PETITION FOR RECONSIDERATION

The undersigned submit this petition for reconsideration of the July 7, 2009 decision of the Commissioner of Food and Drugs in Docket No. FDA-2006-P-0270.

A. Decision involved

On February 28, 2006, pursuant to 21 C.F.R. § 10.30, we petitioned FDA to withdraw approval of propoxyphene, citing the drug's considerable human toxicity, addiction potential, susceptibility to abuse, and very limited therapeutic usefulness. On July 7, 2009, FDA denied the relief that we requested and instead ordered other measures short of withdrawal.

B. Action Requested

For the reasons explained in detail below, we request that the Commissioner reconsider the matter and begin the process of withdrawing propoxyphene from the market.

C. Statement of Grounds

In denying the relief requested in our citizen petition, FDA failed to consider all the available scientific evidence, entirely omitted key information, and misrepresented other evidence. Such evidence, all known to the agency prior to the decision and a part of the administrative record, includes information not presented by the FDA at the advisory committee meeting, inaccurate FDA conclusions concerning safety, efficacy and the benefit risk balance of propoxyphene at the meeting and in FDA's response to our petition, and events and new information since the meeting but before the decision was issued. Further, the remedial measures announced by FDA---new labeling and warnings---are inadequate to address the concerns raised in our petition because such measures because they:

a/ were tried by the FDA and failed after our 1978 petition to ban propoxyphene

b/ were rejected by the UK when it initiated the phase-out of propoxyphene in 2005 and

c/ were also rejected in June of this year by the EMEA when it decided to remove propoxyphene from the market---rather than order labeling changes---as the only realistic way of addressing the serious public health problems caused by the drug.

The events and new information at or since the meeting, either entirely ignored or barely mentioned in the FDA response include, but are not limited to, the following:

1/ Information from the Florida state medical examiner system we presented at the 1/30/09 FDA advisory committee meeting concerning 460 deaths caused by propoxyphene in that state alone between 2003 and 2007, including 110 of these which occurred in people in whom propoxyphene was the only drug responsible for causing the death. Such forensic information was thought to be critical by the UK and EMEA in their decisions to withdraw propoxyphene.

2/ A March 17, 2009 letter to the FDA from Scottish Clinical Toxicology expert Dr. D. N. Bateman, explaining the unique opioid properties of propoxyphene, the physiological basis by which so many deaths occur from its use and discussing the reason for and the early evidence of success in Scotland of the UK withdrawal of the drug.

3/ The June 18, 2009 article in the British Medical Journal which documented the success of the UK withdrawal of propoxyphene in severely reducing deaths from the drug in England and Wales. The article also showed that there was no compensatory increase in deaths from other drugs whose use increased as a result of the withdrawal.

4/ The June 25, 2009 EMEA Decision to withdraw propoxyphene for reasons only minimally acknowledged by the FDA. The full set of reasons, detailed below, raise serious questions about the basis for the FDA decision not to withdraw the drug.

This petition for reconsideration is endorsed, as is the 2006 petition to ban the drug, by former FDA Commissioner Dr. Donald Kennedy who was at the FDA when our original petition was filed in 1978. It is also endorsed by Dr. Jerry Avorn, a Harvard Professor whose research involves drug epidemiology and who published a study in 1987 documenting how the FDA's earlier efforts to remedy the propoxyphene public health problem by labeling and education failed either to reduce the use of the drug or the rate of propoxyphene-related deaths. It is also endorsed by Forensic Toxicologist Dr. Stephen Karch, whose testimony was included in our January 30, 2009 presentation at the FDA advisory committee meeting. Dr. Nick Bateman, a Scottish Clinical Toxicology expert who recently published an article on the positive effects of the UK ban on suicides in Scotland has also supported our petition and wrote to the FDA in March (to Acting Commissioner Dr. Frank Torti) but the contents of his letter were not evident in the FDA 7/7/09 response. It is also endorsed by Swedish propoxyphene experts Ulf and Birgitta Jonasson.

In each of the following sections on Efficacy, Safety, Benefit Risk Balance, and the Proposed Labeling Remedy we will begin with the FDA conclusion from the 7/7/09 letter denying the relief requested in our petition and then respond with evidence including earlier FDA statements, our petition and testimony, a statement by Dr. Avorn who studied the ineffectiveness of FDA actions in the late 1970's, a statement by former FDA Commissioner Dr. Donald Kennedy, and conclusions that were the basis of the UK and EMEA actions as well as studies documenting the effectiveness of the UK withdrawal.

