treatment option.[27]

Presentations were also made by six people on behalf of FDA. These presentations related to the regulatory history and clinical efficacy data on propoxyphene products,[28] the clinical pharmacology of propoxyphene,[29] nonclinical toxicology findings,[30] utilization trends for propoxyphene products,[31] Adverse Event Reporting System (AERS) data pertaining to propoxyphene,[32] and DAWN data pertaining to propoxyphene.[33]

After hearing all of these presentations, and discussing the information presented, the Anesthetic and Life Support Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee were asked to comment on three questions and vote on one question. The three discussion questions were as follows: (1) Whether there is evidence that propoxyphene contributes to the efficacy of propoxyphene and

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[21] See Transcript of the 2009 Advisory Committee meeting, at 47-49.

[22] See Transcript of the 2009 Advisory Committee meeting, at 50-51.

[23] See Transcript of the 2009 Advisory Committee meeting, at 51.

[24] See Transcript of the 2009 Advisory Committee meeting, at 52-59.

[25] See Transcript of the 2009 Advisory Committee meeting, at 60-62.

[26] See Transcript of the 2009 Advisory Committee meeting, at 69-83.

[27] See Transcript of the 2009 Advisory Committee meeting, at 83-86 (Lauren Shaiova, M.D.), 86-98 (Gerald M. Sacks, M.D.).

[28] See Transcript of the 2009 Advisory Committee meeting, at 116-126 (Jin Chen, M.D.).

[29] See Transcript of the 2009 Advisory Committee meeting, at 127-139 (Sheetal Agarwal, Ph.D).

[30] See Transcript of the 2009 Advisory Committee meeting, at 140-147 (Steve Leshin, Ph.D.).

[31] See Transcript of the 2009 Advisory Committee meeting, at 148-156 (Hina Mehta, Pharm.D.).

[32] See Transcript of the 2009 Advisory Committee meeting, at 157-167 (Joann Lee, Pharm. D.).

[33] See Transcript of the 2009 Advisory Committee meeting, at 168-179 (Capt. Kathy Poneleit, DAWN Project Director).

acetaminophen combination products; (2) (a) whether there is evidence that propoxyphene is cardiotoxic in the therapeutic range, and (b) whether additional data are needed to adequately assess the potential for cardiac effects, and if so, what data; and (3) what are the potential risks associated with the replacement of propoxyphene with alternative products should propoxyphene-containing products be removed from the market.

The fourth question presented, the voting question, was whether the balance of risk and benefit support continued marketing of propoxyphene-containing products for the management of mild to moderate pain. The Committee voted by a narrow margin (14 to 12) against the continued marketing of propoxyphene products.[34]

On June 25, 2009, the European Medicines Agency (EMEA) recommended that member states gradually withdraw propoxyphene products from their markets. The EMEA's recommendation was based largely on two factors: First, EMEA's concern about the number of intentional (suicides) and accidental fatal overdoses occurring in EMEA countries with dextropropoxyphene-containing drugs; and second, EMEA's conclusion that the available data do not provide evidence that propoxyphene products are more effective than other painkillers.

Currently, drug products containing propoxyphene (alone or in combination with other ingredients) are approved and marketed in the United States in the following formulations:[35]

Propoxyphene (mg)	Acetaminophen (mg)
65 (HCl)	650
100 (Napsylate)	500
100 (Napsylate)	650
100 (Napsylate)	325
50 (Napsylate)	325
65 (HCl)	
100 (Napsylate)	

If FDA determines that a drug product is no longer safe or effective, FDA may initiate proceedings to withdraw that drug product from the market. (*See* 21 U.S.C. 355(e); 21 CFR 314.150(a)(2).) Title IX, subtitle A, section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the FDCA to provide FDA with new authorities to require holders of approved drugs to make safety-related labeling changes (section 505(o)(4) of the FDCA), to develop and comply with Risk Evaluation and Mitigation Strategies (REMS) (section 505-1(a) of the FDCA (21 U.S.C. 355 (a)), and to conduct postmarketing studies and clinical trials for certain purposes, if FDA

[34] See Transcript of the 2009 Advisory Committee meeting, at 291.

[35] Our records reflect that there are 14 companies marketing a total of 28 propoxyphene products.

makes certain findings required by the statute (section 505(o)(3)(A) of the FDCA), based upon new safety information[36] that becomes available after approval of the drug. This provision took effect on March 25, 2008.

For the reasons discussed below, we believe initiating the withdrawal of propoxyphene products in the United States is not appropriate at this time. We have taken the EMEA recommendation and underlying rationale into consideration, but we believe that the overall risk-benefit profile for propoxyphene products remain favorable in properly selected patients. However, based on safety information that has become available since the approval of the marketed propoxyphene-containing products, FDA is invoking its authority under FDAAA to initiate the process to require holders of approved applications for propoxyphene products to make safety-related labeling changes, develop and comply with a REMS, and conduct a clinical trial to assess the risk of QT prolongation. The letter to application holders setting forth these requirements and the new labeling that FDA has prepared are attached to this response.[37] These actions are also further addressed in the discussion that follows.

II. DISCUSSION

Your petition requests the phased removal of all propoxyphene-containing products from the market. In support of this request, Public Citizen states that the risks of propoxyphene products outweigh their benefits as evidenced by five factors: (1) they are cardiotoxic;[38] (2) there are a substantial number of deaths associated with their use;[39] (3) they are over-prescribed in the elderly;[40] (4) they are addictive and have great potential for abuse;[41] and (5) they are relatively ineffective as pain medications.[42] We address each of these arguments, in turn, below.

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[36] As defined in section 505-1(b)(3) of the FDCA, *new safety information* is information derived from a clinical trial, an adverse event report, a postapproval study (including a study under section 505(o)(3)), or peer-reviewed biomedical literature; data derived from the postmarket risk identification and analysis system under section 505(k) of the FDCA; or other scientific data deemed appropriate by the Agency about, among other things, a serious or an unexpected serious risk associated with use of the drug that the Agency has become aware of (that may be based on a new analysis of existing information) since the drug was approved.

[37] Enclosed with this response to your petition are a copy of the letter to application holders (FDAAA Letter, Enclosure 1) and FDA's revised labeling (Revised Labeling, Enclosure 2).

[38] See Petition at 4-7.

[39] See Petition at 7-11.

[40] See Petition at 11-12.

[41] See Petition at 12-13.

[42] See Petition at 3-4.

A. The Available Data Support the Safety of Propoxyphene Products When Used as Directed

In support of your request that propoxyphene products be withdrawn from the market, you make several arguments concerning the safety of these products. The FDCA authorizes FDA to initiate the withdrawal of a drug product if clinical or other experience, tests, or other scientific data show that the drug is unsafe for use under the conditions of use upon which the application was approved, or if new evidence of clinical experience, not available or contained in the application prior to approval, evaluated together with evidence available at the time the application was approved, show that the drug is not shown to be safe for use under the conditions upon which the application was approved.[43]

We have reviewed the safety information that you submitted along with information available from other sources, including information received in connection with the 2009 Advisory Committee meeting and data from AERS, IMS Health (IMS), DAWN, and National Poison Data System (NPDS). As discussed below, based on our review of this and other available information, we believe that it would be inappropriate to withdraw propoxyphene products from the market at this time. Instead, we are addressing the safety concerns with these products by invoking our authority under FDAAA to initiate the process to require updates to the labeling of all propoxyphene products, a REMS, and a clinical trial. We believe that these safety measures will address the safety concerns that you have raised.

