



DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
ROCKVILLE, MARYLAND 20857

MAR 17

NDA-10-997

Richard D. Wood
Chairman of the Board, President and
Chief Executive Officer
Eli Lilly and Company
P.O. Box 618
Indianapolis, IN 46206

Dear Mr. Wood:

I am addressing this letter directly to you because the issue involved is one that should come to the attention of Lilly's chief executive officer.

As you are aware, propoxyphene-containing products are commonly associated with drug-related deaths. In fact, the Darvon line of products stands out as the most common brand-name associated with drug-related deaths in the United States. Because of this, Lilly offered last year to conduct an informational campaign to alert practitioners that these products are not as safe as was once thought and that certain specific precautions must be exercised in prescribing them. Lilly's representatives committed the company to use its sales force to contact personally 125,000 physicians identified as significant prescribers of propoxyphene products.

Lilly's commitment to an informational campaign directed at prescribers of Darvon products was an important factor in the decision of the Department of Health, Education and Welfare not to seek rescheduling of propoxyphene at that time.

When Lilly's commitment was made, FDA representatives told Lilly that we would be using the IMS National Detailing Audit verbatims to monitor the Lilly informational campaign. These verbatims are taken from forms filled out by practitioners after detail persons leave their office.

The results of this survey for the months of August through November 1979 are now available. The character of this "informational campaign" is so different from what we expected that I am obliged to bring this matter to your attention.

Richard D. Wood
Eli Lilly and Company
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In August 1979, the first month of the campaign, the informational message to the prescriber was adequate in dealing with the new information on Darvon products in, at best, 60% of the detail visits for which a message was reported. By September, this figure had dropped to 45%. In October and November, less than 10% of the details on Darvon conveyed a message about the important new warnings.

Furthermore, we would not have expected the informational material to be combined with a sampling program in a campaign intended solely to inform physicians about new adverse information. Nevertheless, samples of Darvon products were left behind in nearly 50% of visits in August 1979, 60% of visits in September and more than 75% in October and November.

In addition FDA had presumed that Lilly sales personnel would be making special calls to talk solely about the new information on Darvon products. This was not the case. In fact, Darvon products were not even the first drugs mentioned in the majority of visits. On the average, Darvon products were discussed second in each of the months surveyed.

Finally, FDA had expected that the new information about Darvon products would be the major topic of the detail persons' visits. In fact, in August, less than half of each visit was devoted to Darvon products and in September, October and November, less than one third of each visit was devoted to these products.

To give you a feeling for the impressions left by Lilly representatives, here are a few of the messages written down by practitioners immediately after detailing visits (from the reported verbatims for October 1979):

"Darvon & Lilly won FDA battle"

"Safe in spite of Nader report"

"OK by Drug Commission"

"Analgesic - few if any side effects"

The inescapable conclusion is that Lilly has not yet met its commitment for a personal contact informational campaign intended solely to sensitize prescribers and dentists to the precautions necessary for the safe use of propoxyphene products. Instead Lilly has conducted a standard promotional campaign for its Darvon products that happened to include, in a minority of the visits made, reference to the new labeling information.

OVERDOSE/FATALITIES
FOURTH QUARTER 1979

	<u>Month Closed/ No. Cases</u>	<u>Class</u>	<u>Outcome</u>
Darvon Compound-65	October - 1	*	F
Darvocet-N 100	November - 1	**	NF
	Total 2		

Grand Total for 1979 - 33 (6 NF; 26F, 1 unknown)

* Confirmation of a propoxyphene fatality
**Insufficient information to determine propoxyphene
related death

NF - Non-Fatal
F - Fatal

1/10/80
IFB:PMK

DEPENDENCE 1979 FOURTH QUARTER

	<u>Month Closed/No. Cases</u>	<u>Class</u>	
Darvon	October	1	*
	November	1	**
	December	2	*
		1	**
Darvon Compound/ Darvon Compound-65	October	0	
	November	0	
	December	0	
Darvon-N	October	0	
	November	1	*
	December	0	
Darvon-N with A.S.A.		0	
Darvon with A.S.A.		0	
Darvocet-N/ Darvocet-N 100	October	1	*
	November	0	
	December	3	*
		1	**

Total 11

*Confirmation of a propoxyphene dependence.
 **Insufficient information for definitive diagnosis of dependence.