I. EFFICACY

A. FDA 7/7/09 Response to Petition

The section that begins with the statement: "The Available Data Support the Effectiveness of Propoxyphene as a Mild Analgesic" goes on to say, referring to all of the studies, that "propoxyphene demonstrates sufficient effectiveness to remain on the market." The section goes on to say that "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" and that, "despite their [study] limitations, the data are sufficient to demonstrate that böth propoxyphene and the combination of propoxyphene/acetaminophen are superior to placebo"

Despite the evidence cited above, CDER concludes that "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."

In other words, as will be repeatedly seen in other parts of the FDA response, evidence is somewhat thrown aside and a labeling remedy is decided to be superior to a ban.

B. FDA Presentation at 1/30/09 Advisory Committee (AC) Meeting and Meeting Documents

FDA's Office of Surveillance and Epidemiology (in CDER), in conjunction with their safety review, advised that: "the regulatory action recommended for FDA by the upcoming AC should be based on clear clinical evidence of propoxyphene efficacy satisfactory to inform a robust discussion of the risk/benefit profile for these drugs." As will be seen below, no such clear evidence exists.

A much more negative view of propoxyphene efficacy was presented by CDER at the advisory committee meeting than appears in the 7/7/09 response to our petition. The efficacy portion concluded that "While most of the studies show that in combination with acetaminophen, the propoxyphene component appears to contribute little or no additional analgesic effect beyond the efficacy of the acetaminophen when studied in patients with acute pain, there is at least one study that does support the contribution of propoxyphene to the efficacy of the combination."

FDA similarly stated in slide 20 at the AC meeting, but not mentioned in the 7/7/09 response, that "Propoxyphene has no or little contribution to efficacy of the APAP [acetaminophen] combination for acute pain. Limited information is available to assess analgesic effects on chronic pain." A 1997 published meta-analysis (Po & Zhang: *BMJ* 1997) also not discussed in the 7/7/09 FDA response but presented by the FDA at the AC meeting, found the "Difference in pooled SPID [pain scores] between the combination [propoxyphene and APAP] and APAP was not statistically significant."

Yet another study cited by CDER in the 1/30/09 briefing documents but not referred to in the 7/7/09 response was a 1973 study by Hopkinson which found that "A global evaluation at the end of treatment (4 hours) showed no difference between the PPX/APAP combination and the single-ingredient APAP in the percentage of patients reporting "effectiveness:" The results follow:

- 64% in the combination [APAP propoxyphene] group
- 62% in the single-ingredient APAP group
- 34% in the single-ingredient propoxyphene group

- 30% in the placebo group"[1]

C. Conclusions by the UK and by the EMEA Concerning Efficacy

UK: When the phased withdrawal was announced, the British government stated that: "There is no robust evidence that efficacy of this combination product [APAP and propoxyphene] is superior to full strength paracetamol [APAP] alone in either acute or chronic use."

EMEA: Similarly, when the EMEA announced its ban in June, they stated that "The available evidence suggests that the combination of dextropropoxyphene and paracetamol is no more effective than paracetamol on its own."

II. SAFETY

A. FDA 7/7/09 Response to Petition

Unlike the efficacy data, concerning which the FDA's AC meeting presentation included much more evidence-based arguments against its efficacy than did the FDA response to our petition, the safety presentation at both the AC meeting and in the response were weaker and more incomplete.

The main FDA arguments concerning safety and against market withdrawal in the 7/7/09 response were that:

1/ the drug is cardiotoxic in overdoses but there is no evidence for cardiac toxicity when used as directed

2/ the " [U.S.] DAWN data show very few deaths associated with propoxyphene products"[2]

3/ "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"

4/ "we believe (and have seriously considered) the evidence that propoxyphene is more lethal in overdose than other opioids"

5/ The FDA disagrees with our cited evidence of over prescribing to older adults by its opinion that the Beers and similar decisions, such as that of the American Geriatrics Society (AGS), stating that the drug should not be used by elderly people, are based on opinion, not peer-reviewed evidence. Ironically, in the same section of the letter, in the context of the dangers of older adults switching from propoxyphene to NSAIDs, the FDA cites a recent AGS pain management guideline stating that "the use of nonselective NSAIDs and COX-2 inhibitors should generally not be prescribed for elderly patients." (It

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[1] FDA AC Efficacy Briefing Document, page 18.

[2] Transcript of the 2009 FDA Advisory Committee meeting, at page 175.

should be mentioned here that the FDA ignores a study listing explicit criteria for placing drugs on this so-called Beers list, which for propoxyphene, says it should be avoided in the elderly because "It offers few analgesic advantages over acetaminophen, yet has the side effects of other narcotic drugs.[3]

6/ "We also have seen no evidence that physicians have been prescribing or will prescribe excessive doses of propoxyphene products. Furthermore, as discussed in section ILB.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."
(Here, curiously, FDA does not see physician misprescribing as a problem but seeks, in its black box warning and other labeling remedies, to effect physician behavior—as well as patient behavior.)

