

UNITED STATES  
DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

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OFFICE OF THE SECRETARY

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In re:

Petition to Suspend  
New Drug Applications  
For Propoxyphene

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ORDER OF THE SECRETARY  
DENYING PETITION

February 15, 1979

79P-0066

PON

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U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

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I. ISSUE

The issue presented to me is whether, as currently labeled and distributed, propoxyphene, a drug for use in the relief of pain, should be declared an "imminent hazard" under section 505(e) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 355(e), and approval of the new drug applications for the drug summarily suspended prior to the initiation of the ordinary procedures for withdrawal of approval of those applications. Thus, I must decide whether there is now sufficient evidence available showing that the continued use of propoxyphene constitutes so serious a threat to public health as to warrant an interim suspension of general distribution of the drug pending initiation and completion of the procedures to determine whether propoxyphene should be removed permanently from the general market.

This proceeding was initiated by a petition filed by the Health Research Group (HRG), a consumer advocacy group concerned with health matters. HRG also petitioned the Department of Justice to impose new restrictions on the production and dispensing of propoxyphene under the Controlled Substances Act, 21 U.S.C. 801. In its petition to me, HRG requests that, in the event I do not suspend marketing of the drug, I support the HRG petition at the Department of Justice.

## II. BACKGROUND

Propoxyphene hydrochloride, alone or in combination with aspirin, phenacetin, and caffeine, was first approved and marketed in 1957. The most widely sold brand names of propoxyphene products are Darvon, Darvon Compound, and Darvon Compound-65, all manufactured by Eli Lilly and Company.

The original approval of propoxyphene was on the basis of safety only. After the enactment of the Drug Amendments of 1962, the efficacy of propoxyphene products was reviewed by the National Academy of Sciences/National Research Council, which concluded that the products are effective for the relief of pain. In the early 1970's, the Food and Drug Administration approved as safe and effective additional products manufactured by Eli Lilly and Company containing propoxyphene: the napsylate salt of propoxyphene

either alone (Darvon-N) or in combination with acetaminophen (Darvocet-N) or aspirin (Darvon-N with ASA). All propoxyphene products are "new drugs" and are subject to new drug application (NDA) requirements.

In 1977, through joint activity by the Department of Health, Education, and Welfare and the Department of Justice, all products containing propoxyphene were controlled under Schedule IV of the Controlled Substances Act for the first time, because of their potential for abuse. This action limited refills on propoxyphene prescriptions, and imposed certain labeling and recordkeeping requirements on manufacturers. In 1978, FDA revised the labeling of these products to contain additional warnings on adverse reactions, particularly adverse interactions of propoxyphene with alcohol, tranquilizers, sedative-hypnotics, and other central nervous system depressants; and to advise on management of propoxyphene overdoses.

### III. HISTORY OF THIS PETITION

On November 21, 1978, Sidney M. Wolfe, M.D., Director of HRG, petitioned me to take one of two actions:

- (a) Ban immediately the marketing of propoxyphene as an imminent hazard under the Food, Drug, and Cosmetic Act, 21 U.S.C. §355(e), and make it available only as an investigational drug for treating narcotics addicts or, in the alternative,

(b) "Support [the Health Research Group's] petition... [to the Attorney General and the Administrator of the Drug Enforcement Administration] to reschedule [propoxyphene] as a Schedule II narcotic which would impose production quotas and prohibit refills of prescriptions."

Dr. Wolfe argues that propoxyphene is relatively ineffective: "[a]t present the preponderance of properly-controlled studies fail[s] to show that DPX [propoxyphene] is any more effective than aspirin and many show it to be less effective than aspirin, or, in some cases, no more effective than a placebo. It is clearly less effective than codeine." HRG also contends that propoxyphene is unsafe because its limited effectiveness is outweighed by the several hundred deaths per year that are associated with its use. These deaths are reported in the Drug Enforcement Administration's Drug Abuse Warning Network (DAWN). HRG suggests that many of these deaths are the result of accidents rather than suicide.

Upon receiving the HRG petition, I requested FDA Commissioner Donald Kennedy and his scientific colleagues in the Bureau of Drugs to evaluate it and advise me on the proper response. On January 17, 1979, Commissioner Kennedy forwarded to me the Bureau's detailed analysis of the use and risks of propoxyphene, accompanied by a discussion of the options available to me and copies of the materials

cited in the analysis. Additional materials were compiled by the Bureau and submitted to me on February 10, 1979.

On January 30, February 1, and February 5, 1979, the Senate Select Committee on Small Business held hearings on the safety and effectiveness of propoxyphene. The testimony presented at those hearings has been included in the materials submitted to me.