IFB:PMK
 1/10/80

investigate the role of propoxyphene in suicide attempts and incompleated suicides. She was concerned about the role of propoxyphene in manic-depressive disorders; does propoxyphene increase the possibilities for suicide? In her opinion, there needs to be more research into the role of stress, confusion, ambivalence, and crisis in relationship to drug use and abuse. And finally, she pointed out, that there is very little research about the relationship between the use of propoxyphene and the use of other drugs, including alcohol.

There has been a good deal of research concerning the relationship between propoxyphene and unexpected deaths as evaluated by medical examiners. Finkle and colleagues assessed this problem in 1976. All of the research on propoxyphene was extensively reviewed by Furman in 1979. It is interesting that the analgesic drug, codeine, which alone or in combination is used extensively for minor pain relief, has not received the same sort of concern and attention recently. Yet, preliminary surveys by our staff indicate that the number of codeine related deaths in Los Angeles, at least, is approximately equal to propoxyphene related deaths. One outstanding reference is the work of Nakamura, et al in 1976. These investigators from the medical examiner's office in Los Angeles, reviewed 45 fatalities involving codeine during a 12 month period.

More data is needed to answer a number of important questions concerning propoxyphene/codeine related deaths as follows:

1. In what proportion of the cases are propoxyphene/codeine irrelevant to the fatal outcome in that only small amounts of the drug are present in the body and investigation indicates that the analgesic drugs were taken in prescribed amounts by a person who committed suicide using other drugs, for example, barbiturates
2. What proportion of the deceased persons were not frequent or habitual users of propoxyphene or codeine, but obtained and ingested large amounts of the drugs on a one-time basis for suicide or for some other purpose.
3. What proportion of the deceased persons who took an unusually large dose under circumstances suggesting suicide, had been in severe, chronic physical pain using propoxyphene or codeine for pain relief as prescribed by physicians? It is possible that the number of such cases could be reduced if physicians were educated to be more alert to the premonitory clues to the identification of persons in pre-suicidal states.
4. What proportion of the cases could be rigorously determined to be "accidental"? Two possible types of cases are most likely, as follows:
 - a. persons who were using a great deal of propoxyphene or codeine for pain, who also ingested, at the same time, a considerable amount of alcohol or other drugs so that the additive effect was fatal, although the person did not intend it to be fatal.

Investigations of Propoxyphene and/or Codeine Related Deaths

Summary Statement: We propose to identify and investigate, by the method of "psychological autopsy" deaths in Los Angeles County involving the drugs propoxyphene and codeine over a time period of approximately one year.

A. Specific Aims:

1. To clarify for each of these drugs the following:
 - a. the frequency with which each of these drugs is associated with fatal outcome and
 - b. In each case, to what degree the fatal outcome was intentional (suicide vs. accident).
2. To obtain information suitable for evaluating the character and life-style of the deceased, the degree of recent stress or crisis and the role of the medical and pharmaceutical professions in the death.
3. To answer the following:
 - a. Whether propoxyphene and/or codeine was used individually or in combination with other drugs, including alcohol, and in what combination.
 - b. Whether the deceased was habituated or addicted to any drug including alcohol and to what degree.
 - c. Whether the drug responsible for the death was obtained primarily from physicians or from other sources.
 - d. Whether the analgesic drug was used primarily for the relief of pain, either physical or psychological, or primarily for the purpose of "getting high"; or whether both purposes were involved.
4. To clarify the attitudes of physicians prescribing analgesic drugs towards patients in situations in which there might be drug abuse.
5. To clarify the attitudes of friends and families of persons who are thought to be abusing analgesic drugs.