For reasons that are unclear, the FDA repeats three times in their 7/7/09 letter that if they banned the drug it would not stop the problem of intentional drug overdoses:

Page 12: "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."

Page 15: "we disagree with your assertion that withdrawing propoxyphene products from the market would reduce the number of completed suicides as a whole."

Page 16: "in our view, it is unlikely that withdrawal of propoxyphene would make a significant difference in the overall U.S. suicide rate"

FDA's repetition of this now demonstrably incorrect statement (see recently-published evidence of suicide reduction following the announcement of the UK market withdrawal, discussed below [4]) strongly suggests that the agency's rejection of our petition to ban is seriously weakened by the fact that such a ban has actually worked. This provides one important basis for your reconsideration of the FDA decision. (This article was published in the BMJ on June 18, 2009, a little more than two weeks before the FDA's July 7th letter rejecting our petition to ban propoxyphene.)

B. FDA Presentation/Review Documents at 1/30/09 Advisory Committee (AC) Meeting

A more thorough, but still incomplete, discussion of propoxyphene toxicity was presented in FDA briefing documents and at the 1/30/09 AC meeting. Before going through some of the information presented at the 1/30/09 AC meeting, it is worth reviewing one important set of data from Florida that were not discussed by the FDA in

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[3] Beers MH, Ouslander JG, Rollingher I, Reuben DB, Brooks J, Beck JC. Explicit criteria for determining potentially inappropriate medication use by the elderly. Arch Intern Med Jul 1997;151:1531-36.

[4] Hawton K, Bergen H, Simkin S, Brock A, Griffiths C, Romeri E, Smith KL, Kapur N, Gunnell D. Effect of withdrawal of co-proxamol on prescribing and deaths from drug poisoning in England and Wales: time series analysis. BMJ 2009;338:b2270.

either the 7/7/09 response or the AC meeting but which we presented at the 1/30/09 meeting.

But first, a brief discussion of FDA's conclusion of the DAWN data in the 7/7/09 response. As mentioned above, the FDA has stated that " [U.S.] DAWN data show very few deaths associated with propoxyphene products". This FDA mis-representation of the AC DAWN presentation mentioned on the previous page needs to be corrected since there were actually 503 propoxyphene-related deaths reported to DAWN medical examiners in 2007 as presented at the AC meeting. This hardly represents "a few deaths associated with propoxyphene products".

As improved as DAWN data are since 2003, acknowledged by the FDA on page 15 of the 7/7/09 response ("after 2003 DAWN expanded its data collection to include reports of all 'drug-related' deaths"), there are additional important and useful details in the data from Florida medical examiners.

Florida Deaths Caused by Propoxyphene:
For Florida's medical examiners, the presence of a drug in a decedent is categorized as "cause" if the Medical Examiner concluded that there was enough of the drug present to have been either the sole cause or a contributory cause of the death. Other drugs are listed as merely "present" if the Medical Examiner did not conclude that the drug played a role in the patient's death. In their words: "The state's medical examiners were asked to distinguish between the drugs being the "cause" of death or merely "present" in the body at the time of death."

In 2007, for example, of a total of 314 propoxyphene-related deaths reported in Florida, 85, or 25%, were cases in which the medical examiner concluded that the drug was a "cause of death".[5]

Of the total 85 deaths in which propoxyphene was listed as a cause, in 25 cases it was the only causal drug and in another 60 cases, there was one or more other drugs also judged to be causal to the deaths, along with propoxyphene. Of these 85 deaths, 66 were judged to be accidental and 16, suicidal.

For 2003-2007, there were a total of 460 deaths in Florida which were caused by propoxyphene. In 110 of these people, propoxyphene was the only causal drug.

It should be noted that with 18.7 million people, Florida constitutes 1/16 of US population.

The omission of any discussion of these Florida data in the 7/7/09 FDA response, other than stating that we had presented it (with no information about the content) or at the AC meeting leaves out critical evidence of large numbers of propoxyphene caused deaths, forensic evidence thought to be crucial for both the UK and EMEA decisions to with draw propoxyphene.

----END OF DISCUSSION OF FLORIDA DEATHS CAUSED BY PROPOXYPHENE----

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[5] Drugs Identified in Deceased Persons by Florida Medical Examiners: 2007. Report by the Florida Department of Law Enforcement

The FDA's documents and presentation at the 1/30/09 AC meeting included the following information either not mentioned or put into perspective in the 7/7/09 response:

Cardiotoxicity/Toxicity Overall: From FDA Clinical Pharmacology Review Documents of 1/30/09 meeting

"Norpropoxyphene is pharmacologically active. It has, however, substantially lower CNS depressant effects than propoxyphene but is thought to have a greater local anesthetic effect, which is similar to that of amitriptyline and antiarrhythmic agents, such as lidocaine and quinidine."

