

JAN 17 1979

The Secretary
Through: The U _____
H _____

The Commissioner of Food and Drugs

Recommendations Regarding Declaring Propoxyphene an Imminent Hazard

This memorandum is in response to your request for the advice of the Food and Drug Administration on a petition of November 21, 1978 from the Health Research Group (HRG) requesting that you immediately suspend approval of the new drug applications for propoxyphene pursuant to section 505(e) of the Federal Food, Drug, and Cosmetic Act on the ground that the drug constitutes an imminent hazard to the public health. As an alternative course of action, HRG asks that you support its petition to the Drug Enforcement Administration to move propoxyphene from Schedule IV to Schedule II of the Controlled Substances Act.

As you are aware, prior to 1977 the "imminent hazard" provision of the Act had never been invoked by the Secretary. On July 27, 1977, you issued an order suspending approval of the new drug applications for phenformin. In your decision you set forth five factors which should be considered in evaluating whether approval of a new drug application should be suspended on the ground that continued use of the drug will constitute an imminent hazard to the public health. The validity of these five criteria for determining the existence of an imminent hazard was upheld by the District Court for the District of Columbia in Forsham v. Callano, 442 F. Supp. 203, 208 (D.D.C. 1977).

As a result of the HRG petition and your request for recommendations, the Bureau of Drugs conducted an extensive review of the data cited by HRG, other available reports of studies on propoxyphene in the scientific literature, information available from the Drug Enforcement Administration's Drug Abuse Warning Network as well as data in the new drug applications for drugs containing propoxyphene. In addition, the Bureau also reviewed data submitted on November 22, 1978, by Eli Lilly and Company on fatalities resulting from the manufacturer's propoxyphene products.

In a separate memorandum, Dr. Ronald Kartzinel, Director of the Division of Neuropharmacological Drug Products in the Bureau of Drugs, discusses in detail the scientific and medical issues, and analyzes those in terms of the five criteria you established for making the imminent hazard

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exist. This memorandum is enclosed as Attachment I. Dr. Kartzinel concludes on the basis of his review of the data that a substantial majority of the fatalities that have resulted from propoxyphene have occurred as a consequence of deliberate abuse or overuse far in excess of the recommended dosage for the drug and that there are no well documented examples of deaths when the drug is taken under the approved conditions of labeling.

There are, however, a number of reports regarding fatalities resulting from the consumption of propoxyphene in amounts moderately or slightly above recommended dosages in association with tranquilizers and/or alcohol. Moreover, recent studies have raised doubts about the degree of effectiveness of propoxyphene at the recommended dosage in relieving pain. The methodology for testing analgesics is fraught with technical difficulties, including a high rate of response to a placebo. The best one can say at present is that propoxyphene is a mild oral analgesic and its popularity is greater than the evidence suggests it ought to be. But it is a useful analgesic in certain patients who do not tolerate aspirin or codeine well.

The Division and the Bureau have made a recommendation to me regarding the declaration of imminent hazard. I concur in that recommendation. We are prepared to discuss it with you at your convenience, and to suggest a draft memorandum to be sent to Dr. Wolfe.

Donald Kennedy

Attachments:

Attachment I - Dr. Kartzinel's memorandum

cc:

8 copies w/attachments to Secretary's Office

HFA-224 HFJ-1

HF-1 (2) HFJ-5

HF-2 HFL-1

HFD-1 HFY-1

HFD-2

HFD-120/Kartzinel

GC-1

Prepared by: RKartzinel/1/12/79 - 34020

Revised by: JRCrout/1/12/79 - 32994

Edited by: DKennedy/JRCrout/1/16/79

F/T:clg:1/17/79

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

TO : Director, Bureau of Drugs (HFD-1)
Through: Associate Director for New Drug
Evaluation - (HFD-100)

DATE: January 15, 1979

FROM : Director, Division of Neuropharmacological Drug Products (HFD-120)

SUBJECT: Evaluation of Propoxyphene - ACTION MEMORANDUM

ISSUE

The Health Research Group (HRG) petitioned the Secretary of DHEW on November 21, 1978 to suspend the new drug applications (NDAs) for propoxyphene (DPX) containing products as an imminent hazard under section 505(e) of the Federal Food, Drug, and Cosmetic Act, or, if that can not be accomplished, to support the HRG petition to the Drug Enforcement Administration (DEA) that DPX be placed in Schedule II of the Controlled Substances Act, (CSA) 21 USC 801 *et seq* (Tab A). This memorandum provides an analysis of the imminent hazard issue with recommendations for action.

