FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANALGESIA AND ANESTHESIA PRODUCTS

Memorandum

DATE:	November 18, 2010
TO:	Janet Woodcock Director Center for Drug Evaluation and Research
FROM:	Bob A. Rappaport, M.D., Director Division of Analgesia and Anesthesia Products
CC:	NDA files: 10-996, 10-997, 16-862, 17-122
RE:	Propoxyphene-containing Products

I have reviewed the memo written by Drs. Hertz and Avigan, as well as the other reviews and documents in the propoxyphene file, and I concur with Drs. Hertz and Avigan's conclusion that propoxyphene-containing products (hereafter referred to as PPX) should be removed from the market based on the higher incidence of deaths compared to other similar analgesic drug products seen in some of the epidemiological data and the new clinical data documenting the drug's cardiotoxicity at the approved doses. Nevertheless, it is important to explicate certain issues that I considered in making this determination, and my reasoning as I addressed these issues and concluded that the benefits of PPX no longer outweighs its risks.

As noted in the Hertz/Avigan memo, PPX is an opioid analgesic that was initially approved by FDA in 1957. While its use has declined since that time, a fairly high number of prescriptions are still written for PPX to this day, and a not inconsequential number of patients have been treated with these drugs successfully and without any obvious toxicity for years or even decades. The treatment of chronic pain is notoriously hampered by two important factors: a paucity of analgesic drug products that are effective and that do not have potentially serious toxicities related to their use, and the high degree of variability in response to and tolerability of these products, which often changes over time requiring switching from one product to another. Therefore, if a patient is responsive and tolerant to an analgesic drug product, and remains responsive and tolerant on a chronic basis, eliminating that product from the analgesic armamentarium appears to be antithetical to our efforts to provide more effective analgesia to the many patients in the US suffering with chronic pain. Additionally, those patients would then

need to be switched to other analgesic drug products which may well have even more significant toxicities and risks for an individual than the PPX they had been taking.

I considered whether it would be possible to keep PPX available by changing the product labels to add additional boxed-warnings that, in addition to clearly stating the potential for cardiac toxicity, would make the product "second line." This second-line status would limit the use of these products to patients who had had an inadequate response to or were intolerant of other analgesics with a similar potency to PPX. This would likely limit prescribing considerably while still providing access to the drugs for those patients who had been treated with them successfully and for appropriately screened patients who would be prescribed the products de novo.

There have long been concerns about PPX's safety. Reviews of the drug generated over the years have demonstrated PPX to be only mildly effective (although the studies are quite old and analgesic studies frequently demonstrate only limited efficacy) and have documented certain concerning features of the drug. Preclinical toxicology studies have found that PPX inhibits Purkinje fiber contractility and cardiac muscle inotropy, inhibits inward sodium current similar to Class IC anti-arrhythmics, and perturbation of hERG currents, all potentially serving as a backdrop to clinical cardiotoxicity in the form of arrhythmia. Post-mortem toxicological studies of overdose have demonstrated that some of the patients had blood levels of propoxyphene within the range seen in pharmacokinetic data for elderly normal volunteers administered the approved doses. And while most of the post-marketing adverse event data do not support a higher risk of serious adverse events for PPX compared to comparable analgesic products, the Florida medical examiners report and the DAWN Emergency Department (ED) and medical examiner data do document an excess incidence of deaths and ED visits associated with PPX compared to the comparable analgesic products tramadol and hydrocodone. But, as noted in the Hertz/Avigan memo, there have been no documented cases of Toursades de Pointes since the first PPX approval. Until now, there have been concerns raised, but no clear evidentiary basis upon which to find that the risks of PPX outweighed the benefits.

A recent pharmacokinetic study of propoxyphene performed at the Agency's request, however, has raised further concerns about the cardiac toxicity of the drug. Not only did that study demonstrate that it is clearly associated with QRS and PR interval prolongations, but also QT interval prolongations well into the range considered high risk for the development of Toursades de Pointes, (not only in the high-dose mean analysis, but in outliers at the low-recommended dose as well). With this new information it became apparent that the risk for the individual patient can change at any time, even after prolonged chronic use, with just a slight change in the patient's metabolic status, concomitant drug use, or renal function. And while the other commonly prescribed analgesic drug products for use in chronic pain have toxicities that are also potentially lethal (respiratory failure and addiction with opioids, gastrointestinal bleeding and cardiovascular thrombotic events with NSAIDs, and hepatotoxicity with acetaminophen), the risk of these toxicities occurring can be mitigated with proper use, appropriate risk management strategies and monitoring. Cardiac arrhythmia due to PPX cannot be monitored for in patients treated with PPX, and can apparently occur at any dose within the approved dosing range.

This new data has changed the risk-benefit balance of PPX to a degree that I can no longer support its continued availability.

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/s/

BOB A RAPPAPORT
11/18/2010