Conclusion of FDA Clin Pharm Review

"Nonclinical studies conducted in response to the 1979 Advisory Committee meeting revealed small dose-related changes in prolongation of PR, QRS, and QTc intervals in association with reduced cardiac function. Recent receptor studies provide evidence that propoxyphene and/or norpropoxyphene may directly influence cardiac function through Na+ channels and K+ repolarization (hERG) channels of cardiac myocytes, or through interaction at neural α3β4 nicotinic receptors and NMDA receptors. Thus the nonclinical studies support the clinical findings and the hypothesis that deaths due to overdose of propoxyphene could be due to cardiotoxicity from propoxyphene and/or norpropoxyphene. Unfortunately, whether these effects occur at therapeutic dose levels is uncertain from the in vivo animal studies submitted to the various propoxyphene NDAs, since there is insufficient animal toxicokinetic information with which to compare

to human exposure."

Figure 6
Summary of cardiac effects in intact animals (from Nickander 1984)

Table 7 Acute cardiovascular effects of dextropropoxyphene or norpropoxyphene in intact animals

	Effect	*Blood concentration P/NP (μg/ml)*	*Reference*
PR interval (AH interval)	↑+++	1.5/2	Holland & Steinberg (1979) Lund-Jacobsen (1978)
QRS duration (HV interval)	↑++	2/1.5	Holland & Steinberg (1979) Lund-Jacobsen (1978)
Heart rate	↓+	3/—	Holland & Steinberg (1979) Lund-Jacobsen (1978) Sorenson (1984)
Contractility (dP/dt)	↓++	3/—	Sorenson (1984)
Mean blood pressure	↓++	5/—	Sorenson (1984)

P or NP refers to minimum level of dextropropoxyphene or norpropoxyphene respectively, causing the indicated effect. NP levels reflect dosing with that substance rather than that formed from P

1/30/09 Review Documents from CDER Division of Pharmacovigilance II And Division of Epidemiology: Pages 28 and 20 of this review document.

Although the following table, from a 1984 review of 222 consecutive cases of propoxyphene poisoning, [6] was included in the above review documents, the study was not discussed at all during the FDA presentation. (see our comments below)

Sloth 1984[16]	222 consecutive cases of propoxyphene poisoning. • Impaired circulation in 48% • Bradycardia in 9% • Tachycardia in 15% • ECG abnormalities in 41% (43 patients with widened QRS complexes, 1 with 1st degree AV Block, 19 with ventricular arrhythmias

OVERALL FDA CONCLUSIONS [based on updated FDA AERS review]
 Propoxyphene products may have had additive effects that contributed to cardiac events given the temporal association (5/11, 45%) and positive dechallenge (3/11,

[6] Acta Anaesthesiol. Scand 1984;28:661-665

27%) in some cases.

- Over one-third (10/26, 38%) of the cases involving the elderly patients (65 years or older) reported psychiatric (e.g. hallucination, confusion, mental status changes) events which may reflect pharmacodynamic effects of propoxyphene in this population.

- Cases of plausible drug interactions in this review suggest that propoxyphene taken concomitantly with certain drugs may be associated with increased concentrations of propoxyphene or the co-administered drug, resulting in potentially life threatening toxicity (including cardiac events).

- The increased risk of fatalities from overdosage when propoxyphene products are used in combination with opioids, benzodiazepines, antidepressants, or other CNS depressants noted in this review is consistent with current product labeling. However, a direct causal role in fatalities for therapeutically administered propoxyphene could not be established given patients' underlying medical history, or use of multiple co-suspect drugs, or both, noted in a majority of reviewed cases.

- Despite current propoxyphene label warnings, narcotic pain relievers and other CNS related drugs continue to be prescribed and used with propoxyphene containing products, including in elderly patients.

- Literature review revealed mostly anecdotal reports of propoxyphene-related cardiotoxicity and lacked sound scientific evidence to support an association between propoxyphene-containing products and cardiotoxicity.

C. Information from Public Citizen 1/30/09 Presentation and Update by Dr. Steven Karch and response to FDA above

In addition to the aforementioned Florida death data, our presentation included other safety information omitted from the 7/7/09 response and from the 1/30/09 review documents:

Concerning the above mentioned 222 consecutive cases of propoxyphene poisoning, most of whom lived,[7] the additional findings included the authors' comments that "experimental evidence of a negative chronotropic effect (slower pulse) and negative inotropic effect (weaker heart contraction) with propoxyphene that would explain some of these clinical findings, including the fact that only a few of the patients with circulatory failure exhibited a compensatory tachycardia (faster pulse) to make up for the decreased circulation because of the negative chronotropic effect."

In addition, concerning the 17/222 patients who died, the authors found that nine (53%) of the deaths were from heart failure, a total of 13 (76%) of deaths were from all cardiovascular causes and 4 deaths (24%) were from brain damage.