BACKGROUND

DPX hydrochloride (Darvon) and combinations with aspirin, phenacetin and caffeine (Darvon Compound, Darvon Compound-65) were first marketed in 1957 by Eli Lilly and Company. These drugs were approved for marketing based only on safety. After the Kefauver-Harris Amendments to the FD&C Act of 1962, the National Academy of Sciences/National Research Council (NAS/NRC) reviewed the published literature on DPX products and concluded that they were effective for the relief of pain (Tab B). The Chairman of the NAS/NRC Drug Efficacy Study Group Panel on Drugs for Relief of Pain was Louis Lasagna, M.D., an expert in the field of clinical pharmacology and analgesia. A 1966 article review by William T. Beaver, M.D. (Tab C), another expert in the field of analgesia, concluded as follows:

"In summary, dextropropoxyphene is a mild oral analgesic which has proven superior to placebo in doses of 65 mg or more but which is of questionable efficacy in doses lower than 65 mg. The drug is definitely less potent than codeine, the best available estimates of the relative potency of the two drugs indicating that dextropropoxyphene is approximately 1/2 to 2/3 as potent as the latter drug. Likewise, dextropropoxyphene in 32 mg to 65 mg doses is certainly no more, and possibly less effective than the usually used doses of aspirin or A.P.C."

At that time, according to Beaver, it was felt that "the abuse potential of dextropropoxyphene was slight, substantially less than even that of codeine."

The drug was not considered "by the World Health Organization to present a sufficient addiction hazard to require international narcotics control. These predictions seem to have been substantiated thus far by the fact that, in spite of the extremely wide use of dextropropoxyphene, only one case of dependency on the drug has been reported in the literature."

The FDA announced the results of the DESI review in 1969 (Tab D) and stated that DPX products were effective "for the relief of mild to moderate pain." In an amendment (Tab E) to the previous announcement, FDA stated that "in regard to the 32 mg dose of propoxyphene, recent studies have shown that this dose does have an analgesic effect in a certain fraction of the population of patients with mild to moderate pain. While 32 mg of propoxyphene is a weak analgesic dose, only the physician attending a particular patient can determine by titrating the dose whether that individual patient is one of the minority who will respond adequately to the 32 mg dose, or is one of the majority who will require at least 65 mg to achieve adequate analgesia." Labeling was also revised in 1972 (Tab F). Subsequently many other generic equivalent products have been marketed under approved abbreviated new drug applications (ANDAs).

Products containing the napsylate salt of DPX either alone (Darvon-N) or in combination with acetaminophen (Darvocet-N) or aspirin (Darvon-N with ASA) were marketed by Lilly in the early 1970's after approval of full NDAs. Table I lists the ANDA/NDA numbers, approval dates, tradenames, and manufacturers of all currently marketed DPX products.

Because of misleading statements with respect to the effectiveness of Darvon made to physicians in a letter from Eli Lilly and Company we required the manufacturer to make the following statement to all physicians in a "Dear Doctor" letter in 1972 (Tab G):

"There is no substantial evidence to demonstrate that 65 mg of Darvon is more effective than 650 mg of aspirin (two 5-grain tablets), and the preponderance of evidence indicates that it may be somewhat less effective. The preponderance of evidence indicates that Darvon is somewhat less potent than codeine. The best available evidence is that Darvon is approximately two-thirds as potent as codeine. Furthermore, there is no substantial evidence that, when administered at equianalgesic doses, Darvon produces a lower incidence of side-effects than codeine."

Because of the abuse potential of DPX containing products, they were controlled under Schedule IV of the Controlled Substances Act (CSA) in 1977 (Tab H), and the labeling further revised in 1978 (Tab I) to contain additional warnings on adverse reactions; interactions with alcohol, tranquilizers, sedative hypnotics, and other central nervous system depressants; and management of overdosage. A copy of the current labeling for DPX products is attached (Tab J).