In addition to the materials referred to herein, I have relied on an examination of the full record created with FDA's assistance.

#### IV. PROCEDURES AND CRITERIA FOR SUSPENSION OF A NEW DRUG APPLICATION

##### A. The Statutory Framework

The Secretary of Health, Education, and Welfare, and his delegate, the Commissioner of Food and Drugs, are responsible for the administration of the Food, Drug, and Cosmetic Act (the "Act"). 21 U.S.C. 301; 21 CFR 5.1. The provisions of the Act require that all "new drugs" be subject to a new drug application "approved" by the Secretary before they may be shipped in interstate commerce. 21 U.S.C. 505(a). To obtain approval for an NDA, a manufacturer must prove, inter alia, that such a drug is safe and effective.

The burden of establishing safety and efficacy of a new drug under the conditions prescribed, recommended, or suggested in the proposed labeling of the drug remains at all

times on the manufacturer. Whenever new evidence warrants the conclusion that an approved new drug is unsafe or ineffective, the Food and Drug Administration is required to remove the drug from the market. Section 505(e) of the Act establishes two procedures for removing an approved drug from the market: "withdrawal" and "suspension".

(1) Procedures for Withdrawal of Approval of an NDA

The Act requires the Commissioner to withdraw an NDA if new evidence shows either that a drug is "unsafe for use" under the conditions for which it was approved, or that the manufacturer can no longer sustain its burden of demonstrating that the drug is safe and effective. The administrative procedure for withdrawing approval of an NDA ordinarily includes notice to the manufacturer of an opportunity for a hearing, the conduct of a full evidentiary hearing before a hearing officer, and a decision by the Commissioner based on the hearing record.

This procedure usually requires at least six months, and sometimes much longer. A drug may remain on the market for years while withdrawal proceedings are underway.

(2) Procedures for Suspension of Approval of an NDA

The elaborate procedural protections against improvident withdrawals emphasize the importance of the immediate suspension provision available under section 505(e) of the Act.\*

\*Section 505(e) provides, in pertinent part, as follows:

If the Secretary (or in his absence the officer acting as Secretary) finds that there is an imminent hazard to

Established in 1962, this summary procedure permits the Secretary to act promptly to suspend approval of an NDA temporarily, and thereby remove the drug from the market, if it represents an "imminent hazard" to the public health. Once having suspended approval, the Secretary must provide the manufacturer with an expedited hearing on whether the drug should be permanently removed from the market. This special authority is vested solely in the Secretary, and may not be delegated.

The summary suspension procedure provides a critical procedural tool to carry out the obligation of this Department and of FDA to protect the public health and safety. Rapid action may be necessary if scientific data raise serious new questions concerning the safety of the drug. If new evidence or further and more careful analysis of existing evidence indicates that a life-threatening or other serious risk is present, the summary suspension procedure allows the Secretary to end promptly this serious risk. The summary procedure does not eliminate the need to conduct a full administrative proceeding to arrive at a final and conclusive judgment as to whether the drug should be permanently removed from the market.

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the public health, he may suspend the approval of such [new drug] application immediately and give the applicant the opportunity for an expedited hearing under this subsection . . . .

B. Criteria for Suspension

In my 1977 order suspending the NDA's for phenformin under the "imminent hazard" provisions of the Act, I examined at length the text of section 505(e), the legislative history of the suspension provision, and pertinent court decisions.

In re New Drug Applications for Phenformin, Order of the Secretary Suspending Approval, pp. 24-35 (DHEW July 15, 1977).

I there concluded that the following factors should be weighed in determining 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:

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.

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

3. The risk to patients currently taking the drug that might be occasioned by the immediate removal of the drug from the market, taking into account the availability of other therapies and the steps necessary for patients to adjust to these other therapies.

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

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

These criteria were reviewed and upheld in Forsham v. Califano, 442 F. Supp. 203 (D.D.C. 1977).

V. EVALUATION OF PROPOXYPHENE UNDER THE CRITERIA FOR SUSPENSION

In analyzing the record in this matter, I have been guided by the expert advice and opinions provided by FDA. In assessing and weighing the evidence, I have recognized that the record of a full evidentiary hearing is not before me.

Under the criteria set forth in part IV above, I am not persuaded that suspension of the propoxyphene NDA's should be ordered at this time. Although I am troubled by the evidence that propoxyphene carries life-threatening risks and is of limited efficacy, I believe that the standards for summary removal of a drug from the market have not been met by the evidence now before me. Therefore, I am denying for the present the HRG petition to declare propoxyphene an imminent hazard.