[7] Acta Anaesthesiol. Scand 1984;28:661-665

Dr. Karch's presentation during the 1/30/09 AC is also not referred to in the FDA response nor are many of the points he made referred to by the FDA in their 1/30/09 presentation. Excerpts from his presentation follow:

"Dextropropoxyphene received FDA approval more than 50 year ago, at a time when it was impossible to measure propoxyphene metabolite directly, at a time when the family of CYP450 polymorphisms had not yet been discovered, when the ion channels in the heart had not yet been characterized (or, in some cases even discovered), and at a time when unintended drug reactions were difficult to identify and often went unnoticed.

Use of this drug involves important safety issues. It is widely used, around the world, in suicidal gestures and for frank suicide. The physical properties of this drug make it particularly well fitted since it is widely available, rapidly absorbed, can exert toxicity even when the plasma concentration is within the "therapeutic range." Indeed, most who attempt suicide with DPX die before they reach the hospital.

Simple DPX poisoning is straightforward and easy to understand. Even though DPX is a very weak mu agonist, when present in sufficient quantities, or taken with alcohol, it can cause respiratory depression.

However, the most dangerous aspect of DPX is that its cardio toxic oxidative metabolite, norpropoxyphene (NPX), is very long acting, and is also 2.5 times more potent than its parent compound in producing cardiac depression. It has a half-life (time before ½ of the substance is cleared from the body) of approximately 36 hours. In other words, the half-life of NPX is nearly three times longer than that of propoxyphene, which means that it will accumulate.

DPX accumulates particularly in the heart and liver. Because NPX also accumulates in the liver, it can cause disruption in the metabolism of many of the most important drugs now in use.

In the heart, NPX blocks both the IK and hERG currents. Blockade of the former can cause conduction delay and even heart block. Blockade of hERG (slow rapid depolarizing K channel) may cause QT interval prolongation leading to torsades des pointes and sudden death.

Patients who have overdosed with DPX have widening of the QRS complex, and the degree of widening is dose dependent. These findings have clinical relevance to the management of patients with DPX poisoning; heart block must be anticipated.

Disruption of liver function may be even more profound. CYP3A4 is the major CYP enzyme catalyzing DPX metabolism. The variability in pharmacodynamic and pain relieving effectiveness of DPX is likely due to large inter-subject genetic variability in hepatic CYP3A4 expression and/or drug-drug interactions.

DPX is also a competitive inhibitor of CYP3A4 and this enzyme oxidizes a large number of other important drugs. These include, calcium channel blocking agents, macrolide antibiotics, isonazid, and proton pump inhibitors. Perhaps most importantly, if the breakdown of carbamazepine, a commonly used anticonvulsant, is slowed because of propoxyphene, toxic levels may accumulate.

Strong evidence suggests that DPX is also an inhibitor of another drug-metabolizing enzyme, CYP2D6. This opens up the possibility for other types of drug interactions. Most beta blockers are metabolized by CYP2D6. A report of bradycardia in a user of metoprolol (a beta-blocker) suggest that symptomatic drug interactions are, in fact, occurring.

DPX toxicity increases in the presence of alcohol. When DPX is co-administered with Etoh, first pass hepatic metabolism is decreased, which means that DPX concentrations increases. Etoh is frequently present in DPX-related deaths. In a study of 123 DPX-related suicides in the UK, alcohol was found to be involved in 58.5% of the cases. In addition, these individuals generally had lower blood propoxyphene levels, and consumed fewer tablets."

The following is from Dr. Karch's response to the 7/7/09 FDA letter

"The government plan [labeling changes and patient education] may sound reasonable, except for that fact that more innocents will continue to die while the FDA fails to acknowledge the successful experience of the U.K. government. (see discussion of this study below) It is difficult to understand how anyone, let alone the agency charged with regulating the safety of the U.S. drug supply, could interpret these findings as evidence that propoxyphene should remain on the market.

Since propoxyphene is a weak μ receptor binder, most pathologists would presume respiratory depression was the cause of death, especially given the lack of any effort by FDA to informer the forensic community that norpropoxyphene binds the HERG receptor, making it cardiotoxic. This omission is difficult to explain given that the FDA has been aware of the danger for many years.