On November 22, 1978, DHEW received a petition from HRG requesting that the Secretary immediately suspend approval of the NDAs for DPX containing products under section 505 (e) of the Food, Drug, and Cosmetic (FD&C) Act on the grounds that the continued marketing of these drugs represents an imminent hazard to the public health. HRG cites as the reasons for this request that, according to information obtained from DEA, DPX leads all other prescription drugs in the United States in drug-related deaths and that in 14 cities DPX-related deaths outnumbered morphine and heroin-related deaths. The petition states that "If you determine that there is no legitimate use for DPX as a pain-killer, and that the drug should therefore be eventually removed from the market the magnitude of DPX deaths during the 2-3 years that would transpire before the 'slow' banning procedures mandate use of the imminent hazard provision" (emphasis my own).

Alternatively, HRG requested that the Secretary support its petition to DEA that DPX be rescheduled as a Schedule II narcotic under the CSA, 21 U.S.C. 801 et seq. Under the CSA the Secretary of HEW, through his delegate the Assistant Secretary for Health, provides DEA with a scientific and medical evaluation, and recommendations, as to whether a drug should be controlled. This recommendation is binding upon DEA in the sense that DEA cannot control a substance if HEW recommends against control nor can DEA control a drug in a schedule higher than that recommended by HEW. The issue of whether DPX should be moved from Schedule IV to Schedule II has been placed on the agenda of the Drug Abuse Advisory Committee meeting scheduled for February 12-13, 1979 (Tab K).

EFFICACY OF DPX-CONTAINING PRODUCTS

On pp 20-22 of the HRG petition to DEA, the efficacy of DPX is questioned in the section entitled "Analgesic Impotence of Propoxyphene." In a review paper published in 1970 by Miller et al (Tab L) less than 10% of the published reports on DPX hydrochloride that they reviewed consisted of double-blind placebo comparisons. This is not surprising in view of the fact that DPX hydrochloride was marketed before there was a requirement for this type of study. Moreover, the methodology for the clinical assays of analgesic efficacy was being developed during that period, and many of these early reports would not meet today's criteria as adequate and well-controlled studies (21 CFR 314.111). It should be noted, however, that Miller did cite 9 of 18 placebo controlled trials where DPX was more effective than placebo. Miller's conclusion that "Propoxyphene is no more effective than aspirin or codeine and may even be inferior to these analgesics....When aspirin does not provide adequate

analgesia it is unlikely that propoxyphene will do so" is almost the identical conclusion reached by Beaver 4 years earlier. Prior to 1972 labeling changes referred to previously (Tab F), Dr. Beaver again reviewed the published scientific literature on DPX products and concluded that they were effective (Tab M).

At the time of these reviews, it was thought that the majority of studies which failed to demonstrate efficacy showed significant methodological problems or lack of assay sensitivity in that they were unable to distinguish between codeine or aspirin "standards" or placebo. However, recent studies have not shown these problems; they are adequate and well-controlled and repeatedly demonstrate the efficacy of other analgesics but have failed to do so with DPX.

The petition cites three recent "negative" studies. The first is a 1972 study by Moertel et al (Tab N), where DPX was compared to other marketed analgesics and placebo in a single dose trial in cancer patients. Aspirin (650 mg) was found to be the most effective agent, followed by pentazocine, acetaminophen, phenacetin, mefenamic acid and codeine. DPX, ethoheptazine and promazine were not superior to placebo in the relief of pain. In a study reported in 1973, Hopkinson et al (Tab O) compared single doses of DPX hydrochloride (65 mg), acetaminophen (650 mg), DPX + acetaminophen and placebo in 200 patients with postepisiotomy pain and found that DPX was statistically no better than placebo in the relief of pain. Gruber (Tab P) in a 2 dose study in 46 patients compared DPX napsylate (50 to 100 mg) to codeine (30 or 60 mg) and placebo and found that while there was no measurable difference between either active drug and placebo after the first dose, there was a significant difference between both drugs and placebo after the second dose.

Not all recent reports are negative. A 1972 study by Sunshine et al (Tab Q) found DPX napsylate at 200 mg (twice the recommended dose) to be significantly better than placebo. The least dose used (50 mg) was slightly better than placebo but the usual dose (100 mg) was not tested. These reports reinforce the conclusions of Beaver in 1966 that the results of DPX efficacy studies "of apparently suitable design...are to a degree contradictory." In a second review by Miller in 1977 (Tab R), 3 studies showed DPX to be no more effective than placebo and in 5 others DPX was no more effective than the standard.

Regarding the efficacy of DPX combinations, the important question is not whether they are effective per se since it is presumed they are at least as effective as the aspirin, acetaminophen or APC component. Rather, does the DPX component contribute to the efficacy of the combination?