1. The Potential for Propoxyphene Cardiotoxicity Does Not Support Its Removal From the Market

You state that propoxyphene should be withdrawn from the market because it is a potent cardiotoxic agent and can cause severe cardiovascular effects with overdose or even when used as directed.[44] You also suggest that these cardiovascular effects are of particular concern because they are not reversed by opioid antagonists (e.g., naloxone).[45]

We have thoroughly reviewed the relevant literature and available data and agree that, in propoxyphene overdose, there is evidence of cardiac effects that do not appear to respond to an opioid antagonist, like naloxone. However, we disagree with your assertions that propoxyphene is cardiotoxic when used as directed, including in the elderly, and that the potential for cardiac effects in overdose requires withdrawal of propoxyphene from the market. Instead, we believe that the labeling revisions that will result from the exercise of our FDAAA authority, in conjunction with the MedGuide, will adequately warn against the possibility of adverse effects of excessive doses of propoxyphene. We also

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[43] 21 U.S.C. 355(e)(1), (2); see also 21 CFR 314.150(a)(2)(i), (ii).

[44] See Petition at 4.

[45] See Petition at 4.

believe that better data on the potential for cardiotoxicity is needed and, therefore, are requiring a clinical trial on that subject under our FDAAA authority.

a. Cardiotoxicity When Used as Directed

In support of your assertion that propoxyphene can be cardiotoxic even when used as directed, you refer the Agency to table 1 in your petition,[46] which purports to document that patients who took propoxyphene at or slightly above the prescribed dose developed dangerous levels of norpropoxyphene[47] in their blood. Given that this table appears to have been derived from a combination of clinical and anecdotal data,[48] from both published and unpublished sources, it does not, in and of itself, provide adequate evidentiary support for a regulatory decision. In addition, we do not find the one peer reviewed paper referenced in the table[49] persuasive, and our independent review of the literature revealed a dearth of scientifically sound evidence to support an association between propoxyphene use and cardiotoxicity. In keeping with these observations, the majority of the Advisory Committee members at the January 2009 Advisory Committee meeting did not believe the available data are indicative of cardiotoxicity when propoxyphene is used as directed.[50]

Furthermore, our review of the AERS data suggests that propoxyphene is not cardiotoxic when dosed in accordance with the labeled instructions, and that its use is no more frequently associated with cardiotoxicity than any other approved analgesic. We found 427 total crude reports[51] relating to propoxyphene in the AERS database from February 2005 to April 2006. Of those 427 crude reports, we found 108 (approximately 25 percent) relating to cardiac events, most of which reflected the ingestion of excessive doses of propoxyphene. While these reports may suggest that in propoxyphene overdose, a metabolite emerges at levels high enough to become cardiotoxic, because most of the reports involved excessive doses of propoxyphene, these AERS data cannot appropriately be used to conclude that there is an association between the cardiotoxic metabolite and propoxyphene used at the labeled dosage. Moreover, in our review of serious adverse events reported to AERS in 2006 and 2007, there was insufficient evidence to support any association between propoxyphene and cardiotoxicity. During this period, the

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[46] See Petition at 5, Table 1.

[47] Norpropoxyphene is the metabolite of propoxyphene.

[48] According to the petition, some of the data upon which the table is based were reported to the petitioner via "personal communications." The petition cites no other source for this data.

[49] See Petition at 5 (citing Verebeley K. and Inturrisi C.E., 1973).

[50] Twenty-four committee members said the available data do not support evidence of cardiotoxicity in the therapeutic range, six thought there was evidence of cardiotoxicity, and two did not respond directly to the question.

[51] We use the term *crude reports* to indicate that there may be duplicates among the 427 total reports identified.

majority of reports involving cardiac events were heavily confounded by an underlying medical history of cardiac issues and the use of concomitant medications that could have led to the cardiac events reported.[52]

The DAWN data also suggest that there is no remarkable connection between propoxyphene use and cardiotoxicity. Specifically, the DAWN data show that of the 3,154 total reports pertaining to propoxyphene alone in 2007, 415 of those reports (13 percent) involved a cardiac event.[53] Moreover, of the cases involving a cardiac event, most involved hypotension and chest pain and were not indicative of the lethal cardiotoxicity that you describe. The DAWN data for 2007 also contain fewer reports of cardiac events associated with propoxyphene than reports of cardiac events associated with codeine.[54] Importantly, the DAWN data also show very few deaths related to propoxyphene products[55] and fewer deaths associated with the use of propoxyphene products than with the use of other opioids, including oxycodone, hydrocodone, or methadone.[56]

Likewise, the NPDS data fail to demonstrate an association between propoxyphene use and cardiotoxicity. According to the NPDS data presented at the Advisory Committee meeting, cardiac events associated with propoxyphene use were rarely reported to NPDS; 1 percent of adverse drug reaction cases included cardiac events associated with propoxyphene, while 2 percent of adverse drug reaction cases included cardiac events associated with hydrocodone, 2 percent of adverse drug reaction cases included cardiac events associated with oxycodone, and 3 percent of adverse drug reaction cases included cardiac events associated with morphine.[57]

Despite these observations, we are concerned about the dearth of reliable studies examining a potential link between propoxyphene use (and misuse) and cardiotoxicity. Therefore, as described in the attached letter to the NDA holder, under our FDAAA authority, we are requiring the NDA holder to conduct a clinical trial to assess the risk of cardiovascular events, including life threatening arrhythmias, that may occur in association with use of propoxyphene.[58]

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[52] See Transcript of the 2009 Advisory Committee meeting, at 161 (Joann Lee, Pharm. D.).

[53] See Capt. Kathy Poneleit Slide 23, 2009 Advisory Committee meeting (concluding small number of cardiovascular events involving propoxyphene).

[54] See Capt. Kathy Poneleit Slide 5, 2009 Advisory Committee meeting.

[55] See Transcript of the 2009 Advisory Committee meeting, at 175 (Capt. Kathy Poneleit) (explaining 6 percent out of 503 cases were propoxyphene only, 1 percent were propoxyphene-acetaminophen combinations, and 1 percent were propoxyphene only and acetaminophen only).

[56] See Capt. Kathy Poneleit Slide 21, 2009 Advisory Committee meeting.

[57] See Transcript of the 2009 Advisory Committee meeting, at 76 (Jody L. Green, Ph. D.).