Finally, there is the issue of metabolism. In our initial presentation to the Panel we pointed out that, even though propoxyphene is metabolized primarily by CYP3A4, this same drug has the ability to inhibit activity of CYP2D6 (Xenobiotica, 2004). A substantial proportion of the population has a genetic predisposition to decreased CYP2D6 activity, and it has been shown that propoxyphene treatment can diminish that activity even further. Should a "slow metabolizer" be unfortunate enough be treated both with propoxyphene and a drug metabolized by CYP2D6, he is at risk for dangerous drug interactions, and these cases have already been reported (Clin Pharm Ther, 2006)"

C. 3/26/09 Letter to Acting FDA Commissioner, Frank Torti, MD MPH.from Scottish Clinical Pharmacologist and Expert on Suicide Prevention, DN Bateman BSc MD FRCP FRCP(E) FBPharmacolS FBTS. Professor in Clinical Toxicology, Consultant Physician & Director, National Poison Information Service, Edinburgh

"The pharmacology of dextropropoxyphene is very interesting, the parent compound itself, and its major metabolite norproxyphene, both have sodium channel blocking activity, and it is therefore rather a unique member of the opioid family. No other opioids we are aware of have this unique combination of properties. In chronic pain situations it might be hypothesised that sodium channel blockade would be helpful, but to my understanding, and having searched for studies in the literature, no one has ever tried to demonstrate this, and without evidence of efficacy this is merely hypothesis. However, as I am sure you are also aware, sodium channel

blockade is itself a potential hazard, particularly if drugs are taken in overdose.

We are therefore faced with the situation where we have a drug which is in its combination formulation no more effective at standard doses than merely taking a full dose of the less toxic component (acetaminophen. In contrast it is a compound which when taken in only moderate excess is associated with high mortality as judged from extensive epidemiological studies in the UK. It is certainly more toxic than the acetaminophen in our experience as patients do not survive to reach hospital for antidotal therapy.

When we studied this situation in the UK we were initially surprised to document the extent of the mortality we found when we looked for it. Essentially patients by and large died before they reached any hospital for attention, often within just a few hours of ingesting the tablets. There is anecdotal data to suggest that this rapidity to mortality may be associated with co-ingestion of alcohol, but this has not been scientifically proven to my satisfaction. Our present hypothesis is that a combination of respiratory depression (brought on by the opioid) and attendant hypoxia and acidosis, together with sodium channel blockade results in cardiac arrhythmia and sudden death. We have shown in clinical situations, evidence of sodium channel blockade by measuring QRS duration on the ECG in acute poisoning. The patients we studied were all in hospital, and fortunately none of them came to any major harm. Indeed it is extremely unusual for patients who reach hospital to die from this preparation, indicating even more the hazards of having it in the community without medical attention available in the case of acute ingestion.

A number of us in the UK have tried for several years to have this product removed from the market because of our concerns about its dangers in overdose since we are aware of several hundred patients dying annually in the UK from dextropropoxyphene in the context of an acute intentional or accidental overdose in the home environment."

D. Safety information from the UK and the EMEA

UK: In the decision to withdraw the marketing approval for propoxyphene, the UK stated in 2005 that: "the risk of toxicity in overdose, both accidental and deliberate, is unacceptable." They further pointed out that ""Each year there are 300-400 fatalities following deliberate or accidental drug overdose involving co-proxamol [propoxyphene/acetaminophen] in England and Wales alone. Approximately one-fifth of these deaths [60-80] are considered to be accidental." They also advised that "In relation to safety, there is evidence that fatal toxicity may occur with a small multiple of the normal therapeutic dose and a proportion of fatalities are caused by inadvertent overdose. Pharmacokinetic and pharmacodynamic interactions with alcohol further reduce the threshold for fatal toxicity." [8]

EMEA: In its recent decision to recommend the withdrawal of propoxyphene from all EU countries, the EMEA concluded that: "In terms of safety, the major concern of the Committee was the 'narrow therapeutic index' of dextropropoxyphene. This means that

[8] http://www.mhra.gov.uk/home/groups/pl-a/documents/websiteresources/con019461.pdf

the difference between the dose needed to treat the patient and the dose that could harm the patient is small. Patients may easily take too much dextropropoxyphene and risk a fatal overdose, as dextropropoxyphene can be rapidly fatal. Data assessed by the Committee highlighted that many of the cases of fatal overdoses seen have been accidental. Quite often, the patients had taken medicines prescribed for someone else. The CHMP also concluded that data from several Member States, specifically those from forensic centres and national mortality statistics, showed a significant number of deaths associated with overdose in patients taking dextropropoxyphene."[9]

III. BENEFIT/ RISK

FDA: In the FDA 7/7/09 response, the section in which the overall assessment of benefits and risks contains the following: "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."[10]

UK: In announcing the UK withdrawal, the government stated that: "It has not been possible to identify any patient group in whom the risk-benefit [ratio] may be positive."[11]

EMEA: In the recent EMEA announcement of withdrawal of propoxyphene, the agency stated that: "Based on evaluation of the currently available data and the scientific discussion within the Committee, the CHMP concluded that the benefits of all medicines containing dextropropoxyphene, either on its own or in combination, do not outweigh their risks. Therefore, the Committee recommended that the marketing authorisations for these medicines be withdrawn across the EU."[12]

Public Citizen: Our conclusion, stated at the beginning of our 1/30/09 testimony, was that propoxyphene has "one of the most unfavorable benefit-to-risk ratios ever seen for a drug"

IV. PROPOSED LABELING REMEDY

FDA: The FDA concluded that, as it had done when rejecting our 1978 petition to ban propoxyphene, it would strengthen the label and increase education of doctors and, this time, patients, about the dangers of propoxyphene, rather than initiating market withdrawal. In the 7/7/09 response to our petition, the agency stated that: "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."