The petition cites 3 references. Hopkinson et al (mentioned previously) found that acetaminophen alone and in combination with DPX was significantly more effective than DPX alone and placebo. There was no

significant difference between the efficacy measures for acetaminophen alone or in combination with DPX. Moertel et al in a 1974 study (Tab S) of the efficacy of combination drugs containing aspirin found three compounds (codeine, pentazocine and oxycodone) significantly increased the analgesic efficacy of aspirin (650 mg) whereas DPX napsylate (100 mg), ethoheptazine, pentobarbital and caffeine did not. Moertel noted the "conflicting evidence in the literature regarding the effectiveness of propoxyphene" and concluded that "it remains to be clearly established that its popularity reflects true analgesic effectiveness".

Bauer et al in 1974 (Tab T) reported a factorial efficacy study of DPX, aspirin, and APC in 610 subjects by 2 investigators in 2 separate institutions. The addition of DPX to the antiinflammatory analgesics (aspirin at 3 different doses, phenacetin at 3 doses, plus or minus caffeine) did produce a significant increment in analgesia. However, DPX was never tested alone, and the increased analgesia of the DPX combinations was accompanied by a significant increase in side effects. The authors noted that the aspirin containing products were packaged improperly but the possible loss of efficacy due to pharmaceutical instability was not tested by chemical analyses. This positive multi-factorial study of the contribution of DPX to the efficacy of DPX combinations is large, contains 10 medication test groups but no placebo control, and has other methodological problems. According to the authors the data obtained at the two institutions "differed significantly and possibly should not be pooled"; however, the results were pooled and no individual assessment is possible. Moreover the most effective treatment group used DPX napsylate at 200 mg (twice the recommended dose). There was also a failure of relative potency assay assessment of the different doses of aspirin, thought possibly to be due to the instability of the aspirin due to the defective packaging.

This is the only study that Miller in his 1977 review (Tab R) accepted as showing DPX's contribution to the DPX-APC combinations. The problems of design and analysis in this study, as noted above, are however, substantial. Miller found no acceptable studies published since his previous review in 1970, showing that DPX contributed significantly to the efficacy of DPX-aspirin or DPX-acetaminophen combinations and in fact, the only recent well-designed studies (Moertel & Hopkinson) showed no contribution of DPX to the combinations.

This is in contrast to the 1971 review by Beaver (Tab M) where he concluded that "although the design and results of available studies comparing combinations of DPX and either aspirin or APC with their individual constituents leave much to be desired, there is substantial evidence that these combinations are more effective than their constituents administered separately".

RISK ASSESSMENT OF DPX

Before discussing the safety (or lack of safety) of DPX, some data on the extent of use of the DPX compounds must be assessed to provide a background for considerations of risk factors, death, abuse and adverse reactions. The use of DPX as determined by total prescriptions dispensed in the years 1964-1978, is presented in Figure 1 and 2 broken down into categories according to salt and combination products. The 1978 data is an extrapolated figure for the year based on 9 months of data. (Figures 1-4 and Tables II-VII are supplied by Dr. Judith Jones, Acting Director, Drug Experience, BD).

It is of note that there is a decreased use of the propoxyphene products following the placement of the drug in Schedule IV, but this may be consistent with the downward trend which is evident beginning in 1974. Overall, propoxyphene prescriptions decreased 6% from 1975-1976, 5% from 1976-1977 and 7% from 1977-1978 (based on projected values). This is associated with an overall downward trend of lesser degree in prescriptions for all drugs during this period of time (Figure 3).

Data on the recipients of the prescriptions and the prescribers provide some background for addressing the question of the risk of these products as well as the impact of a possible withdrawal of such products from the market. As presented in Table II, which displays data from the National Disease and Therapeutic Index (NDTI) for July 1977-June 1978, it is apparent that the recipients of the DPX compounds are of all ages, although the largest percentage of prescriptions go to those aged 60 or older. This is of significance with regard to risk considerations and for comparison with the demographic features of reported deaths to be discussed later.

Another estimate of sales from October 1977-September 1978 is shown in Figure 4, which shows dosage units of DPX compounds dispensed versus codeine and morphine. It is important to note that this includes only data from retail pharmacies and does not reflect use in a hospital setting, which is of importance with regard to morphine and single-entity codeine preparations. DPX and codeine each represent a total of almost 1.2 billion dosage units dispensed during this time period; their prescription sales are, therefore, comparable.