[58] See Enclosure 1 (FDAAA Letter).

b. Cardiotoxicity and Overdose

In support of your argument that propoxyphene is cardiotoxic and should be withdrawn from the market, you cite mortality data from DAWN and assert that the cardiotoxicity of propoxyphene leads to a high percentage of accidental deaths from overdose — over 40 percent of all propoxyphene-related deaths.[59] However, as indicated above, the DAWN data show very few deaths associated with propoxyphene products and even fewer deaths associated with propoxyphene than with other opioids, including oxycodone, hydrocodone, or methadone.[60] Moreover, neither AERS data nor NPDS data appear to confirm your estimate. AERS data reflect that 12 percent of the deaths reported were accidental, and neither these reported deaths nor the other reported adverse events had significant indicia of cardiac toxicity.[61] Similarly, our analysis of the NPDS data indicates that one-third of the propoxyphene exposures resulting in a telephone call to a poison control center were unintentional,[62] and only a small percentage (0.42 percent) of those exposures resulted in death.

In support of your request for withdrawal, you also assert that the majority of propoxyphene is metabolized into norpropoxyphene, a cardiotoxic metabolite that clears the body more slowly than its parent compound.[63] We agree that propoxyphene is converted to norpropoxyphene and that norpropoxyphene has a longer half-life than propoxyphene.[64] We are also aware of the in vitro research and case studies demonstrating that both propoxyphene and norpropoxyphene have negative effects on inotropy (i.e., decreased contractility of the heart) and cause prolonged QRS duration (i.e., lengthening the period of time of electrical conduction within the heart).[65] However, consistent with our interpretation of the AERS data discussed in section II.B.1.a above, all of these effects are seen in overdose situations, not when

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[59] See Petition at 4.

[60] See Transcript of the 2009 Advisory Committee meeting, at 176 (Capt. Kathy Poneleit) (explaining the propoxyphene deaths were much lower than other opioids).

[61] Moreover, our review of the AERS data from January 1, 2006, through December 31, 2007, revealed that in 73 percent of the propoxyphene-related cardiac cases reported to AERS during this period, there was a history of other cardiac-related events (including hypertension, chronic diastolic heart failure, cardiomyopathy, coronary artery bypass graft, atrial fibrillation, hypercholesterolemia) and use of concomitant medications labeled for cardiac-related events.

[62] These unintentional exposures consist of therapeutic errors (e.g., a patient with liver disease was prescribed propoxyphene) and unintentional misuse (e.g., a patient accidentally took more than the prescribed number of pills).

[63] See Petition at 4.

[64] See Flanagan et al., 1989; Verebeley and Inturrisi, 1973.

[65] See Amsterdam et al., 1981; Ulens et al., 1999; Whitcomb et al., 1989; Hantson et al., 1995; Afshari et al., 2005; Marraffa et al., 2006.

propoxyphene is used as labeled. Moreover, we have no reason to believe that withdrawal of propoxyphene products from the market will curb the incidence of intentional drug overdoses in the United States, particularly given the multitude and availability of other products on the market that can be substituted for propoxyphene for that purpose. This point is further supported by our review of AERS death reports associated with Darvocet products from 1969 to 2005.[66] During this time, the majority of death reports involving the Darvocet products (primarily drug overdoses and suicides) involved multiple drugs, thus, making it impossible for us to attribute these deaths to the use of the Darvocet products.

Moreover, although the observations described above about the metabolization of propoxyphene could theoretically be linked to accidental overdose generally and increased risk of accidental overdose in geriatric patients in particular, we have found no data to suggest that this is the case. We also have seen no evidence that physicians have been prescribing or will prescribe excessive doses of propoxyphene products. Furthermore, as discussed in section II.B.1.c. below, we believe that the updated dosing instructions in the new labeling, along with the MedGuide, will reinforce appropriate dosing and will be effective in preventing adverse events associated with unintentional overdose.[67]

c. The New Product Labeling Will Adequately Inform of the Available Data on Cardiotoxicity and the Risk of Overdose

In our view, the labeling revisions that will result from the exercise of our FDAAA safety labeling authority will appropriately capture the uncertainty of the available data on cardiotoxicity. The proposed CLINICAL PHARMACOLOGY section provides in pertinent part:

> Propoxyphene is a centrally acting opiate analgesic. In vitro studies demonstrated propoxyphene and the metabolite norpropoxyphene inhibit sodium channels (local anesthetic effect) with norpropoxyphene being approximately 2-fold more potent than propoxyphene and propoxyphene approximately 10-fold more potent than lidocaine. Propoxyphene and norpropoxyphene inhibit the voltage-gated potassium current carried by cardiac rapidly activating delayed rectifier (hERG) channels with approximately equal potency. It is unclear if the effects on ion channels occur within therapeutic dose range.[68]

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[66] This review included all AERS reports that referenced any Darvocet product, therefore, including both Darvocet and Darvocet-N and all strengths of these products.

[67] See Enclosure 2 (Revised Labeling), DOSAGE AND ADMINISTRATION (providing in bold print twice, "Do not exceed the maximum daily dose.")

[68] Enclosure 2 (Revised Labeling).

Furthermore, as in the current labeling, the new labeling clearly and repeatedly cautions about overdose.[69] FDA's proposed revised boxed warning states:

> There have been numerous cases of accidental and intentional overdose with propoxyphene products either alone or in combination with other CNS depressants, including alcohol. Fatalities within the first hour of overdosage are not uncommon. Many of the propoxyphene-related deaths have occurred in patients with previous histories of emotional disturbances or suicidal ideation/attempts and/or concomitant administration of sedatives, tranquilizers, muscle relaxants, antidepressants, or other CNS-depressant drugs. Do not prescribe propoxyphene for patients who are suicidal or have a history of suicidal ideation.[70]

The WARNINGS section of FDA's proposed new labeling reiterates this warning in a subsection on *Risk of Overdose*,[71] and as mentioned in section II.B.1.b above, we have included bolded warnings in the DOSAGE AND ADMINISTRATION section directing patients not to exceed the maximum daily dose.[72]

We are also requiring that the holders of applications for propoxyphene products prepare a MedGuide that highlights important safeguards for use of the drug, and will be required

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[69] The current product labeling also provides significant cautionary statements about the hazard of propoxyphene overdose: The current boxed warning states, "Tell your patients not to exceed the recommended dose . . . ." The boxed warning also provides in pertinent part:

> Propoxyphene products in excessive doses, either alone or in combination with other CNS depressants, including alcohol, are a major cause of drug-related deaths. Fatalities within the first hour of overdosage are not uncommon. In a survey of deaths due to overdosage conducted in 1975, in approximately 20% of the fatal cases, death occurred within the first hour (5% occurred within 15 minutes). Propoxyphene should not be taken in doses higher than those recommended by the physician. The judicious prescribing of propoxyphene is essential to the safe use of this drug.

[70] Enclosure 2 (Revised Labeling).

[71] This subsection provides:

> There have been numerous cases of accidental and intentional overdose with propoxyphene products either alone or in combination with other CNS depressants, including alcohol. Fatalities within the first hour of overdosage are not uncommon. Many of the propoxyphene-related deaths have occurred in patients with previous histories of emotional disturbances or suicidal ideation/attempts and/or concomitant administration of sedatives, tranquilizers, muscle relaxants, antidepressants, or other CNS-depressant drugs. Do not prescribe propoxyphene for patients who are suicidal or have a history of suicidal ideation.