Nevertheless, because of my concerns about propoxyphene-associated deaths, I have ordered that several steps be taken to minimize as rapidly as possible avoidable harm from the drug and to gather further information on its risks and benefits.

I have directed the Commissioner to have FDA complete expeditiously a comprehensive review of all available information concerning propoxyphene to determine whether the various products containing the drug meet the safety and efficacy requirements of the Act and, thus, whether proceedings should be begun to withdraw the new drug applications for any or all of those products. In the course of this review, FDA will hold a public hearing to receive information and views on the continued marketing of propoxyphene. This hearing is scheduled for April 6, 1979. If at any time during this review evidence appears suggesting that propoxyphene meets the criteria for suspension, FDA will immediately submit it to me. I will then consider, in light of that evidence, whether to suspend any or all of the NDA's for propoxyphene products.

Three other steps, described below, will provide information to physicians, dentists, pharmacists, and the general public, in order to increase awareness of the risks of propoxyphene, and may result in the imposition of additional restrictions on the production and distribution of the drug under the Controlled Substances Act.

A. Severity and Likelihood of Harm to the Public Health.

The principal harm from propoxyphene is death. As HRG points out, propoxyphene is associated with a significant number of deaths. In 1977, the DAWN system reported

607 propoxyphene related deaths, more than those associated with any other prescription drug.

The DAWN data provide, however, only a very rough basis for estimating the true number of deaths that may be caused by use of propoxyphene. The DAWN reports include all deaths in which propoxyphene is found in the bloodstream of the deceased. In some of these cases, propoxyphene, particularly in conjunction with alcohol or a tranquilizer, may have caused the death. On the other hand, if propoxyphene happened to be found in the blood of a person who died in an unrelated car accident, that case would be reported in the DAWN statistics as a propoxyphene-associated death. The DAWN statistics also do not reflect all of the deaths in the country, but include only deaths in 24 major cities, covering slightly over 30% of the total U.S. population. Thus, it is likely that additional deaths associated with propoxyphene are occurring in areas which are outside the DAWN reporting system.

The absolute number of deaths must be viewed in perspective with the actual consumption of the drug. Propoxyphene is very widely used; last year, about 31 million out-patient prescriptions were filled, and additional quantities of propoxyphene were used in hospitals, clinics, and physicians' offices. The ratio of propoxyphene-associated deaths (i.e., the number of times the drug is mentioned in

coroners' reports included within the DAWN system) to dispensed out-patient prescriptions is lower than that for the barbiturates, the non-barbiturate sedative-hypnotics, amitriptyline, doxepin, and pentazocine. In fact, propoxyphene now ranks 12th out of 27 drugs in ratio of drug-associated deaths to dispensed prescriptions.

The reason for these deaths has long been thought to be suicide. Undoubtedly this motivation accounts for a significant proportion of the deaths. In its petition, HRG contends, however, that many of the deaths are the unintended result of drug abuse. The petition appears to suggest that in a search for euphoria, or because of a dependence on the drug, a user may take an excessive dose of propoxyphene or combine the drug with alcohol, narcotics, tranquilizers, sedative-hypnotics, or other substances that depress the central nervous system. The result can be an accidental death.

It is true that most identified propoxyphene-associated deaths appear to be the result of misuse of the drug, either in attempting suicide or in a drug abuse accident. In the report by Baselt et. al. (ref. 1), some of the cases classed as "accidental" involved such large quantities of propoxyphene that it is very likely that the drug was not being used for therapeutic purposes at the recommended dosage level.

Since filing the HRG petition, Dr. Wolfe has raised the question whether many of the deaths attributed to propoxyphene are due to a cardiotoxic effect of its major metabolite, norpropoxyphene. This hypothesis, which would imply the existence of previously unidentified cases of propoxyphene-caused deaths possibly occurring at therapeutic doses of the drug, deserves serious consideration during FDA's review of the drug. At present, however, there is little evidence that this mechanism is a common factor in the deaths associated with propoxyphene.

Indeed, there is no clear evidence to date demonstrating that the therapeutic use of propoxyphene, in the absence of tranquilizers or alcohol, has caused accidental death. For example, although about one-third of the prescriptions for products containing propoxyphene are written for patients over age 60, these same patients experience only 8% of the deaths reported to be associated with propoxyphene. The largest incidence of deaths associated with propoxyphene products occurs among those in the 20-40 age range, who only receive about one-third of the prescriptions, but experience roughly half the deaths. If propoxyphene-associated deaths were predominantly accidental, one would expect a much higher proportion of the deaths to occur among users over 60,

assuming that older users are at least as likely to have fatal accidents as younger users.