B. Significance:

Propoxyphene and codeine are two important frequently prescribed analgesic drugs. Recently, there has been considerable publicity with expressions of concern about the role of propoxyphene in suicides and in accidental deaths. A typical example was provided by K.R. Jamison, Ph.D. in a position paper presented at a hearing of the FDA Drug Abuse Advisory Committee, April 17, 1979. Dr. Jamison's paper, titled "Propoxyphene: Suicidal Potential, Drug Abuse and the FDA" expressed her concern that someone should more systematically

physicians will be interviewed for each case. A questionnaire containing 80-100 items will be filled out as a result of the information gathered during the interview. In addition, the interviewers will have a de-briefing session with Dr. Litman and a summary of the special circumstances of each case will be prepared. It is estimated that each interview with relatives and friends will take approximately one hour and the interviews with physicians will take approximately 20 minutes. Previous experience indicates that it takes considerable time to contact informants, set up interviews, and travel to the places where the interviews will be conducted.

2. Data Analysis. A current revision of the interview form is included as Appendix 2. This form has been used many times for the investigations of drug-related deaths, most recently for a study of phencyclidine-related deaths in Los Angeles.

Interview data will be coded and prepared for computer analysis. Preliminary analysis will provide tabular data with which propoxyphene and codeine ingestion represent the cause of death, both in combination with other drugs and with alcohol. These data will be examined by breaking the sample down by cause of death (i.e. propoxyphene/codeine as a direct cause, as an indirect cause in combination with other drugs and alcohol, and as a drug which did not significantly contribute to the cause of death) and determining the frequency of intentional vs. accidental death in each category. Significance of differences between and among categories will be determined by t-test, chi-square, and analysis of variance as appropriate.

The sample of propoxyphene/codeine related deaths, including the subsamples defined above in terms of death, will then be described on the basis of information obtained from the psychological autopsies. This information will include data on personal and family backgrounds, social activities and styles of life, experiences of stress and crises in the last three months of life, histories of drug and alcohol use, psychiatric conditions, attitudes of family and friends towards the decedents, attitudes of the physicians towards the decedents and towards prescribing analgesic drugs, and other variables. Discriminant function analysis will be used to find a subset of variables from among those obtained from the psychological autopsies which are associated with mode of death (suicide vs. accident) and propoxyphene/codeine involvement as cause of death.

3. Factors in evaluating accident vs. suicide in drug overdose deaths
 - a. Risk taking by deceased:
 - amount and type of drug ingested.
 - knowledge of deceased concerning drug dangers.
 - provisions to impede discovery and rescue.

- b. Persons who customarily or habitually abused analgesic drugs by taking extremely large amounts, for example, well over a gram a day of propoxyphene or over $\frac{1}{2}$ gram a day of codeine. Such persons repetitively overdose, putting themselves into comatose or near comatose states. While comatose, the person could move into a position that could cut off the airway.

If substantial numbers of persons are meeting their deaths through propoxyphene or codeine overdose when those persons did not intend to risk their lives, then the dangers of these two drugs have been underrated and an actual national information campaign is necessary to alert professionals and the public to the dangers of abusing these analgesic drugs.

5. We feel it is important to evaluate both propoxyphene and codeine and to make a comparison of these drugs. It is our hypothesis that in Los Angeles, these two drugs are used and abused at approximately the same rate and that they are quite similar in their involvement in drug-related deaths. Therefore, if propoxyphene were made less available, it is reasonable to anticipate an increase in the prescription and use of codeine analgesics to take the place of propoxyphene. The simultaneous investigation of codeine-related deaths will be useful in evaluating whether the substitution of codeine for propoxyphene could be expected to result in a substantial saving of lives.

