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Excerpts from the chronology of U.S. FDA inaction on Propoxyphene (Darvon, Darvocet)

1978: Public Citizen petitions to ban propoxyphene or place it in a very restrictive DEA schedule II. It was rejected.

2005: UK Statement (1/31/05) on announcing the phased withdrawal of propoxyphene from the market: the British government stated that the efficacy of this product "is poorly established and the risk of toxicity in overdose, both accidental and deliberate, is unacceptable." It further said that "It has not been possible to identify any patient group in whom the risk-benefit [ratio] may be positive ... 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."

2006: From February Public Citizen petition to the FDA to ban propoxyphene:

Toxicity: Extremely Low Margin of Safety

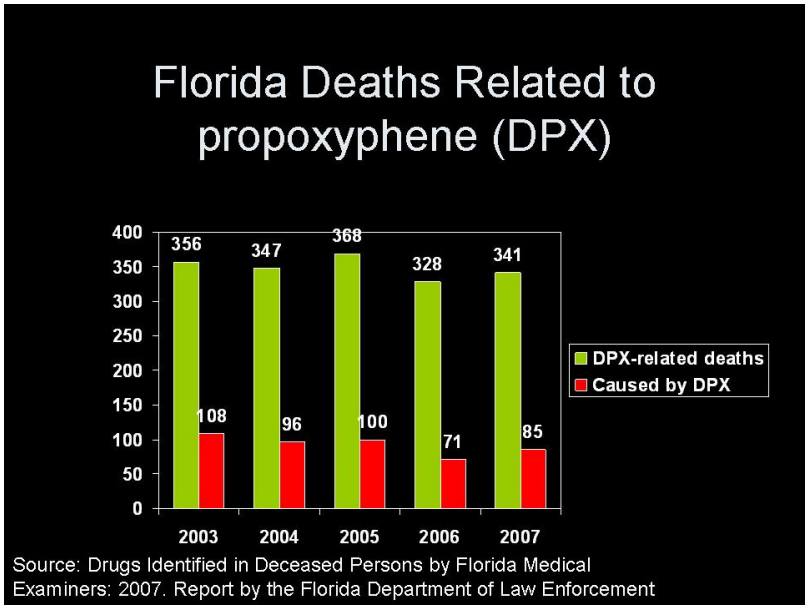
"Propoxyphene, a potent cardiotoxic agent, can cause severe cardiovascular effects with overdose or even when used as directed. Upon metabolism, the majority of propoxyphene is converted into norpropoxyphene (NPX), which is particularly dangerous as it is 2.5 times more potent than its parent compound in producing cardiac depression and has a half-life (time before ½ of the substance is cleared from the body) of approximately 36 hours, three times longer than that of propoxyphene**. Adverse cardiovascular events are marked by prolongation of the QRS complex on an electrocardiogram (which can increase the risk for an abnormal cardiac rhythm) and include bundle branch block (interruption of cardiac conduction), bradycardia (slowed heartbeat), asystole (absence of contractions), diminished myocardial contractility (ability of the heart to contract), and hypotension. These events are not reversed by opiate antagonists such as naloxone and up to 76% of deaths from propoxyphene overdose are a result of cardiac toxicity.** This high toxicity accounts for the finding that only 30-40% of

propoxyphene-related deaths are attributed to suicidal overdoses; over 40% have been found to be accidental."

"The fact that norpropoxyphene [the major metabolite of propoxyphene] is cleared from the body more slowly than its parent compound and thus reaches considerably higher blood levels and is more cardiotoxic, explains the high risk of accidental overdose." **According to Dr. Randall Baselt, FDA expert toxicology witness at the April 6, 1979, FDA hearings on Darvon: "This accumulation of drug sets the stage for accidental overdosage; one or two additional depressant drugs, such as alcohol or diazepam, may be sufficient even in normally used amounts [of alcohol or diazepam] to cause death in susceptible persons."**

"Furthermore, comparable blood levels (above 1 µg/g) of norpropoxyphene in animals can cause significant blockage of conduction through the heart – a toxicity which can lead to arrhythmias and death."

From January 30, 2009 Public Citizen testimony at FDA advisory committee meeting



(in 2009, there were 59 deaths caused by DPX in Florida alone)

Forensic Toxicologist Dr. Steven Karch as part of Public Citizen testimony at 1/30/09 FDA Hearing:
"DPX accumulates particularly in the heart and liver. Because NPX [the metabolite norpropoxyphene] 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."**

From our 1/30/09 testimony on the higher lethality of DPX in overdose than codeine-containing drugs:

"A recent study estimated the frequency of overdose and death for the three most popular acetaminophen-opioid compound analgesics: propoxyphene and acetaminophen and two different codeine preparations and acetaminophen. Adjusting for relative amounts of prescriptions of the three drugs, **overdoses involving propoxyphene and acetaminophen Scotland were 10 times more likely to be fatal [than ones involving the codeine compounds]."**

FDA Statement at January 30, 2009, advisory committee meeting

"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."