A factor of considerable significance is that minor tranquilizers and non-barbiturates are frequently the drugs prescribed in conjunction with DPX. It is of note that only an average of 50% of the usage of DPX is alone; the remainder is in association with other drugs. The prescribers are more frequently internists and general practitioners than surgeons. In almost half of the cases a continuation of therapy is mentioned suggesting at least some degree of chronic or nonacute use. The usage most frequently mentioned involved either surgical after-care or diseases of bone and movement followed by use in conjunction with accidents.

On the first page of the petition, HRG stated that "the narcotic propoxyphene (as in Darvon)...leads all other prescription drugs in the United States in drug related deaths." This conclusion is apparently based on data derived from the Drug Abuse Warning Network (DAWN). DAWN-reported emergency room (ER) mentions and deaths due to DPX in relation to the number of prescriptions issued are shown in Table III along with similar data for other drugs; these data are from DAWN and IMS America (NPA). These data support the fact that DPX is one of the more frequently mentioned drugs. However, the ratio of DPX associated deaths (coroners' mentions) to dispensed prescriptions is lower than that for the barbiturates, ethchlorvynol, glutethimide, methaqualone, amitriptyline, doxepin, and pentazocine; DPX ranks 12 of 27 in this analysis.

Table V compares total coroners reports of deaths (associated with DPX alone or in conjunction with other factors) with ER room visits. Although there is a slight increase in deaths in 1977 as compared with the previous 2 years, this difference is of questionable significance. If ratios of these two sources are considered, it suggests that 13-16% of emergency room visits associated with DPX have a lethal outcome and only 3-5% of deaths are associated with DPX alone.

Further analysis of these deaths reveals that they are predominantly due to suicide. Table IV reveals that 58% of DPX deaths were intentional; this compares with 50% for codeine. This contrasts with the petition which states on page 6 that most DPX deaths fell into the "accidental overdose" group. Both the Baselt (Tab Q) and Finkle (Tab R) reports considered some deaths "accidental" rather than "intentional" but neither defines the criteria upon which such a classification was made. In the Baselt report some of the accidental cases ingested such large amounts that the nonpurposeful nature of the ingestion is difficult to sustain. Finkle does discuss the reluctance of coroners to designate ambiguous deaths suicides and infers that the accidental category may be over recorded.

Further confirmation that most deaths are intentional rather than accidental is seen in Table VI where data from the NDTI, Poison Control Centers, adverse reaction reports, DAWN, and the Finkle study are compared.

A comparison between this table, which demonstrates that deaths due to suicides occur predominantly in the younger age groups, and Table II which demonstrates that most DPX use is disproportionately higher in the older age groups supports the hypothesis that most DPX deaths are the result of use in younger age groups for suicidal purposes. In fact,

only 1-8 % of the suicide attempts are in the over 60 age group which accounts for 35% of the prescriptions. This population is presumably more subject to cardiovascular, respiratory and CNS problems but the paucity of deaths in this age group is notable. In contrast, 12-37% of the suicide attempts are in the 10-19 age group which accounts for only 7% of the prescriptions; 27-41% are in the 20-29 age group with approximately 15% of the DPX prescriptions. It is apparent, however, that DPX is one of the most frequently used drug "instruments" of suicide and suicide gestures, ranking behind only the barbiturates as a group.

It is impressive in looking at overdose fatalities, that the majority of deaths occur when DPX is taken with alcohol or other drugs (Table VII). However, approximately 23% of deaths occur when DPX is taken alone. There is also some evidence in the Finkle report that a small percentage (5-7%) of the deaths occurs in a particularly "susceptible" group where death occurs within 15 minutes of ingestion. These were mostly drug combination deaths.

Although there are many problems with interpretation of blood concentrations of DPX and its metabolites, 15% of deaths in the Finkle study showed blood levels not greatly different from those of high therapeutic doses. Dr. Edward Press, Oregon State Public Health Officer, in a personal communication (Tab W) described at least two cases out of seven reported deaths where the overdose appeared clearly accidental. While these reports are anecdotal and incomplete they do lend support to the idea of accidental overdose.