[72] See Enclosure 2 (Revised Labeling).

to be dispensed to patients with all propoxyphene products.[73] We will work with the application holders in preparing the MedGuide to ensure that it, too, captures important dosing information, including specific dosing instructions and the risks of overdose. The MedGuide will be required to convey that propoxyphene products are to be taken exactly as prescribed and that the dose should not be changed unless at the direction of a physician. The MedGuide will also indicate the maximum number of tablets that should be taken in any one day and provide information about what a patient should do if she or he has taken more propoxyphene than prescribed or an overdose. Unlike the current Patient Information Sheet, the MedGuide will also underscore that propoxyphene overdose can be lethal within 1 hour of the overdose.

2. *The Number of Deaths, Intentional and Accidental, Associated With Propoxyphene Use Does Not Support Its Removal From the Market*

In the petition, you request that propoxyphene be withdrawn from the market because of the number of deaths, accidental and intentional, associated with propoxyphene use. You support this request with reference to DAWN data from 1981 through 1999, which you state show an increasing number of accidental deaths reported[74] and support your assertion that withdrawing propoxyphene products from the market would reduce the number of completed suicides as a whole.[75] We have carefully considered your arguments, but disagree that they warrant removing propoxyphene products from the market.

First, DAWN mortality data must be used with great caution when seeking to detect a trend in deaths involving any drug over a lengthy period of time, including propoxyphene. And, we believe that the DAWN data are not reliable for evaluating trends of deaths involving propoxyphene from 1981 to 1999. For that period, trend analysis can only be done by identifying a consistent panel of medical examiners and coroners from metropolitan areas who submitted sufficient data to DAWN each year and comparing only those jurisdictions that remain within the consistent panel from year to year. In addition to having a very limited number of medical examiners and coroners who form a consistent panel over such an extended period of time, the medical examiners and coroners who do become part of the consistent panel are not representative of any particular geographic region; they are simply those medical examiners and coroners who submitted data for at least 10 months of each year during the years for which the trend analysis is being done. Because of these drawbacks, DAWN abandoned the consistent panel approach to trend analysis in 2000. DAWN continues to collect data from medical examiners and coroners in metropolitan areas, but now collects statewide data from state

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[73] The MedGuide differs from the Patient Information Sheet in that our regulations require that the MedGuide be in a specific format and that it be dispensed with the product, whereas our regulations do not require a specific format or contain any distribution requirement for the Patient Information Sheet. See 21 CFR 208.24(e) (requiring dispenser to provide MedGuide directly to patient).

[74] See Petition at 8-9.

[75] See Petition at 10.

medical examiners, which greatly improves the ability to perform trend analyses. Another problem with the reliability of DAWN data for trend analysis between 1981 and 1999 is that, during those years, DAWN only collected data related to "drug abuse" deaths, whereas after 2003 DAWN expanded its data collection to include reports of all "drug related" deaths. In other words, the scope of the data collected by DAWN after 2003 is far superior to data collected prior to that year in that it captures emergency department visits involving pharmaceutical misuse where there is no direct documentation of abuse. Despite these issues with performing trend analysis with DAWN data during the period you reference, what the DAWN data do reveal is that in 2007 (the most recent year available), propoxyphene was implicated in fewer deaths than oxycodone, hydrocodone, or methadone.[76]

In keeping with this observation, the graph that you provide as Figure 1[77] also fails to support your assertion that propoxyphene-associated deaths have been "creeping steadily upwards."[78] In your "Deaths Per Year" illustration, the graph actually shows a relatively stable number of deaths each year between 1981 and 2002. Your focus on the "Cumulative Deaths" illustration is misplaced, as that represents the cumulative total of deaths reported by medical examiners and coroners to the DAWN system between 1981 and 2002, rather than a steadily rising number of deaths each year. Accordingly, we disagree that the DAWN data you rely upon demonstrate an increase in the number of propoxyphene-associated deaths, either accidental or intentional.

Second, we disagree with your assertion that withdrawing propoxyphene products from the market would reduce the number of completed suicides as a whole. According to the NPDS database, formerly known as the TESS database, propoxyphene products were implicated — typically as part of a multiple-drug overdose — in approximately 1 percent of all U.S. drug-related deaths reported to NPDS in 2003 (14 of 1,106 total). The AERS death cases involving Darvocet products from 1969 to 2005, likewise, primarily involved ingestion of multiple drugs. Of the 490 adverse event reports for Darvocet products during this time period, there were a total of 472 domestic reports. Of those 472 domestic reports, there were 91 death reports, 74 of which appeared to be multi-drug overdoses.[79] Moreover, in the NPDS database, propoxyphene ranked lower than hydrocodone and oxycodone for both the total number of intentional exposures and for the rate of intentional exposures per 100,000 prescriptions dispensed.[80] The NPDS database also reflected that the overall rate of death associated with propoxyphene is 0.14

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[76] See Capt. Kathy Poneleit Slide 21, 2009 Advisory Committee meeting.

[77] See Petition at 8.

[78] Petition at 8.

[79] At the 2009 Advisory Committee meeting, Captain Kathy Poneleit's review of the DAWN data indicated that in 2007, 92 percent of deaths involving propoxyphene also involved other drugs. Her review further indicated that the vast majority of propoxyphene-involved deaths for the years 2004 through 2007 involved other drugs.

[80] See Transcript of the 2009 Advisory Committee meeting, at 79-80 (Jody L. Green, Ph. D.).

deaths per 100,000 prescriptions dispensed, which is the lower than the rates of death associated with either morphine or oxycodone.[81]

The multifactorial causes of suicide, compounded by the fact that most self-poisonings involve multiple drugs, make it impossible to know whether withdrawing propoxyphene from the market would result in fewer completed suicides. However, in our view, it is unlikely that withdrawal of propoxyphene would make a significant difference in the overall U. S. suicide rate, in large part because of the number of toxic substances (including many drug products) available to someone wishing to commit suicide, compounded by the many other non-drug-related suicide methods available.

In reaching this conclusion, we have taken into consideration the information you provided concerning withdrawal of propoxyphene products in the United Kingdom. As an initial matter, our understanding is that propoxyphene has not truly been withdrawn from the market in the United Kingdom. Propoxyphene remains available to patients in the United Kingdom on a named-patient basis, which means that any physician may prescribe co-proxamol (dextropropoxyphene plus acetaminophen) for any patient in the physician's care so long as the physician judges the medication to be in the best interests of the patient.[82] In addition, the issue of suicide is qualitatively and quantitatively different in the United States and the United Kingdom. The suicide rate is greater in the United Kingdom than in the United States.[83] In 2001, the suicide rate was 10.7 per 1 million in the United States compared to 17.7 per 1 million in the United Kingdom.[84] Furthermore, "poisoning" by drugs or other ingested toxins[85] was the method of suicide in approximately 17 percent of U.S. suicides, whereas "drug-related poisoning" was the method of suicide in 29 percent of U.K. suicides.[86] Given these differences in suicide statistics, removing propoxyphene products in the United Kingdom may be predicted to have a greater impact on the reduction of suicides than would removing propoxyphene products in the United States.