The only serious health risk from propoxyphene other than the deaths described above is that the drug can cause physical dependence. Otherwise, it does not cause significant adverse reactions in many cases. Miller and Greenblatt (ref. 3) found that adverse reactions in hospitalized patients are infrequent and mild. Moreover, although the adverse reactions from propoxyphene that did occur were qualitatively similar to those from codeine and other analgesics used in the hospital setting, they occurred less frequently. Standard tolerance studies in volunteers revealed no significant difference between propoxyphene and placebo. In contrast, Goodman and Gilman (ref. 4) state that in equianalgesic doses, propoxyphene and codeine may be expected to produce similar incidences of side effects.

Thus, the principal harm posed by propoxyphene, and the basis of the HRG petition, are the deaths associated with the use of the drug in suicide attempts or accidental overdosing or interactions with other nervous system depressants in drug abuse situations.

B. Possible Harm from Immediate Suspension  
of Propoxyphene from the General Market

The principal harm from immediate suspension of a drug is the loss to patients of the benefit of its therapeutic effectiveness. Therefore, to assess the harm from suspension of propoxyphene, it is necessary to evaluate the available information concerning its effectiveness.

I recognize that the efficacy of analgesics is particularly difficult to assess. Pain is a subjective symptom. I am informed that although it can be quantitatively measured for purposes of clinical trials, the conduct of such trials is complicated by the fact that any analgesic will have a large placebo effect, typically in the range of 30-35% of the patients. In addition, many experts believe that in the case of prescription analgesics, such as propoxyphene, the placebo effect associated with the drug is increased by the facts that the drug is prescribed by a physician after consultation with the patient, that the capsules and tablets are colored rather than white, and that the drug is dispensed by a pharmacist.

Moreover, the overwhelming majority of prescriptions for products containing propoxyphene are for compounds

containing it in combination with another analgesic, such as aspirin or acetaminophen. These combinations are clearly effective because of these other analgesics, and propoxyphene may make an additional contribution to their efficacy.

The literature on the efficacy of propoxyphene itself is mixed. HRG gives major attention to a literature review conducted by Miller et al. in 1970 (ref. 5). Miller cited 9 of 18 placebo controlled trials in which propoxyphene was found to be more effective than the placebo. Miller concluded that "[p]roxyphene 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." HRG also cites three subsequent studies that found no significant difference between propoxyphene and placebo. On the other hand, a 1978 study by Sunshine et al. (ref. 6) found propoxyphene napsylate at 200 mg (twice the recommended dose) to be significantly better than placebo. The lowest dose used (50 mg) was slightly better than a placebo. The usual dose (100 mg) was not tested. In a second review of the literature in 1977, Miller (ref. 7) reported that three studies showed that propoxyphene is no more effective than a placebo and that five studies showed that it is as effective as (but not more effective than) a standard analgesic.

For purposes of this preliminary assessment of propoxyphene's efficacy in reaching an imminent hazard determination, I conclude that propoxyphene has some, but limited, efficacy.

Thus, it is possible that there may be some risk to patients who do not adequately respond to (or, in relatively few cases cannot safely take) aspirin, acetaminophen, or other analgesics, and who would be deprived of propoxyphene. Moreover, propoxyphene does induce some degree of physical dependence, so that sudden unavailability could lead to withdrawal symptoms for some patients. Other patients who depend particularly on propoxyphene for relief from pain may experience some suffering as the result of the abrupt removal of the drug from the market. For these people, the most likely substitute for propoxyphene is codeine, which is widely believed to be even more addictive than propoxyphene. If presented with the sudden disappearance of propoxyphene from the market, physicians would still be reluctant to prescribe codeine for more than intermittent use, and patients would be reluctant to take it.

C. Likelihood of Final Action to Withdraw the Drug from the General Market\*

The Bureau of Drugs in FDA has responsibility for initiating a withdrawal proceeding (21 CFR 314.200), but has not proposed that the NDA's for propoxyphene be withdrawn. Possible grounds

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\* Because final responsibility for deciding whether the new drug applications for propoxyphene should be withdrawn is delegated to the Commissioner of Food and Drugs, I have not asked Dr. Kennedy to comment on this matter, and he has reserved judgment until formal administrative procedures have developed a complete record for his review.

for withdrawal of these NDA's include (1) that evidence from clinical experience shows the drug to be unsafe, (2) that new evidence not available when the NDA's were approved, together with the original evidence supporting the approvals, demonstrates that the drug is no longer shown to be safe, and (3) that the new evidence, evaluated together with the evidence in the original NDA's, supports a finding that there is a lack of substantial evidence that the drug is effective. 21 U.S.C. 355(e)(1), (2), and (3).