Another safety parameter is the occurrence of adverse reactions rather than death. According to Miller and Greenblatt (Tab X) adverse reactions to DPX in hospitalized patients are infrequent and mild. Moreover, the adverse reactions, although qualitatively similar were quantitatively less than with codeine and other analgesics used in hospitalized patients. Standard tolerance studies in volunteers revealed no significant differences between DPX and placebo (Tab Y). In contrast, Goodman and Gilman (Tab Z) state that in doses equianalgesic to codeine it is likely that the incidence of side effects would be similar to those of codeine.

On p. 8 of the petition the writer considers "why is DPX so toxic". DPX in overdose causes respiratory depression and this effect is substantiated by a large number of case reports from a wide variety of sources. However, the petition raises the issue of a specific and primary cardiotoxic effect, of atrio-ventricular nodal conduction, and this issue is more problematic. Most of the reports of cardiac arrhythmias in DPX overdoses are reports of such effects after central depression has occurred. The cardiac conduction abnormalities observed are thought to be precipitated by the anoxia following respiratory depression and arrest (Tab AA). However, there is one recent case report by Starkey (Tab BB) where cardiovascular depression and heart block, although occurring after respiratory arrest, appeared to respond dramatically to naloxone suggesting a specific DPX induced cardiotoxicity. Cardiotoxicity at a therapeutic dose has not been observed.

Further information on the relative safety of DPX is found in several INDs where DPX napsylate was used at doses of 600 to 1200 mg per day (1 1/2 to 3 times the usual daily analgesic dose) for several weeks. In approximately 100 patients no deaths were reported and adverse reactions were of the same magnitude as in analgesic studies.

BENEFIT-RISK CONSIDERATIONS

Key factors in considering whether the benefits of DPX justify the risk are as follow:

1. Mild to moderate pain is a disturbing sign and symptom of many disease processes. Although chronic and/or severe pain certainly can interfere with normal daily life activities, this is not usually the case for mild pain. Nevertheless, relief of mild to moderate pain provides substantial benefit to patients with this symptom.
2. There are two safe and effective over-the-counter (OTC) drugs for the treatment of mild to moderate pain, namely aspirin and acetaminophen. Like all drugs they are toxic at high doses and can be lethal, but there is no abuse liability. They do, however, produce adverse reactions in certain individuals including severe allergic reactions and, in the case of aspirin, gastrointestinal bleeding and peptic ulcer.
3. Other alternative prescription analgesics include codeine (Schedule II), codeine combinations (Schedule III), pentazocine (recently Schedule IV) and a pentazocine combination. Two other mixed agonist-antagonists have recently been marketed in parenteral form (butorphenol and nalbuphine) and will likely be marketed in oral forms as well. Finally, several nonsteroidal anti-inflammatory agents, some already approved for other indications, are under development as oral analgesics. These agents have shown no abuse potential and 2 members of the group will probably be approved for marketing in the next year.
4. DPX is an effective prescription drug roughly equivalent in effectiveness to the OTC drugs, aspirin and acetaminophen, and less powerful than other prescription analgesics, such as codeine and pentazocine. DPX has a potential for abuse, which was recognized when it was listed under Schedule IV of the CSA in 1977. It may have some specific benefits over other analgesics in patients who can not tolerate aspirin, acetaminophen or codeine, and in post-operative patients as a non-antipyretic analgesic, to avoid the masking of fever and when constipation should be prevented.
5. Pain is a very subjective process; patients may respond to one drug but not another based largely on psychogenic rather than physiological or pharmacological factors. The fact that aspirin

and acetaminophen can be purchased without a prescription suggests to many patients that they are weaker pain relievers; the drug that can be obtained only after a visit to the physician for a prescription is often judged to be stronger by the patient.

6. Epidemiologic data indicates that DPX is implicated, alone or together with other drugs and alcohol, in some 600 deaths per year. This ranks DPX behind only the barbiturates as a leading cause of drug deaths, although when considered on the basis of prescriptions issued, DPX ranks 12th out of 27.

7. The evidence indicates that most of these deaths are suicides or abuse related.

8. However, there are cases in which death appears to be accidental. These are usually where DPX is taken in association with alcohol and/or tranquilizers. There are no cases known to the Division at present where death appeared to be caused by DPX taken alone in customary doses and neither alcohol nor tranquilizers were also implicated.

9. The mechanism of death appears to be respiratory depression, a typical action of narcotics. Cardiac toxicity has been postulated but convincing clinical examples are not available.

10. When viewed in relation to aspirin, acetaminophen, and codeine, DPX appears to pose a relatively greater risk of death from a societal point of view but not to the user taking the drug properly under the conditions of labeling.