In addition, we would like to underscore that in reaching the conclusion that the number of propoxyphene-related deaths in the United States does not support removing

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[81] See Transcript of the 2009 Advisory Committee meeting, at 81 (Jody L. Green, Ph. D.).

[82] This information was provided to FDA directly by the Medicines and Healthcare products Regulatory Agency, FDA's counterpart in the United Kingdom.

[83] Data for this analysis was obtained from the CDC website, http://webappa.cdc.gov/sasweb/ncipc/mortrate 10_sy.html and from http://www.statistics.gov.uk/downloads/theme_health/HSQ20.pdf.

[84] Our review of the data focused on the year 2001. From year to year, there are slight variations in the data on these Web sites, but all of the data available are comparable to the data from 2001, so they do not alter our analysis or conclusion.

[85] In the United States, the term "poisoning" includes prescription drugs, illicit drugs, carbon monoxide, and other toxic ingestions.

[86] More specifically, in the United Kingdom, "drug-related poisoning" was the method of suicide for 20 percent of men and 46 percent of women.

propoxyphene from the market, we believe (and have seriously considered) the evidence that propoxyphene is more lethal in overdose than other opioids. However, as discussed further in section II.A.3 below, we also believe that withdrawal of propoxyphene from the market would leave patients with treatment alternatives (including other opioids and nonsteroidal anti-inflammatory drugs (NSAIDs)) that are known to have serious risks, including some with more significant risks than propoxyphene risks. It is, in part, with this concern in mind, compounded by our awareness of the importance of treating pain,[87] that we favor labeling revisions and patient outreach as an alternative to initiating the action for withdrawal that you request.

3. *Propoxyphene Use By the Elderly Does Not Support Its Removal From the Market*

You request that propoxyphene be withdrawn from the market, stating that it is over-prescribed for, and misused by, the elderly.[88] As support for this request, you rely on the criteria described by Beers et al.[89] and the recommendation of the American Geriatrics Society.[90] Dr. Beers consulted a panel of expert clinicians who opined that propoxyphene is not recommended in the geriatric population, and the American Geriatrics Society adopted Dr. Beers' recommendation.

Dr. Beers' articles are not persuasive evidence that the geriatric population should not use propoxyphene products because the conclusions reached by Dr. Beers were not based on peer-reviewed scientific data, but rather on opinions offered by geriatricians. In fact, because of the recently recognized hazards of NSAIDs (including potentially life-threatening gastrointestinal bleeding and renal toxicity (side effects more likely to occur in the elderly)), we believe that propoxyphene products are a useful alternative for some elderly patients who cannot tolerate NSAIDs and are not responding adequately to acetaminophen alone.[91]

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[87] Pain is one of the most common medical complaints. However, despite its prevalence, many individuals still suffer with unrelieved or undertreated pain. Undertreated pain has a negative impact on daily activities in the majority of pain sufferers, including deleterious effects on mental health, employment status, sleep, and personal relationships. See McCarberg B.H., et al., 2008. And, there is great variability in response to analgesics and in tolerability of analgesics across patients, making it extremely important to have a wide range of choices of analgesics.

[88] See Petition at 11-12.

[89] See Petition at 12 (citing Beers, Ouslander et al., 1991); see also Beers, 1997; Fick et al., 2003.

[90] American Geriatrics Society, 2002.

[91] See Bauer R.O., Study 3a submitted to NDA 16-844 and 17-122 by Eli Lily and Company, December 17, 1971; see also Cooper S.A., et al., 1981 (supporting the contribution of propoxyphene to the efficacy of the propoxyphene/acetaminophen combination).

Moreover, we do not think it is possible to assess what you term "over-prescription in the elderly" based on the available data. Our research reveals that, in 2007, 38 percent of retail propoxyphene-acetaminophen prescriptions were dispensed to patients over 64 years of age, but there is no way for us to measure whether this percentage (or any other percentage) constitutes "over-prescription." In addition, your suggestion that propoxyphene over-prescription is evidenced by the fact that propoxyphene may "increase the likelihood of falls and hence fall-related fractures in the elderly"[92] is also not helpful to our analysis. We believe that any sedating drug product used in an elderly population may be correlated with an increased number of falls and, hence, fall-related fractures. The fact of these potential outcomes cannot be considered without also considering that many of the alternatives that may be prescribed in lieu of propoxyphene are equally likely to lead to fall-related fractures.

Furthermore, according to the NPDS data, adverse drug reactions in patients 65 and older were less commonly reported in association with propoxyphene than in association with either oxycodone or morphine and are on par with reports of adverse reactions in association with hydrocodone.[93] And, according to the DAWN data, not only did propoxyphene have fewer death reports associated with its use than either hydrocodone or oxycodone, but the fewest number of death reports in association with propoxyphene were in the 65 and over category.[94]

In evaluating whether or not to initiate an action for withdrawal, we are also cognizant of, and particularly concerned about, the adverse event profiles for the other opioids and NSAIDs that are likely substitutes for propoxyphene if it were removed from the market, particularly in the elderly population. The available analgesic alternatives to propoxyphene are listed in the following table, along with their most commonly associated adverse events.

Analgesic Alternatives to Propoxyphene

Alternative Drug	Common Adverse Events
Aspirin	Gastrointestinal bleeding, tinnitus, hypersensitivity/asthma
Acetaminophen	Hepatotoxicity
NSAIDs	Gastrointestinal bleeding, serious cardiovascular events renal injury, liver injury, serious skin reactions,
Tramadol	Respiratory depression, seizures, nausea, vomiting, serotonin syndrome
Hydrocodone in combination with acetaminophen	Nausea, vomiting, constipation, addiction, hepatotoxicity

[92] Petition at 12.

[93] See Transcript of the 2009 Advisory Committee meeting, at 77 (Jody L. Green, Ph.D.); see also Dr. Jody Green Slide 17, 2009 Advisory Committee meeting.

[94] See Capt. Kathy Poneleit Slide 22, 2009 Advisory Committee meeting.

Codeine in combination with acetaminophen	Constipation, sedation, nausea, vomiting
Schedule II opioids	Respiratory depression and apnea, nausea, vomiting, constipation, addiction

The side effects associated with these drugs are both more frequent and more severe in the elderly. Tramadol, for instance, which is an unscheduled opioid analgesic, is one possible alternative. However, as noted in the package insert for Ultram, an immediate-release Tramadol product, "In studies including geriatric patients, treatment-limiting adverse events were higher in subjects over 75 years of age compared to those under 65 years of age. Specifically, 30 percent of those over 75 years of age had gastrointestinal treatment-limiting adverse events compared to 17 percent of those under 65 years of age. Constipation resulted in discontinuation of treatment in 10 percent of those over 75."[95]

The risk of gastrointestinal bleeding with use of NSAIDs, including the COX-2 inhibitors, in the elderly is so significant that, just this past April, the American Geriatrics Society published a new pain management guideline stating that the use of nonselective NSAIDs and COX-2 inhibitors should generally not be prescribed for elderly patients.[96] The American Geriatrics Society also cautioned against the long-term use of drugs like ibuprofen, naproxen, and high-dose aspirin, and indicated that elderly patients who cannot get relief from acetaminophen may be better off taking opiates.