The issues concerning the safety and effectiveness of propoxyphene are difficult and complex.

Although the drug is associated with a large number of deaths, many of these deaths appear to be related to misuse of the drug rather than to its use in accordance with the labeling directions. It is not clear that many of these deaths -- those related to suicide attempts -- would be prevented if propoxyphene were immediately removed from the market.

In addition, the record currently does not contain sufficient evidence for me to make a finding of imminent hazard based on two as yet unresolved issues raised by HRG's petition:

- 1) the extent to which propoxyphene is dangerous, if at all, when used in accordance with the labeling;

- 2) the extent to which labeling restrictions are effective in controlling use of propoxyphene that may lead to death.\*

On the basis of the information with respect to propoxyphene available to me at this time, I cannot conclude whether or not one or more of the new drug applications is likely to be withdrawn. That determination cannot be made until the issues concerning the efficacy and safety of propoxyphene in light of all the data now available have been developed more fully.

D. Potential Alternative Means To Prevent Hazard

During the period FDA is evaluating further the safety and efficacy of propoxyphene, three steps can be taken to protect the public health. I am concerned by the various dangers posed by propoxyphene: use in suicides, accidental deaths from the interaction of the drug with alcohol or other drugs that act on the nervous system, and dependence on the drug. Therefore, I am directing that these problems be addressed immediately without awaiting the final FDA decision on whether propoxyphene meets the statutory standards of safety and effectiveness. I believe that implementation of the following actions will reduce the hazards to the public health.

First, the Department will promptly evaluate HRG's proposal to transfer propoxyphene from Schedule IV to Schedule II of the Controlled Substances Act. If this

\* In the phenformin case, the evidence did support a finding that phenformin was dangerous even if used in accordance with the labeling. In addition, the evidence showed that phenformin was being used widely outside of the indications set out in the labeling.

transfer were made, the production of propoxyphene would be limited by government-determined quotas; all distribution of the drug would be on special order forms; and prescriptions for the drug would not be refillable and would have to be in writing (i.e., telephone prescriptions would be prohibited). The Assistant Secretary for Health, who has delegated authority to make drug scheduling recommendations on behalf of the Department, will make a recommendation to the Department of Justice on propoxyphene in the near future, after consideration by FDA and its Drug Abuse Advisory Committee.

Second, FDA will expeditiously prepare and distribute appropriate information for physicians, dentists, and pharmacists regarding the risks associated with the use of propoxyphene. This information will encourage physicians and dentists to reconsider the risks of and need for the drug in specific cases. It should also help deal with the problems of suicide and accidental deaths from drug interactions by making physicians and dentists more cautious in prescribing the drug for patients who may be suicidal or who may be using alcohol or other drugs affecting the central nervous system. This information will also encourage pharmacists, when dispensing propoxyphene, to put on the container warnings against taking the drug in combination with tranquilizers or alcohol.

Third, FDA will promptly prepare and distribute appropriate information for the general public, in the form of a published article or otherwise, regarding the risks associated with the use of propoxyphene.

Although I believe these actions will help protect the public, I do not believe that the completion and evaluation of these actions are necessary before a decision on the suspension or withdrawal of the propoxyphene NDA's can be made.

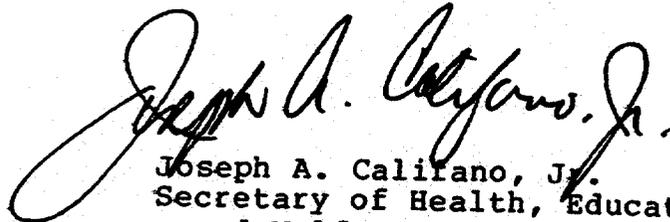
#### VI. CONCLUSION

At this time, I do not believe that there is sufficient evidence available showing that the continued use of propoxyphene constitutes so serious a threat to public health as to warrant the extraordinary action of summary suspension of general distribution of the drug, pending initiation and completion of the procedures to determine whether propoxyphene should be removed permanently from the general market. Based on the record currently before me, I am unable to declare propoxyphene an "imminent hazard."

The Act carefully balances the safeguards against improvident withdrawals of NDA's and the need to protect the public health from significant risks. The suspension power vested in the Secretary should be used sparingly, when it is likely that the drug will ultimately be withdrawn from the market and immediate action will prevent serious harm during the pendency of the withdrawal

proceedings. The issues in the case of propoxyphene are in significant doubt, and I am not prepared to predict their outcome at this time.