Comments by Former FDA Commissioner Dr. Donald Kennedy

"As Commissioner of the FDA in 1978, I received a petition from the Health Research Group that urged me to initiate proceedings to ban Darvon and its formulations in combination with over-the-counter analgesics. The evidence offered considered the

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[9] http://www.emea.europa.eu/pdfs/human/referral/dextropropoxyphene/40106109en.pdf
[10] Page 27, 7/7/09 FDA Response
[11] http://www.mhra.gov.uk/home/groups/pl-a/documents/websiteresources/con019461.pdf
[12] http://www.emea.europa.eu/pdfs/human/referral/dextropropoxyphene/40106109en.pdf

involvement of propoxyphene in a number of Drug Abuse Warning Network reports involving deaths of persons having taken these drugs, often in combination with alcohol or other abused drugs. The HRG petition also pointed to evidence that propoxyphene itself, in amounts equivalent to that used in the combinations, was less effective than the combined drugs required to be ordered by prescription. At the time, I judged that numbers of persons, including elderly patients suffering from arthritis, depended on the Darvon compounds -- and that a ban could be harmful for that cohort.

That was over three decades ago. Now actions in the United Kingdom and the European Union have taken account of new efficacy studies that confirm earlier doubts about the need for propoxyphene, and have enhanced the estimates of risks associated with this opioid drug. Indeed, the results of its withdrawal from the British market demonstrate that the risks of continued use substantially outweigh the benefits of continued availability -- especially considering that now propoxyphene is available in a wider variety of generic forms. Accordingly, I would have made a different decision today. "

Comments by Dr. Jerry Avorn, author of study showing the failure of FDA's previous 1979 attempt to solve the propoxyphene problem with labeling changes

"Concern about the very unfavorable benefit-risk relationship of propoxyphene and its combinations is not new. The drug was one of the most common sources of unintentional and intentional overdose hospitalizations and deaths in the late 1970s and early 1980s (DAWN data); for these and other reasons it was chosen by us as one of just three drug groups targeted for the first "academic detailing" program to warn doctors about hazardous and/or ineffective medications[13]. Propoxyphene was identified for intervention because of its unimpressive therapeutic properties as reflected in the randomized trial literature, combined with its striking capacity to confer risk well out of proportion to its effectiveness.

A later quantitative review by the same group[14] rigorously evaluated the impact of a prior FDA-mandated labeling change to determine whether it succeeded in reducing mis- and over-use of propoxyphene. That study demonstrated that the label changes had no measurable effect in ameliorating propoxyphene-related hazards. That is, the labeling and education program ordered by the FDA failed to produce any substantial or long-lasting effect on overall prescribing nor did they generate any durable reduction in the rate of propoxyphene overdose deaths.

Despite clear clinical trial data demonstrating the failure of propoxyphene to provide impressive analgesic relief, the drug continues to be used widely, usually in combination with acetaminophen, whose risks have also been acknowledged recently by the FDA's OTC Advisory Committee. In those deliberations, the committee expressed

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[13] Effect of government and commercial warnings on reducing prescription misuse: the case of propoxyphene.Soumerai SB, Avorn J, Gortmaker S, Hawley S. Am J Public Health. 1987 Dec;77(12):1518-23.

[14] Effect of government and commercial warnings on reducing prescription misuse: the case of propoxyphene. Soumerai SB, Avorn J, Gortmaker S, Hawley S.Am J Public Health. 1987 Dec;77(12):1518-23.

great concern about the risks posed by combination of acetaminophen with codeine-type medications, which themselves do actually confer useful pain relief. It is evident from those discussions that combining acetaminophen with a less effective agent such as propoxyphene which has such a poor risk-benefit relationship should generate even more concern about its effect on the public health.