That said, we do agree with your assertion that even at recommended doses, elderly patients may be exposed to higher doses of propoxyphene for longer periods of time and, therefore, may have an increased risk of adverse reactions to propoxyphene products than patients who are not elderly.[97] Nevertheless, we believe that this potentiality will be adequately addressed by the product labeling and the MedGuide that we are requiring.

The revised labeling has warnings in several sections that address the concerns you have raised regarding use in elderly patients. The SPECIAL POPULATIONS section provides:

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[95] Hydrocodone also is problematic for geriatric patients because it carries a significant risk of central nervous system depression in the elderly.

[96] American Geriatrics Society Panel on Pharmacological Management of Persistent Pain in Older Persons, Pharmacological Management of Persistent Pain in Older Persons, http://www.americangeriatrics.org/education/pharm_management.shtml (providing, among other things, "Nonselective NSAIDs and COX-2 selective inhibitors may be considered rarely, and with extreme caution, in highly selected individuals").

[97] See Petition at 11-12. In our review of serious adverse events reported to AERS in association with propoxyphene in 2006 and 2007, 40 percent of the 65 cases reviewed involved patients 65 years or older. In this population, psychiatric events such as hallucination and other mental status changes, which are already included in the current product labeling, were the most commonly noted.

Geriatric Patients

After oral administration of propoxyphene in elderly patients (70-78 years), much longer half-lives of propoxyphene and norpropoxyphene have been reported (propoxyphene 13 to 35 h, norpropoxyphene 22 to 41 h). In addition, the AUC was an average of 3-fold higher and the Cmax was an average of 2.5-fold higher in the elderly when compared to a younger (20-28 years) population. Longer dosage intervals may be considered in the elderly because the metabolism of propoxyphene may be reduced in this patient population. After multiple oral doses of propoxyphene in elderly patients (70-78 years), the Cmax of the metabolite (norpropoxyphene) was increased 5-fold.[98]

In the PRECAUTIONS section, we have added the following warning:

Elderly Patients

Clinical studies of DARVOCET-N did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. However, postmarketing reports suggest that patients over the age of 65 may be more susceptible to CNS-related side effects. Therefore, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. Decreased total daily dosage should be considered (See DOSAGE AND ADMINISTRATION).

We believe that these additions to the labeling, which will be reiterated in the MedGuide, are sufficient to address the safety concerns that you have raised related to the geriatric population. We find this approach preferable to initiation of an action for withdrawal, particularly in light of the adverse event profiles for the other pain relievers, including opioids and NSAIDs, that are likely substitutes for propoxyphene if it were removed from the market.

4. Propoxyphene Addiction and Abuse Potential Does Not Justify Its Removal from the Market

You request that propoxyphene be withdrawn from the market, stating that it has euphoria and addiction causing properties that create a high potential for abuse.[99] As support for this request, you reference six articles highlighting that propoxyphene has

[98] Enclosure 2 (Revised Labeling).

[99] See Petition at 11-12.

addiction potential.[100] We agree that propoxyphene has addiction potential. We believe, however, that the fact that propoxyphene products are controlled substances under the CSA adequately reflects this addiction potential and that the addiction potential does not justify withdrawal of propoxyphene products from the market.

The one new article referenced in this section of your petition is a retrospective compilation of data from a substance abuse clinic in Mexico.[101] This article summarizes the characteristics of propoxyphene abusers at one specific clinic and merely confirms that propoxyphene has abuse potential, which, again, is reflected in its Schedule IV status. In short, the classification of propoxyphene drug products as Schedule IV is an acknowledgement that propoxyphene does have addiction potential and that the use of propoxyphene may result in physical and/or psychological dependence. We believe withdrawal on this basis is not justified.

In support of your assertion concerning the continued abuse of propoxyphene, you also cite DAWN data, reflecting a stable yearly number of reported emergency room visits related to propoxyphene products between the years 1995 and 2002. Taken as a whole, however, the abuse-related evidence is not sufficient to conclude that withdrawal of propoxyphene products from the market is warranted. Our review of available data suggests that propoxyphene abuse has not increased in recent years. From 2005 to 2007, DAWN data show only small variations in the number of emergency department visits, and from 2005 to 2007, the number of emergency department visits associated with propoxyphene was comparable to the number of emergency department visits associated with codeine. In addition, at the 2009 Advisory Committee meeting, the Substance Abuse and Mental Health Services Administration (SAMHSA) presented data indicating that, although substance abuse treatment center admissions for opioid analgesics appear to have risen in recent years, these admissions have risen at a lower rate than overall admissions to such facilities. Moreover, propoxyphene accounted for only 1 percent of reported admissions.[102]

We also believe that your argument stressing the need to remove propoxyphene from the market because of the potential abuse of propoxyphene by teenagers,[103] among others who access it for nonmedical purposes, is not convincing. Our view is that those seeking access to drugs for nonmedical purposes will find many equally or more addiction-prone drugs readily available to them than propoxyphene and that its removal from the market is unlikely to curtail substance abuse as a whole.

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[100] See Petition at 16, notes 61 through 66. It is noteworthy that all but one of these articles were reviewed and considered by the Advisory Committee in 1979, when it affirmed an earlier Advisory Committee recommendation that propoxyphene products remain on the market as Schedule IV under the Controlled Substances Act.

[101] Ng B. and Alvear M., 1993.

[102] In contrast, oxycodone accounted for 82 percent of reported admissions to such facilities.

[103] See Petition at 12.

Furthermore, both the current propoxyphene labeling and the revised labeling under our FDAAA authority clearly warn of propoxyphene's potential for abuse and dependence.[104] The revised labeling, indeed, strengthens the warnings on abuse and dependence and has an entire section dedicated to explaining these risks. Specifically, the DRUG ABUSE AND DEPENDENCE section of our revised labeling provides:

> **Controlled Substance**
>
> DARVOCET-N is a Schedule IV narcotic under the U.S. Controlled Substances Act. DARVOCET-N can produce drug dependence of the morphine type, and therefore, has the potential for being abused. Psychic dependence, physical dependence and tolerance may develop upon repeated administration. DARVOCET-N should be prescribed and administered with the same degree of caution appropriate to the use of other narcotic-containing medications.
>
> **Abuse**
>
> Since DARVOCET-N is a mu-opioid agonist, it may be subject to misuse, abuse, and addiction. Addiction to opioids prescribed for pain management has not been estimated. However, requests for opioids from opioid-addicted patients occur. As such, physicians should take appropriate care in prescribing DARVOCET-N.
>
> **Dependence**
>
> Opioid analgesics may cause psychological and physical dependence. Physical dependence results in withdrawal symptoms in patients who abruptly discontinue the drug after long term administration, Also, symptoms of withdrawal may be precipitated through the administration

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[104] The CONTRAINDICATIONS section of the current Darvocet-N 50 and Darvocet-N 100 labeling (at 3) provides:

> *Drug Dependence*— Propoxyphene, when taken in higher-than-recommended doses over long periods of time, can produce drug dependence characterized by psychic dependence and, less frequently, physical dependence and tolerance. Propoxyphene will only partially suppress the withdrawal syndrome in individuals physically dependent on morphine or other narcotics. The abuse liability of propoxyphene is qualitatively similar to that of codeine although quantitatively less, and propoxyphene should be prescribed with the same degree of caution appropriate to the use of codeine.