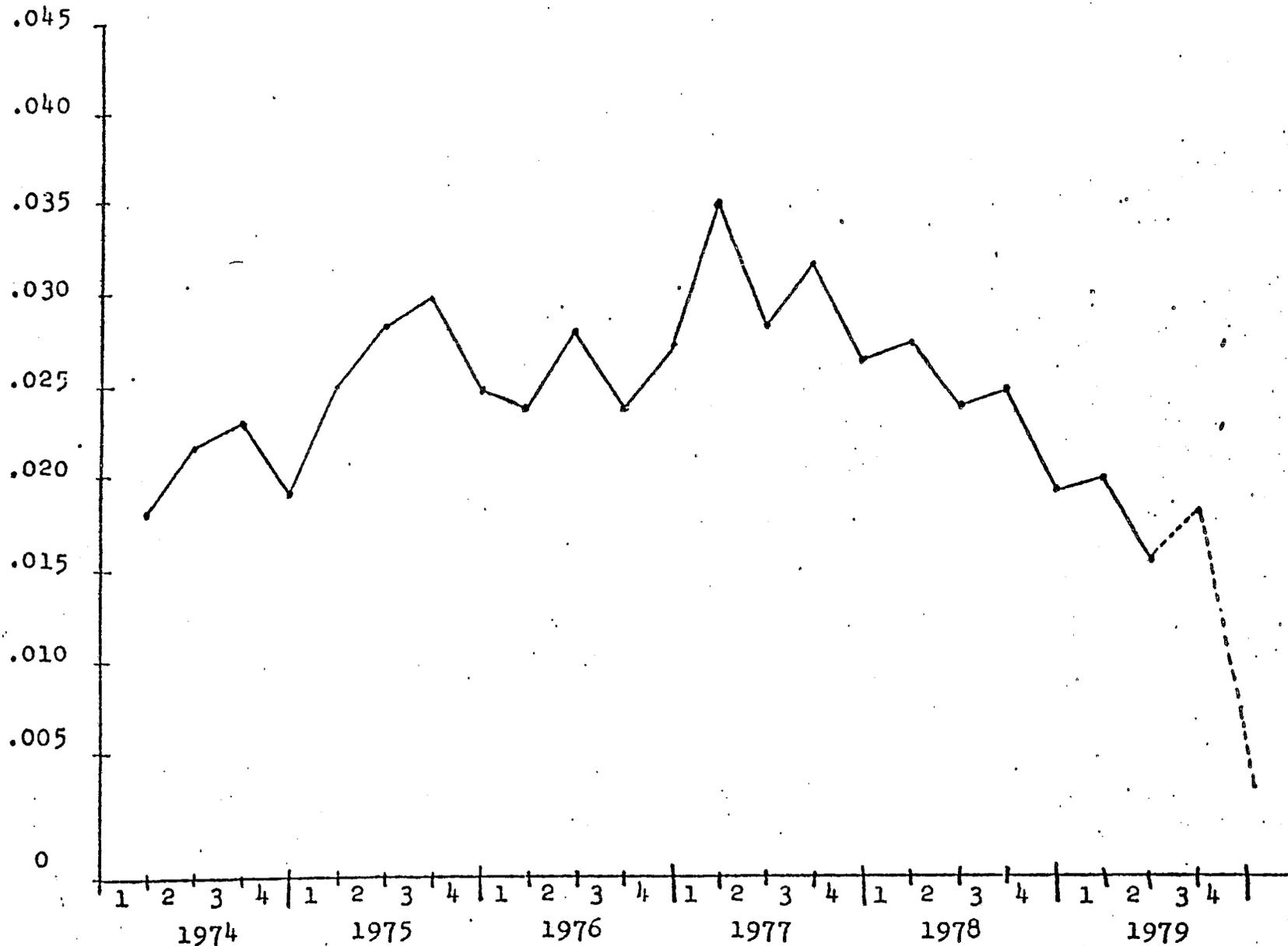
C. Method

1. Psychological autopsy. The historical development and current use of psychological autopsies was described by Dr. Litman in his statement to the FDA Drug Abuse Advisory Committee, April 17, 1979. This statement, together with a bibliography on psychological autopsies is included in this proposal as Appendix

The purpose of the psychological autopsy is to reconstruct or recreate the past history, current life-style, significant events and stresses, and the circumstances involving the death of an individual. Interviews are conducted with survivors who can provide significant information concerning the state of mind of the deceased person in the period before his/her death. The objective is to make the best possible inference concerning the degree to which the person intended to die as a result of the person's own acts. In drug-related deaths, the problem is to make the most appropriate inference as to what the person had in mind when he/she ingested the fatal drugs.