June 25, 2009, European Medicines Agency Decision to ban propoxyphene (allowed 15 months to get people off the drug)

"Because of this, the most reliable data come from forensic analysis and national mortality statistics, and complete review of the fatal overdoses (including accidental overdoses) associated with dextropropoxyphene (alone and in combination with paracetamol/caffeine) supported the major concern over the fatal toxicity of dextropropoxyphene containing products and their narrow therapeutic index."

"The impact of the phased withdrawal of co-proxamol (from 2005 to 2007) on mortality associated with co-proxamol poisoning in Scotland was also evaluated (Sandilands and Bateman. 2008). Results showed a significant reduction in the proportion of poisoning deaths due to co-proxamol following legislation [mean 2000–2004, 37 deaths (21.8% of total poisoning deaths); 2006, 10 (7.8%); $P < 0.0001$]. This was associated with a decline in prescriptions by 60% within first 6 months of the withdrawal period. The total number of poisoning deaths also fell, suggesting that the **phased withdrawal of this product has resulted in a major reduction in the number of deaths associated with co-proxamol poisoning in Scotland, with no compensatory rise in mortality from poisonings from other common analgesics."**

"In terms of safety, the major concern of the Committee was the 'narrow therapeutic index' of dextropropoxyphene. This means that 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."

"The different figures provided by the available data sources (spontaneous reports, forensic and poison centres, national mortality statistics) showed overall a significant number of deaths in which dextropropoxyphene is present at toxic levels."

"In view of the complex context in which cases of fatal overdose occurred and in view of the narrow therapeutic index and the potential for rapid death, the CHMP was of the opinion that the proposed risk minimisation activities (including those beyond the Product Information) would not be able to reduce the risks to an acceptable level."

July 6, 2009 FDA denial of Public Citizen's petition to ban propoxyphene

"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. (Compare this with opposite EMA statement above)"**

"We are also aware of the in vitro research and case studies demonstrating that both propoxyphene and norpropoxyphene have negative effects on the heart and cause prolonged QRS duration (time of electrical conduction within the heart)."

"Despite these observations, **we are concerned about the dearth of reliable studies examining a potential link between propoxyphene use (and misuse) and cardiotoxicity."**

August 6, 2009 Public Citizen's petition to FDA Commissioner Margaret Hamburg for reconsideration of FDA's denial of 2006 petition

Comments by Former FDA Commissioner Dr. Donald Kennedy (included in our petition for reconsideration; he also supported our petition to ban the drug as mentioned in our January 30, 2009 FDA testimony)

"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 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."

Excerpted from Statement of J. Richard Crout, M.D. (submitted to the FDA Docket in support of our petition for reconsideration)

From 1973 to 1982 I served as Director of the then-Bureau of Drugs at FDA (now CDER) and was intimately involved in the FDA response to the original petition from Public Citizen (November 1978) for the removal of propoxyphene from the market as an imminent hazard; accidental deaths and suicides were, then as now, the major public health problem with the drug. I supported the FDA response at that time to require stronger warnings in the labeling and to accept the manufacturer's proposal to conduct an "educational campaign" emphasizing to physicians the narrow safety margin of propoxyphene and the risk of death at higher dosages, especially when taken in combination with alcohol and others drugs.

Subsequent experience has shown that this plan should now be considered a failed experiment. No evidence has appeared through the years to show any important impact of these measures on deaths due to propoxyphene.

By all accounts propoxyphene is a weak narcotic analgesic, less effective than codeine and with similar side effects. It is difficult to envision a set of patients who uniquely require propoxyphene, or in whom the benefit-risk balance with respect to pain management favors propoxyphene over codeine, whether alone or in combination with acetaminophen. The challenge to FDA is to explain, not just assert, why such a compound meets a reasonable benefit-risk test for marketing when it carries a significant risk (yes, even if the epidemiological data are imperfect) of more deaths due to overdose, whether accidental or intentional. This problem derives from the fundamental pharmacology of propoxyphene, and experience has shown it cannot be fixed by labeling.

- The FDA response of July 7, 2009 does not deal with important data submitted by Public Citizen such as the forensic data from Florida and the presentation by Dr. Steven Karsh at the Advisory Committee meeting of January 30, 2009.
- But most importantly, it strains credulity to think that a new re-labeling of propoxyphene products, even with a Med Guide for patients, will have an important impact on physician and patient behavior, when the experience of 30 years with this strategy has shown it to be ineffective in improving safe use of these products."

(The remainder of this section directly quotes from the Public Citizen August 6, 2009 petition for reconsideration)

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

Omitted from the FDA response to our petition (but presented by the FDA at the January 30, 2009 advisory committee meeting by FDA Pharmacologist Dr. Steve Leshin):

"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."**

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

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

Concerning the above mentioned 222 consecutive cases of propoxyphene poisoning, most of whom lived, 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."