There are also two separate warnings about propoxyphene's potential for abuse and dependence included in the Patient Information Sheet. One states: "Do not take more of the drug than your doctor prescribed. Dependence has occurred when patients have taken propoxyphene for a long period of time at doses greater than recommended." The other, in a bolded subsection headed **Dependence** cautions: "You can become dependent on propoxyphene if you take it in higher than recommended doses over a long period of time. Dependence is a feeling of need for the drug and a feeling that you cannot perform normally without it."

of drugs with mu-opioid antagonist activity, e.g., naloxone or mixed agonist/antagonist analgesics (pentazocine, butorphanol, nalbuphine, dezocine). (See also OVERDOSAGE section). Physical dependence usually does not occur to a clinically significant degree, until after several weeks of continued opioid usage. Tolerance, in which increasingly larger doses are required to produce the same degree of analgesia, is initially manifested by a shortened duration of an analgesic effect and subsequently, by decreases in the intensity of analgesia.

In chronic pain patients, and in opioid-tolerant cancer patients, the administration of DARVOCET-N should be guided by the degree of tolerance manifested and the doses needed to adequately relieve pain.

The severity of the DARVOCET-N® abstinence syndrome may depend on the degree of physical dependence. Withdrawal is characterized by rhinitis, myalgia, abdominal cramping, and occasional diarrhea. Most observable symptoms disappear in 5 to 14 days without treatment; however, there may be a phase of secondary or chronic abstinence which may last for 2 to 6 months characterized by insomnia, irritability, and muscular aches. The patient may be detoxified by gradual reduction of the dose. Gastrointestinal disturbances or dehydration should be treated with supportive care.[105]

Moreover, in the PRECAUTIONS section we have also added the following explanation of and warning about tolerance and dependence:

Tolerance and Physical Dependence

Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Physical dependence is manifested by withdrawal symptoms after abrupt discontinuation of a drug or upon administration of an antagonist. Physical dependence and tolerance are not unusual during chronic opioid therapy.

The opioid abstinence or withdrawal syndrome is characterized by some or all of the following: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other symptoms also may develop, including: irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.
In general, opioids should not be abruptly discontinued (see DOSAGE AND ADMINISTRATION: Cessation of Therapy).

If DARVOCET-N is abruptly discontinued in a physically dependent patient, an abstinence syndrome may occur (See DRUG ABUSE AND DEPENDENCE). If signs and symptoms of withdrawal occur, patients

[105] Enclosure 2 (Revised Labeling).

> should be treated by reinstitution of opioid therapy followed by gradual tapered dose reduction of DARVOCET-N combined with symptomatic support (see DOSAGE AND ADMINISTRATION: Cessation of Therapy).[106]

We believe that while the current labeling warns of the potential for abuse and dependence associated with propoxyphene use, the modifications reflected in the language above highlight even further the addiction and abuse concerns that you have raised and are sufficient to address them.

B. The Available Data Support the Effectiveness of Propoxyphene as a Mild Analgesic

In support of your request that propoxyphene products be withdrawn from the market, you state that propoxyphene is relatively ineffective as a pain medication. The FDCA authorizes FDA to initiate the withdrawal of a drug product if new information, evaluated together with evidence available at the time the application was approved, shows "a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof."[107] The standard for an analgesic drug product's effectiveness is typically measured by comparison of the drug product to placebo or an active comparator, as long as the drug under investigation can show superiority to the comparator. In other words, clinical trials of analgesic drug products generally rely on demonstrating *superior efficacy* to either placebo or other drug products with the same or similar indication.[108] It is well documented that, applying this superiority standard, even when using placebo as the comparator, drug products known to be effective as analgesics still may fail to demonstrate efficacy in some clinical trials.[109] Applying this standard, FDA concludes that propoxyphene demonstrates sufficient effectiveness to remain on the market.

In reaching this conclusion, we have relied upon the data from seven clinical trials submitted in connection with the original NDAs for Darvocet and Darvocet-N. We recognize that these clinical trials differ considerably from modern clinical trials of analgesics in that they are of a shorter duration, are conducted in a single study site, and

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[106] Enclosure 2 (Revised Labeling).

[107] 21 U.S.C. 355(e)(3); see also 21 CFR 314.150(a)(2)(iii).

[108] In keeping with this practice, all of the seven clinical trials for propoxyphene were placebo-controlled.

[109] For instance, the CLINICAL STUDIES section of the package insert for RYZOLT (tramadol hydrochloride extended-release tablets) describes that four studies that were conducted, but that efficacy was demonstrated in only one. Specifically, the package insert states:

> RYZOLT was studied in four 12-week, randomized, double-blind, controlled studies in patients with moderate to severe pain due to osteoarthritis. Efficacy was demonstrated in one double-blind, placebo-controlled, randomized withdrawal design study.

evaluate a single dose of the study drug. We also recognize that the statistical methods used to analyze trial data have improved considerably in the decades since these propoxyphene products were first approved. However, despite their limitations, the data are sufficient to demonstrate that both propoxyphene and the combination of propoxyphene/acetaminophen are superior to placebo. Equally important, FDA does not have new information to show "a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling hereof" as required by the FDCA to initiate the withdrawal of a drug product.

Two of the seven trials assessing a propoxyphene/acetaminophen combination demonstrated the analgesic efficacy of propoxyphene alone, and one of the seven trials demonstrated efficacy of the combination of propoxyphene-acetaminophen over the individual components. As noted above, it is understood that some analgesic products known to be effective fail to demonstrate efficacy in some instances.[110] There are a variety of reasons that this failure may occur, including the choice of a study population that is not well suited for the drug product. The study population for the propoxyphene trials was women with postpartum pain due to uterine cramping or episiotomy — a population not commonly treated with propoxyphene today.[111] We believe that the focus of the clinical trials on this population is responsible, at least in part, for the failure of several of the propoxyphene clinical trials to demonstrate efficacy. However, where, as here, more than one clinical trial demonstrates efficacy, a finding of effectiveness is appropriate.

In short, our review of the original NDA data suggests that propoxyphene has some analgesic effects, albeit mild, in some acute pain trials. Moreover, the extant literature supports the original NDA data that propoxyphene has some analgesic effects. The relevant literature includes meta-analyses that analyzed studies in which propoxyphene and the combination of propoxyphene and acetaminophen showed efficacy in the setting of acute pain. For instance, one meta-analysis, analyzing publications from 1954 through 1996, found a single dose of single-ingredient 65 mg of propoxyphene efficacious based on data from six trials. That meta-analysis also found a single dose of a combination of 65 mg of propoxyphene and 650 mg of acetaminophen efficacious based on data from four trials.[112] In another meta-analysis, the authors found, among other things, that the efficacy of 65 mg of propoxyphene was similar to 60 mg of codeine or 50 mg of tramadol.[113]

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[110] See supra note 109.