Current approaches to managing propoxyphene use have not adequately addressed its risk. A 2005 study again documented the markedly elevated fatality rate of propoxyphene-acetaminophen combinations compared to combination of acetaminophen with other (more effective) analgesics [15]. Compelling data also comes from a very recent analysis which examined the effect of withdrawal of this combination from the market in the United Kingdom. That study found a sharp reduction in deaths related to use of propoxyphene-acetaminophen, with no countervailing increases in deaths from other analgesic products to make up for it[16]. Unfortunately, the remedies most recently proposed by FDA are so similar to the earlier, poorly effective attempts it made to contain its danger that it is extremely unlikely that they will succeed any better. Since the 1970s, when the propoxyphene problem first began to attract attention, it remains a widely used analgesic. Yet since that time, additional, safer products have become available, as has improved clinical understanding of pain management. Sophistication has also grown in the measurement of drug risks, and in our understanding of what works and doesn't in managing those risks. Several key studies in this literature have even dealt with propoxyphene itself. Yet the FDA's current approach does not seem to be adequately informed by these developments. Instead, it continues to underestimate the severity of the problem, and persists in putting forward inadequate solutions that have been shown to be ineffective -- even in their application to this very problem.

We therefore conclude that the only way to significantly reduce the death and injury toll from this barely effective and extremely dangerous drug is to follow the lead of the UK and, more recently, the EMEA, and begin the process of removing it from the U.S. market."

UK: The Chairman of the Medicines and Healthcare products Regulatory Agency (MHRA), Sir Alasdair Breckenridge said: "Whilst the risks of co-proxamol are well known to health professionals, the latest evidence is that the measures to strengthen the labelling of co-proxamol have been ineffective in reducing the high fatality rate involving both intentional and accidental overdose. The MHRA and CSM have considered further evidence gathered during a public request for information on the risks and benefits of co-proxamol and have decided that the benefits of the continued availability of co-proxamol do not outweigh the risks and that co-proxamol should be withdrawn from the market.[17]"

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[15] Afshari R, Maxwell S, Dawson A, Bateman DN.ECG abnormalities in co-proxamol (paracetamol/dextropropoxyphene) poisoning. Clin Toxicol (Phila). 2005;43(4):255-9.

[16] Hawton K, Bergen H, Simkin S, Brock A, Griffiths C, Romeri E, Smith KL, Kapur N, Gunnell D. Effect of withdrawal of co-proxamol on prescribing and deaths from drug poisoning in England and Wales: time series analysis. BMJ 2009;338:b2270.

[17] http://www.mhra.gov.uk/NewsCentre/Pressreleases/CON002065

The evidence of the success of this decision was recently published in the British Medical Journal.[18] "The results and conclusions were: A steep reduction in prescribing of co-proxamol occurred in the post-intervention period 2005-7, such that number of prescriptions fell by an average of 859 thousand per quarter, equating to an overall decrease of about 59%. Prescribing of some other analgesics (co-codamol, paracetamol, co-dydramol, and codeine) increased significantly during this time. These changes were associated with a major reduction in deaths involving coproxamol compared with the expected number of deaths (an estimated 295 fewer suicides and 349 fewer deaths including accidental poisonings), but no statistical evidence for evidence for an increase in deaths involving either other analgesics or other drugs." The authors concluded that: "Major changes in prescribing after the announcement of the withdrawal of co-proxamol have had a marked beneficial effect on poisoning mortality involving this drug, with little evidence of substitution of suicide method related to increased prescribing of other analgesics."

EMEA: The decision by the EMEA to withdraw propoxyphene from the European market was made after rejecting the alternative labeling and warning approach. The agency concluded that proposals to limit the use of these products by narrowing the indication, and/or additional safety warnings and contraindications would not be sufficient to limit the risk of fatal overdose reported with dextropropoxyphene and resulting in safe and effective use of the product for the symptomatic treatment of pain.

CONCLUSION

The FDA's decision to once again try changing the label and warnings instead of withdrawing the approval of propoxyphene is akin to rearranging the deck chairs on the Titanic. Why, if an increasing part of the rest of the world knows this is a failed drug with an extremely narrow margin of safety and is actively sinking it by withdrawing its use----- is the FDA still clinging to salvaging it by a Titanic-like move.

We urge the FDA reconsider its decision to deny the relief requested in our petition and to recognize the urgency of beginning the process of removing propoxyphene from the market, as is being done in more and more of the world. This is the right public health decision and is based on the best scientific evidence and experience.

Sincerely,

Sidney M. Wolfe, MD, Director, Health Research Group at Public Citizen

Steven Karch MD, Forensic Toxicologist, Author of *Pathology of Drug Abuse*
Donald Kennedy, Ph.D, President Emeritus, Stanford University, Former Commissioner, FDA and former Editor-in Chief, Science Magazine
Jerry Avorn, MD, Professor, Harvard Medical School, Director of Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital.

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[18] Hawton K, Bergen H, Simkin S, Brock A, Griffiths C, Romeri E, Smith KL, Kapur N, Gunnell D. Effect of withdrawal of co-proxamol on prescribing and deaths from drug poisoning in England and Wales: time series analysis. BMJ 2009;338:b2270.

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