There will be 100 cases, divided evenly between propoxyphen and codeine related deaths. There will be a minimum of three interviews for each case. There will be an interview with a family member, a friend or co-worker, and a physician. Usually, several

Index of Medical Examiners' Reports per '000 Rx's (Quarterly - 1974-1979)



Sources: National Prescription Audit (IMS)
IMS America, Ltd.

EXHIBIT VI
Darvon and Darvon-N Products
NDA Quarterly Report--Jan. 19

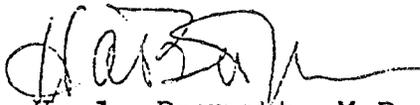
Two hundred additional copies of the film have been ordered and one copy will be placed with each medical and pharmacy school in the states. It is anticipated that these copies will be delivered to the schools before March, 1980.

Lilly representatives will be glad to discuss the contents of this report with FDA personnel.

The company anticipates submitting its next quarterly report at the end of April, 1980.

Very truly yours,

ELI LILLY AND COMPANY



H. A. Barnett, M.D.
Medical Advisor
Regulatory Affairs

information this study might provide, the company may implement the proposal.

13) Investigation of Propoxyphene and/or Codeine
Related Deaths in Los Angeles County--Dr. Litman

Lilly has approved a prospective study to be conducted by Dr. Litman which will include a psychological autopsy of a number of fatalities in the Los Angeles County area involving the drugs propoxyphene and codeine. The time covered would be one year.

A copy of the proposal is attached as Exhibit XIII. Lilly has requested that Dr. Litman provide, to the extent possible, precise identification of the dosage form of any drug involved in each death case, i.e., tablet, capsule, or suspension; product trademark, if any; manufacturer's identifying marks; and code numbers which may appear on dosage forms.

14) Audiovisual Film--Suicide Prevention in Medical
Practice

Information was requested on the extent of distribution on this audiovisual film. One hundred and seventy-one copies of the film have been distributed to 57 Lilly local offices throughout the states. The films are checked out from these offices by a Lilly sales representative for group showings.

of prescription records of propoxyphene products. The selection process utilized by PDS for individual reports required that the patient involved had received a prescription for some form of propoxyphene during the calendar year 1978. PDS identified 54,469 such users out of their data base of approximately 1.8 million patients. They selected every eighteenth patient out of this file and extracted 3,026 patients and a total of 81,761 records. For each patient in the file all prescription history from January 1, 1978, through September 30, 1979, is included.

Lilly is now testing computer based models to analyze propoxyphene usage patterns from this file. In this study, the company intends to compare the findings of its model with the FDA study conducted last year which utilized data from the same source. Information from this evaluation should be available for the company's next quarterly report.

12) Proposed PSRO Study of Darvon and Darvon-N Products Utilization--Dr. Dorsey

Lilly should receive in the near future an outline of a proposed study which would review the utilization of propoxyphene products in the greater Cincinnati area. Depending upon the type of

activities in Wisconsin at least as represented by these two laboratories is substantially lower than in recent years. Exhibit IX contains monthly totals on drugs analyzed at each of the two laboratories as well as monthly totals on the number of laboratory samples which are identified as containing propoxyphene. Also attached for your information is a summary of the Wisconsin Crime Laboratory reports with respect to propoxyphene for the years 1975-1978 identified as Exhibit X.

9) Dependence Reports

Reports of dependence on propoxyphene products received by Lilly in the fourth quarter of 1979 are listed in Exhibit XI.

10) Fatality Reports

The company received and evaluated information on one overdose and one fatality in the last quarter of 1979. That information is contained in Exhibit XII.

11) Analysis of Pharmaceutical Data Services Information

To provide information which would supplement existing data on the character and extent of propoxyphene misuse, Lilly has acquired from the Pharmaceutical Data Services organization a file

Exhibit VII contains a display of the data utilized in the preparation of Exhibits IV, V, and VI.