The benefit/risk considerations are somewhat different for the products which contain DPX in combinations with aspirin, acetaminophen or APC.

1. The major benefit of a fixed combination drug is to increase patient compliance; patients are more likely to take their medication as directed if they only have to take 1 pill instead of 2 or 3 pills 3-4 times a day. This is especially true for the treatment of chronic conditions (such as hypertension and epilepsy), where there is no immediate ill effect apparent to the patient from not taking the medication. However, compliance is not usually a problem in the treatment of pain, especially with drugs that have a short duration of effect; patients are less likely to forget their medications, if they have pain to remind them.

2. When analgesics are used in combination there may be an additive effect, even an occasional "potentiating" effect whereby one drug will increase the effectiveness of the other. In the case of DPX plus aspirin, acetaminophen, or APC, it is not clear that there is even an additive effect.

3. Any argument that DPX is needed as an alternative treatment in patients who can not tolerate aspirin or acetaminophen is irrelevant for these combinations.

4. When drugs are used in combination, there may be a "protective" effect whereby one drug reduces the adverse effects of the other. This is not the case for DPX combinations. The risks of the combinations would be expected to be greater since in overdose, the toxicity of aspirin or acetaminophen must be treated as well as that of DPX.

5. Epidemiological data indicates that both the single ingredient and combinations are implicated in deaths.

CONSIDERATIONS RELATING TO IMMINENT HAZARD

The imminent hazard provision of the law gives to the Secretary of DHEW the authority to remove a drug from the market immediately by suspending a new drug application (and later conducting an expedited hearing) if he feels that an imminent hazard exists. The petition has requested the Secretary to exercise his authority in the present case.

The imminent hazard provisions of the FD&C Act were first invoked on July 25, 1977 when Secretary Califano issued an order suspending approval of the NDA for the drug phenformin. In that order, the Secretary articulated the criteria to be considered in determining whether approval of a new drug application should be suspended on the grounds that the drug is an imminent hazard to the public health. The validity of these criteria was upheld by the United States District Court for the District of Columbia in Forsham vs Califano, 442 F. Supp. 203, 203 (D.D.C. 1977). An analysis of DPX in relation to these criteria follows:

1. "The severity of the harm that could be caused by the drug during the completion of customary administrative proceedings to withdraw the drug from the general market."

According to the National Center for Health Statistics, in 1976, 121 deaths were attributed to DPX and 846 were in combination with other drugs. Some of these deaths were undoubtedly associated with DPX (Table VIII). There were also 736 deaths from unspecified drugs. Given the 607 DAWN coroner mentions in 1977 and the errors of both over and under reporting associated with a specific drug in both data bases, there may be anywhere from a few hundred to one thousand deaths each year associated with DPX. The vast majority of these deaths are from suicide. DPX ranks second to barbiturates as a drug associated with suicide and accidental death, but 12th when considered in relation to availability in society (number of prescriptions issued). Some, perhaps as many as 25% of DPX related deaths, may be accidental, but in these cases the doses are probably at or above the recommended dosage and the drug is used in association with alcohol and/or tranquilizers. There are no identified deaths in which DPX was taken in recommended doses in

the absence of other drugs acting on the CNS.

2. "The likelihood that the drug will cause such harm to users while the administrative process is being completed."

If "users" are limited to patients using the drug as directed by a physician for relief of pain at doses recommended in the approval labeling, there is no sound evidence that deaths will occur without the concomitant use of tranquilizers or alcohol. If the term "users" is extended to include use at higher than recommended doses or in combination with alcohol or other drugs active on the CNS then some deaths will occur. The number is impossible to state but could be several dozens or up to 250 each year. The Division believes this type of use should be considered within the context of medical use; i.e., it is not intentional misuse or abuse and it may reflect an unawareness by physicians and patients of the warning in the package insert on accidental death. If misuse, abuse, and suicide are included then the assumed death rate will be as stated in item 1 above.

3. "The risk to patients currently taking the drug that might be occasioned by the immediate removal of the drug from the market."

With the availability of other prescription and OTC analgesics, there would be no risk to patients from the immediate removal of the drug.

4. "The likelihood that, after the customary administrative process is completed, the drug will be withdrawn from general marketing."