[111] Propoxyphene is not commonly used today for pain due to uterine cramping or following episiotomy because there are products better suited for these conditions, including other opioids and NSAIDs.

[112] See Moore R.A., et al., 2008.

[113] Collins S.L., et al., 1998; *see also* Goldstein and Turk, 2005 (concluding that propoxyphene appears to provide analgesic effects equivalent to most active comparators); Po and Zhang, 1997 (finding that propoxyphene and acetaminophen in combination and single-ingredient acetaminophen were statistically superior to placebo and that propoxyphene and acetaminophen in combination were numerically more

These findings are complemented by the 2006 review of the Veterans Heath Administration Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel, which offered the following conclusion:

> Although new data became available on the single-dose efficacy of propoxyphene and on safety concerns associated with propoxyphene abuse and accidental fatal overdoses, we found no substantive evidence to alter our previous conclusions about the efficacy and safety of propoxyphene relative to other opioids. Our recommendations on the use of propoxyphene in the Veterans Health Administration remain essentially the same as in the previous review.
>
> In the majority of VA patients with mild to moderate acute pain and who do not have certain characteristics associated with intentional or unintentional overdose, single-dose or short-term therapy with DPP + APAP probably provides adequate analgesia with an acceptable safety profile. The efficacy and safety of long-term therapy with DPP + APAP for treatment of chronic pain has not been adequately studied.[114]

Given the large numbers of people using propoxyphene products for pain management, our current understanding of the safety and efficacy profile of propoxyphene itself, and our knowledge of the safety profile of treatment alternatives, we believe that those patients who find propoxyphene particularly useful for the treatment of their conditions should have continued access to it. That said, we also believe that the form and substance of the efficacy data available at this time warrant revisions to the product labeling to more appropriately convey the risk-benefit profile of propoxyphene products and to ensure the safe use of the drug, and we are confident that the revised labeling will capture this information.

Despite its limitations, we believe that the data on effectiveness do not support the initiation of an action to remove propoxyphene products from the market at this time and that revisions to the labeling can appropriately ensure that the benefits outweigh the risks of these products.

C. As a Whole, the Limited Effectiveness and Risk Factors Associated With the Use of Propoxyphene Products Do Not Support Their Withdrawal From the Market

In sections II.A and II.B of this response, we have addressed each of the arguments that you raise in support of your request that we immediately begin the phased removal of

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effective than single-ingredient acetaminophen); Hopkinson, J.H., et al., 1973 (finding that the combination of propoxyphene and acetaminophen was slightly more effective than single-ingredient acetaminophen).

[114] VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel Review of the Efficacy and Safety of Propoxyphene, March 2006, http://www.pbm.va.gov/Clinical%20Guidance/Drug%20Class%20Reviews/Propoxyphene,%20Drug%20Review.pdf

propoxyphene products from the market. Examining each of your arguments independently, we believe that none individually justifies removing propoxyphene products from the market at this time.

We have also considered your arguments as a whole to determine whether weighing the totality of the risks and benefits associated with propoxyphene products leads us to a different conclusion. It does not. We believe that the labeling, with the changes that we are initiating pursuant to our authority under FDAAA, accurately characterizes the overall risks and benefits of propoxyphene products and that there is no basis for their removal from the market at this time. However, in reaching this conclusion, we believe it is also important to underscore that our decision is motivated, in part, by our understanding that the alternatives to propoxyphene have similar or sometimes more serious risks, particularly to geriatric patients, who appear to be the largest population for which propoxyphene is prescribed. We also believe that the data on cardiotoxicity is inconclusive and, therefore, are requiring a thorough QT clinical trial to generate further data about this concern.

D. Next Steps for Safety Labeling Changes and REMS Under FDAAA

Earlier today, letters were issued notifying manufacturers of propoxyphene-containing products that we believe new safety information necessitates that the labeling for propoxyphene products be modified to provide additional warnings, and that a MedGuide as part of a REMS is necessary. In addition, we notified the NDA holder that it is required to conduct a clinical trial to assess the risk of QT prolongation. This notification was based on our new authority with respect to safety labeling changes, REMS, and postmarketing requirements under sections 505(o)(4), 505-1(a), and 505(o)(3) of the Act, respectively. The notification was accompanied by new labeling prepared by FDA.

In accordance with section 505(o)(4) of the Act, within 30 days, the holders of the relevant applications are required to submit a supplement containing the proposed labeling changes (including additional warnings, other labeling revisions, and the MedGuide), or notify the Agency that they do not believe labeling changes are warranted and submit a statement detailing the reasons why changes are not warranted. Within 30 days of the letter, the NDA holder is also required to submit a proposed REMS, which must include a timetable for submission of assessments of the REMS. ANDA holders will be required to have a REMS containing the same MedGuide consistent with section 505-1(i) of the Act. We have also determined that the NDA holder will be required to conduct a clinical trial to assess the risk of QT prolongation with propoxyphene products.

If the relevant propoxyphene application holders do not submit proposed safety labeling changes, or if we disagree with the language that the companies propose, the Act provides strict timelines under section 505(o)(4) for discussions regarding the labeling changes. At the conclusion of these discussions, section 505(o)(4) also allows us to issue an order directing labeling changes we consider appropriate to address the new safety information.

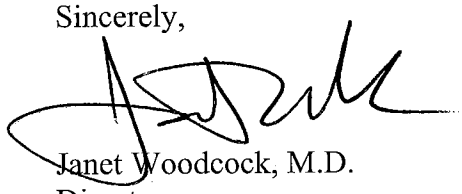
Under these FDAAA procedures, we are awaiting the response of the propoxyphene application holders to our notification that additional warnings, other revisions to product labeling, a REMS, and a clinical trial are necessary. The specific language we have proposed in the labeling is subject to change depending on what language the application holders propose and their reasoning. However, we have taken all the necessary steps that are required under the carefully prescribed procedures of FDAAA to pursue the necessary labeling changes, the REMS, and the clinical trial.

III. CONCLUSION

In sum, we are denying the relief that you have requested because we disagree that the side effects of propoxyphene products, and other concerns that you have raised related to their use, require withdrawal of propoxyphene from the market. In our view, the control of the products in Schedule IV of the CSA, the stringent updated warnings that will be incorporated into the product labeling, and the REMS for the products, including the MedGuide that accompanies propoxyphene products, appropriately address the concerns that you have raised.

We stress, however, that the promise of FDAAA is that FDA's postmarketing surveillance of propoxyphene products does not end with the additional safety measures that we are taking today. Indeed, the assessment component of a REMS under FDAAA provides a clear framework for FDA to continue to monitor propoxyphene products and — as with any other FDA-approved prescription drug product — FDAAA gives FDA the authority to take additional safety measures should new safety information become available. We will keep closely attuned to the safety information provided to us about propoxyphene products, including the development and results of the clinical trial that we are requiring. Should we later discover that additional measures are necessary to ensure the safe and effective use of propoxyphene products, we have the authority to take that action and we will.

Sincerely,



Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

Enclosures:
1. FDAAA Letter
2. FDA Revised Labeling