The fact that I am not granting the HRG petition at this time does not mean that further evidence cannot lead me to an opposite conclusion. If, in the course of FDA's further review of propoxyphene, new information is developed to show that propoxyphene meets the criteria for suspension, I will act promptly. Furthermore, the other steps that I have directed should reduce the risks that propoxyphene poses to the public health, while FDA holds its hearing to determine whether the drug should be removed from the market.

  
Joseph A. Califano, Jr.  
Secretary of Health, Education  
and Welfare

Dated: February 15, 1979

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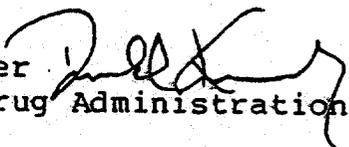
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6. Goodman and Gilman, ed., The Pharmacological Basis of Therapeutics, (5th ed., N.Y., 1975).
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# MEMORANDUM

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

TO : The Secretary  
Thru: U \_\_\_\_\_  
ES \_\_\_\_\_

DATE: February 10, 1979

FROM : Commissioner   
Food and Drug Administration

SUBJECT: Administrative Record, Darvon Petition

Of January 17, 1978, I sent you a memorandum concerning the evaluation of Propoxyphene. Attached to that memorandum, in addition to the Petition from the Health Research Group to suspend the new drug applications (NDAs) for Propoxyphene-containing products as an imminent hazard under section 505(e) of the Federal Food, Drug, and Cosmetic Act, were a number of items which were considered by the agency in making its recommendations for response to the petition.

This memorandum transmits the remaining items that we have considered and that are part of the Administrative Record for this proceeding. A detailed index is attached as Tab A. We are continuing to review our files to assure that the Record is as complete as possible.

Attachments-

- Tab A - Index of additional items in Administrative Record
- Tab B - Part II of Administrative Record

## ATTACHMENTS TO JANUARY 17, 1978 MEMO TO SECRETARY

- A. Petition from Health Research Group, November 21, 1978.
- B. NAS/NRC Drug Efficacy Study of Darvon Compound.
- C. Journal articles: Beaver, William T., M.D., Mild Analgesics - a Review of Their Clinical Pharmacology (Part II), The American Journal of the Medical Sciences, 25:576-599, 1966.
- D-F. Federal Register notices concerning Propoxyphene Hydrochloride, Drug Efficacy Study Implementation. 34 FR 6244, 37 FR 26538, 37 FR 28526.
- G. Dear Doctor letters from Eli Lilly and Company, May 19, 1972 and April 17, 1972.
- H. August 6, 1976 memo to the Assistant Secretary for Health from Commissioner, FDA - Recommendation to the Drug Enforcement Administration for Control of Propoxyphene in Schedule IV of the Controlled Substances Act.
- I. 43 FR 14739 - Labeling for Propoxyphene-Containing Preparations.
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- K. Agenda, Drug Abuse Advisory Committee, February 12-13, 1979.
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- M. Memo to Director, Bureau of Drugs regarding Revised Labeling for Darvon Products, May 18, 1971.
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- Z. Propoxyphene; Excerpt from Goodman and Gilman.
- AA. Singh, Schlagenhauff, et al; Acute Propoxyphene Intoxication: A Case Report and Review; Am.J. of Ther. and Clin. Reports; 1:83-94 (1975).
- BB. Excerpt from British Medical Journal, Nov. 25, 1978, p. 1468, "Acute Poisoning with Distalgesic".
- CC. Minutes, Phenformin Meeting, July 25, 1977.

March 6, 1979

All background material wanted for attachment II will have to  
contact Dr. Crout's Office - 32894

MATERIALS PREPARED FOR BRIEFING BOOK  
PRIOR TO DARVON HEARING

1. December 11, 1978 letter to Commissioner, FDA, from Senator Gaylord Nelson asking for testimony on "nature of your review of HRG petition and the recommendations you will be making to Secretary Califano.
2. November 27, 1978 "Pink Sheet" and November 22, 1978 Washington Post articles on HRG petition.
3. January 23, 1979 Wall Street Journal, and January 19, 1978 New York Times article concerning tighter controls for Darvon.
4. Summary of Actions (FDA, DEA) on propoxyphene products; Brief History of Major Developments relating to propoxyphene products submitted by Eli Lilly and Co.
5. May 26, 1972 Medical Letter article on Darvon.
6. January 23, 1970 Medical Letter on NAS/NRC Drug Review Panel report on Darvon.
7. May 28, 1969 FDA letter to Lilly requesting discontinuance of unqualified use of term "non-narcotic" in journal advertising with sample advertising copy.
8. AMA drug evaluation for Darvon products.
9. Sample current labeling.
10. Reprints from Goodman and Gilman and Remington's on "Placebo Effect."
13. Kartzinel/Crout Action Memo with January 7, 1979 Commissioner/Secretary.
14. Dr. Judith K. Jones data - Risk of Propoxyphene use A Basis for Risk Benefit Analyses.
15. August 6, 1976 scheduling recommendation from Schedule IV to Schedule II - good historical review of addiction liability and abuse patterns.
16. December 18, 1978 Wolfe/Kennedy letter regarding cardiac toxicity of propoxyphene with January 22, 1979

response - Kennedy; also includes Dr. Judith Jones memo on Propoxyphene Issue.