Based on our review of the efficacy, safety, and benefit/risk considerations, it is not clear that the drug should be withdrawn from the market or, if this were attempted, whether the FDA would prevail on the merits. The Commissioner must demonstrate that "there is 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" (21 CFR 314.115(b)(3)) or must demonstrate that "the drug is not shown to be safe under the conditions of use upon the basis of which the application was approved" (21 CFR 314.115 (b)(2)).

Given the previous conclusion by the Agency that the drug is an effective, even if weak, analgesic, it is difficult to allege lack of efficacy as a cause for removal. The drug appears to have some effectiveness, although its reputation seems to be much greater than the evidence indicates. Removal of a drug as unsafe based on other than harm to the patient from the drug as labeled is arguably outside the above provision and at least constitutes a new legal argument that has not been made to date. That does not mean we

should not take that position with DPX. It only means that if we do, we are on unexplored ground without legal precedent and cannot readily conclude that there is a high likelihood that we would prevail. The risk to the public health or society in general (for example, from abuse), rather than risk to the individual user, is an argument that is being considered for the withdrawal of the obesity indication for the amphetamines.

5. "The availability of other approaches to protect the public health."

There are several other options available to the FDA that could be attempted. They include but are not limited to the following:

- A. Revised physician labeling particularly to emphasize even more the possibility of death from DPX use in conjunction with tranquilizers and alcohol. A bold faced warning to this effect has been in the package insert only since April 1978 and its impact may not yet have been felt.
- B. Physician education via FDA Drug Bulletin, "Dear Doctor" letter, publications in professional journals etc.
- C. Patient education via patient package insert, FDA Consumer, etc.
- D. Rescheduling under the CSA from Schedule IV to Schedule II. This is the only other option sought by the petitioner. This subject has been placed on the agenda of the Feb. 12-13 meeting of FDA's Drug Abuse Advisory Committee (Tab K).

Because these other approaches have not been exhausted in an attempt to minimize those deaths from DPX that may be preventable, it can be argued that they should be tried before an attempt is made to remove DPX from the market. Again, this is not an overriding reason that would clearly prevent our prevailing on the merits, but it is an obstacle.

POSSIBLE COURSES OF ACTION

1. If a decision is reached to withdraw one or more DPX NDAs and the five criteria listed above are met, then an order should be prepared for the Secretary to suspend the applications as an imminent hazard.
2. If a decision is reached to withdraw one or more DPX NDAs but the five criteria listed above are not met, then the applications cannot be suspended as an imminent hazard. The section of the petition which requests consideration of removal of DPX from the market as an imminent hazard must be denied, and an NOH on a proposed withdrawal of the NDAs should be published in the Federal Register.

3. If a decision is made not to withdraw one or more DPX NDAs, then the section of the petition which requests consideration of removal of DPX from the market as an imminent hazard must be denied. There are several methods of obtaining additional information on whether an NOH should be published:

- A. More extensive "in-house" review.
- B. More extensive "outside" review by Special Government Employees (SGEs) as consultants to an advisory committee or expert reviewers to the Division.
- C. Advisory Committee presentation.
- D. Informal public hearing.
- E. Special services contracts to one or more experts in the relevant medical area who are not SGEs.

4. If a decision is reached that an NOH should not be published because the requirements of 21 CFR 314.115 can not be met, other actions to highlight the current knowledge on safety and effectiveness of DPX products can be considered, such as revised labeling, physician education (Drug Bulletin), patient education (patient package insert), changes in drug advertising, etc.

5. If the Drug Abuse Advisory Committee ultimately recommends that DPX be placed in Schedule II of the CSA and the FDA, the Secretary of HEW and DEA agree and such scheduling is successfully accomplished, then the portion of the petition which requests rescheduling can be accepted. If there are inadequate grounds for such rescheduling, then that portion of the petition must be denied.

The five options and the actions that would follow are summarized below:

<u>Option</u>	<u>Suspend</u>	<u>Withdraw</u>	<u>Action</u>
1	Yes	Yes	Order by Secretary Califano
2	No	Yes	Portion of petition denied FR publication of NOH
3	No	Undecided	Portion of Petition denied More information gathered by: <ul style="list-style-type: none"> A. FDA staff review B. FDA consultant review C. FR publication of Advisory Committee meeting D. FR publication of an informal hearing E. FDA contract

4

No

No

5

No

No

Portion of petition denied
revised labeling, drug sub-
stance, PPI etc.

Reschedule to II. If accept
portion of petition.
option may stand alone or in
addition to options 3 or 4).