Exhibit VIII compares the absolute and relative ranking of the top 23 drugs mentioned in medical examiner reports for the years 1977 and 1978. In both of these years, propoxyphene was the second most frequently mentioned drug in medical examiner reports. However, when the absolute numbers of medical examiner mentions were divided by the number of new prescriptions, the rank of propoxyphene fell from eleventh in 1977 to thirteenth in 1978 to tie with two other drugs for thirteenth place that year.

8) Wisconsin Crime Laboratory Reports

Wisconsin Crime Laboratory reports prepared by the State Department of Justice have now been received for the full year 1979. Among 5,800 drugs analyzed in conjunction with law enforcement activities at the Department's two Wisconsin laboratories, only 20 were identified as containing propoxyphene. This contrasts with 30 so identified in 1978 and 50 in 1977. The annual incidence of detection of propoxyphene in laboratory samples associated with law enforcement

reports from those consistent reporters in the DAWN VIII panel.

To provide a comparison between new prescriptions for propoxyphene on a quarterly basis and the DAWN medical examiner data which is depicted in Exhibit IV on a quarterly basis, Exhibit V was prepared. It should be noted that quarterly data for propoxyphene prescriptions was not available for the years 1974-1976. Annual figures were divided evenly to provide four quarters of data measured in whole numbers for each of those years. Also, prescription data for the fourth quarter of 1979 may be considered preliminary. Propoxyphene prescriptions have changed in volume from year to year as follows:

1974-1975	1.7 percent decrease
1975-1976	3.5 percent decrease
1976-1977	2.3 percent increase
1977-1978	2.4 percent decrease
1978-1979	20.4 percent decrease

Exhibit VI represents an index of medical examiner reports per thousand new prescriptions of propoxyphene for the period 1974-1975. It indicates a decreasing incidence of medical examiner reports per thousand new propoxyphene prescriptions.

Angeles. Only recently have arrangements been made to obtain access to data at that site.

Dr. Finkle plans to visit that site promptly, and his full report should be available by the end of February. It will be provided the FDA when available as a supplement to this report.

As noted in the October 23 report, Dr. Finkle has advised Lilly that propoxyphene-related deaths appear to have declined in recent years at most of the sites visited. Propoxyphene-related deaths do not appear to have increased at any site.

7.) Drug Abuse Warning Network Medical Examiner Data Involving Propoxyphene

Mentions of propoxyphene in medical examiners' reports have been declining steadily from their highest point in the first quarter of 1977 (150 mentions) through the second quarter of 1979 (58 mentions). DAWN data is considered relatively firm for the first two quarters of 1979.

Exhibit IV illustrates the downward trend of medical examiner mentions in DAWN data. This exhibit is based on propoxyphene "mentions" in 72 consistently reporting medical examiners, and all figures in the chart have been adjusted to reflect

5) Darvon and Darvon-N Products Prescription Volume

Darvon and Darvon-N products have experienced a decrease in prescription volume during the period 1977-1979. Exhibit II indicates new prescriptions for Darvon and Darvon-N products for the period January 1, 1977, through December 31, 1979, in comparison with Percodan and other propoxyphene products.

The increased demand for oral codeine preparations is illustrated by Exhibit III. It demonstrates that the level of demand for Percodan during the years 1977 through 1979 as measured by new prescriptions has remained relatively constant. There has been a decrease in new prescriptions for propoxyphene products from 17.9 million prescriptions in 1977 to 13.9 million prescriptions in 1979.

6) Update of 1975 Finkle Survey

Dr. Finkle and his colleagues have revisited and have collected data from 17 of the 18 medical examiner/coroner offices covered in his 1975 survey. Also, several additional medical examiner/coroner offices have been covered.

It was not possible in late 1979 to secure information from the medical examiner's office in Los

such a survey be conducted by telephone contacts with two hundred pharmacies appropriately distributed throughout the United States. The Consumer/Industrial Research Service will conduct the survey. Information from the survey will be forwarded as a supplement to this report as soon as it is available.