17. NAS/NRC Reports; April 8, 1969 Federal Register - initial announcement; December 3, 1972 Federal Register - Amended.

18. Moertel Article - Lilly "Dear Doctor letter" - correcting "Dear Doctor" letter sequence Wall Street Journal and Washington Post articles.

C.J. Moertel article from New England Journal of Medicine "A Comparative Evaluation of Marketed Analgesic Drugs".

Lilly April 17, 1972 "Dear Doctor" letter rebutting Moertel article - refers to NAS/NRC efficacy finding for Darvon.

Washington Post and Wall Street Journal articles about FDA's testimony before Nelson.

19. Influence of Advertising on Darvon Memorandum by Peter Rheinstein.

20. Other specific question and answers from letter of invitation.

III.

OTHER RELATED ITEMS

1. Memo from Alexander M. Schmidt, M.D., Commissioner of FDA to Assistant Secretary for Health, dated January 20, 1976, with incoming correspondence from Theodore Cooper, M.D., to Mr. Henry S. Dogin, Acting Administrator of DEA, re: Recommendations to the Drug Enforcement Administration on Drugs Under Consideration for Control under the Controlled Substances Act.
2. Letter to Theodore Cooper, M.D. from Peter B. Bensinger, dated March 26, 1976.
3. Memorandum of Telephone Conversation between Sidney Wolfe, M.D. and J. Richard Crout, M.D., dated February 3, 1979, re: Propoxyphene.
4. Draft Summary of FDA Actions of Propoxyphene Products.
5. NAS/NRC Drug Efficacy Study, dated 9/22/60 for Darvon Compounds.
6. Memo from the Director, Bureau of Drugs to The Commissioner, dated January 15, 1979, re: recommended response to the petition to the Secretary on November 21, 1978 from the Health Research Group to suspend the new drug applications for propoxyphene-containing products.
7. Memo from Ronald Kartzinel, M.D., Ph.D., to the Commissioner, dated January 26, 1979, re: additional information on propoxyphene use. Data supplied by the Division of Drug Experience.
8. Memorandum of Telephone Conversation of February 1, 1979, between Dr. Hershel Jick, Boston Collaborative Drug Study Program and Dr. Judith Jones, Division of Drug Experience, re: BDSCP Data on Darvon.
9. Letter from E. A. Burrows, Regulatory Affairs Associate, to Bureau of Drugs, Division of Neuropharmacological Drug Products, dated December 12, 1978, re: NDA 17-1;22 Tablets Darvocet-N 50, Tablets Darvocet-N 100, propoxyphene napsylate with acetaminophen.
10. Letter from E.B. Herr, Jr., Ph.D., Lilly Research Laboratories to Dr. J. Richard Crout, dated December 14, 1978, re: Darvon petition, with attached correspondence from E.B. Herr to The Honorable Joseph A. Califano, Jr., dated December 13, 1978.

11. Discussion of the pharmacology and toxicology of propoxyphene and norpropoxyphene from Lilly, dated January 26, 1979.
12. Letter from E.A. Burrows, Lilly Research Laboratories to Bureau of Drugs, Division of Neuropharmacological Drug Products, dated November 22, 1978, re: NDA 17-122, Tablets Darvocet-N 50, Tablets Darvocet-N 100, propoxyphene napsylate with acetaminophen.
13. Survey of Forensic Toxicological Data Relative to Propoxyphene, based on a study conducted by Bryan S. Finkle and Kevin L. McCloskey, Ladislav Kopjak and Thomas A. Jennison of the Center for Human Toxicology, University of Utah, dated March 23, 1976, submitted by Lilly Research Laboratories.
14. Letter from Glenn Kiplinger, Lilly Research Laboratories to Charles R. Schuster, Ph.D., dated 21, 1976, transmitting Submission of Eli Lilly to the Controlled Substances Advisory Committee of the FDA regarding propoxyphene, dated April 20, 1976.
15. Preliminary Submission of Eli Lilly, dated December 28, 1978, concerning the Health Research Group's letter of November 21, 1978, to Secretary Califano.
16. Computer listing -drug experience reports.
17. Memo dated January 30, 1979. Office of Legislative Services to Director, Division of Drug Advertising. Promotion of Darvon as a non-narcotic. Includes related correspondence and advertising.
18. Memo dated January 30, 1979. Acting Director, Division of Drug Experience to Commissioner. Propoxyphene. Includes attached articles:

Simultaneous Determination of Propoxyphene and in Human Biofluids using Gas-Liquid Chromatography. J. Chromatography 75:1973:195-205.

Lund-Jacobsen; Cardio-Respiratory Toxicity of Propoxyphene and Norpropoxyphene in Conscious Rabbits. Acta. Pharm. et. Tox. 1978:42:171-178.

Gustafson and Gustafsson; Acute Poisoning with Dextropropoxyphene; Acta Med. Science 200:241:1976.

19. Pamphlet - Drug Abuse, Data Systems, and Regulatory Decisions. Medicine in the Public Interest, Inc., 1977.
20. Morris and Shapiro; The Comprehensive Approach to Patient Care § 5 - The Placebo Response, 1977.
21. Drug Abuse Warning Network - Executive Summary, October, 1978.
22. Greene, Nightingale, Dupont; Evolving Patterns of Drug Abuse; Ann. Intern. Med; 83:402-411, 1975.
23. Hallard and Steinberg; Electrophysiologic Properties of Propoxyphene and Norpropoxyphene in Codeine and Cardiac Conducting Tissues in vitro and in vivo; Toxicology and Applied Pharmacology 47:161-171, 1979.
24. Chambers and Moffett; Five Patterns of Darvon Abuse; Int. J. of the Addictions, 6(1) pp. 173-189; March, 1971.
25. Lilly Submission to Drug Abuse Advisory Committee.
26. Calculations, analysis, miscellaneous memoranda.
27. Memorandum dated January 26, 1979. Director, Division of Neuropharmacological Drug Products to Commissioner, F.D.A. Re: Phone request on propoxyphene use, with attachment.
28. DAWN Medical Examiner Mentions. Charts.
29. Testimony, Monopoly and Anticompetitive Activities Subcommittee of the Select Committee on Small Business, January 31, February 1, 5, 1979.
30. Eli Lilly and Company submission regarding the FDA drug Abuse Advisory Committee's Preliminary Consideration of the Status of Propoxyphene Under the Controlled Substances Act as Noted in 44 Fed. Reg. 3315 (January 16, 1979), dated January 25, 1979.
31. Abstracts - Propoxyphene Hydrochloride.

IV.

OTHER DATA REVIEWED  
BUT NOT COPIED  
FOR THE RECORD\*

1. Bibliography of Toxicity and Efficacy Combined of Propoxyphene (pages 1-53), for 1970-75, dated December 1, 1978.
2. Bibliography of Toxicity and Efficacy Combined of Propoxyphene (pages 1-40), for 1976-78, dated November 30, 1978.
3. Bibliography of Toxicity of Propoxyphene (pages 41-87), for 1976-78, dated November 30, 1978.
4. Bibliography of Efficacy of Propoxyphene (pages 88-110), for 1976-78, dated November 30, 1978.
5. Bibliography Citation List Generated by Medlars II on Propoxyphene (toxicity), dated December 1, 1978.
6. Bibliographic Citation List Generated By Medlars II on Propoxyphene (Efficacy), dated December 1, 1978.
7. Drug Abuse Warning Network (DAWN) Episode file.
8. Competitive Problems in the Drug Industry. Hearings Before the Subcommittee on Monopoly of the Select Committee on Small Business. August 6, 11, 17, and 18, 1970.
9. Competitive Problems in the Drug Industry. Hearings Before the Subcommittee on Monopoly of the Select Committee on Small Business. November 23, 24, December 1, and 2, 1970.
10. Competitive Problems in the Drug Industry. Hearings Before the Subcommittee on Monopoly of the Select Committee on Small Business. January 18, 19, February 1, 2, and 3, 1971.
11. Competitive Problems in the Drug Industry. Hearings Before the Subcommittee on Monopoly of the Select Committee on Small Business. May 9, 10, June 21, and July 19, 1972.

\*/ This data will be made available for review request. Please contact the Office of the Hearing Clerk, Room 4-65, 5600 Fishers Lane, Rockville, MD 20857 Phone 443-1753.

13. C. H. Hine, M.D., J. A. Wright, B.S., et al., Analysis of Fatalities Due To Acute Narcotism in a Major Urban Area. Submitted for publication, 1979.

V.

OTHER INFORMATION

Sales and other prescription data for propoxyphene supplied to FDA pursuant to contract with IMS America. FDA is prohibited by contract from making this information publicly available.