4) Survey of Consumers Receiving Darvon and Darvon-N Prescriptions

The extent to which consumers receiving Darvon patient information sheets have reviewed and are aware of the precautionary information contained in such sheets is currently being surveyed by the Medical Research Bureau. Although efforts on this survey were initiated in late 1979, it was not possible to secure the cooperation of pharmacists in the proper identification of recipients of Darvon and Darvon-N prescriptions because of the pressure of business prior to Christmas. However, following the holidays, it was possible to obtain the assistance of pharmacists and the survey is now under way. Results of the survey should be available in March and will be submitted as a supplement to this report.

addition, 91 percent of the physicians were aware that caution should be used in emotionally disturbed or depressed patients. Nearly 90 percent of the physicians felt that it was important to screen patients for potential drug abusers prior to prescribing Darvon products.

The results indicate that physicians have a very high awareness level of precautions applicable to the prescribing of Darvon products. The results also indicate that the physician was made aware of these precautions primarily by the physician mailings or by the sales representative.

There was no statistical difference in these two sources of information. To a much less degree, physicians also indicated that newspapers, medical journals, magazines, and television contributed to their awareness of the precautions applicable to Darvon products.

3) Pharmacy Survey

Dr. Marion Finkel of the FDA has requested that a survey of pharmacists' distribution of Darvon patient information sheets be conducted by Eli Lilly and Company. A completion date of late February was requested. Lilly has proposed that

These percentages are particularly significant because both questions required unaided responses. As indicated by Lilly (prior to initiating this study) such surveys sometimes produce disappointingly low affirmative response levels. This survey exceeded the company's expectations in this regard, even though the survey was not conducted until late 1979 in part due to the extensive discussions regarding its format and composition. Undoubtedly, this delay led in part to a greater level of "can't recall" responses than might have been achieved otherwise.

Since the ultimate intent of the Education Program was to increase physician awareness of the precautions, all physicians were surveyed with regards to these precautions. This was asked even of physicians not recalling being given information on Darvon or any other oral analgesic.

The results showed that most physicians were aware of the precautions associated with the use of Darvon products. Over 97 percent of the physicians were aware that caution should be used when Darvon products are taken with alcohol, and over 93 percent indicated that caution should be used when taken with CNS depressant drugs. In

In general, the survey results indicate a relatively high level of awareness of the dissemination of information obtained through the mail and through detailing on oral analgesic products (see page 1 Statistical Tables). In addition, a higher percentage of physicians recalled mailed literature and detail efforts on Darvon and Darvon-N products than on any other single category of product on which they were questioned (see page 2 Statistical Tables). Although we have no information on the precise level of promotion of other companies' products, the Darvon physician recall level is remarkable considering the extensive promotional activity on oral analgesic products observed during the August/September period. Upjohn was providing information to physicians on its new analgesic indication of Motrin in August and introduced a new dosage form of Motrin in September. Burroughs Wellcome was advising physicians of a modified formulation of Empirin Compound with Codeine. Also, as indicated in the survey results, the number of physicians who recalled Tylenol and Talwin information suggests strong promotional efforts on these products during this period.

Insofar as Lilly is aware, other producers of propoxyphene have only been "requested" by FDA to provide patient information sheets on propoxyphene. As noted in the company's last quarterly report, it would appear desirable for all producers to provide such information.

2) Physician Survey

A telephone survey of physicians was conducted by the Consumer/Industrial Research Service of Media, Pennsylvania. The survey was made to determine the extent of physicians' awareness of precautionary information on Darvon and Darvon-N products recently provided physicians through personal contacts with Lilly representatives or by mailings from Eli Lilly and Company.

The format of the questionnaire utilized and the number of physicians contacted had been previously reviewed with FDA personnel. Exhibit I includes a resume of the questions asked, the number of physicians contacted in total and by medical specialty, and an analysis of the results of the survey.

During this same period over 2.9 million refill prescriptions were filled with Darvon and Darvon-N products, resulting in a monthly refill prescription incidence of 580,000 prescriptions (source, NPA). New and refilled prescriptions filled with Darvon and Darvon-N products totaled 1,400,000 per month. Assuming that prescriptions are filled with Darvon and Darvon-N products at the same rate as occurred from August 1, 1979, until December 31, 1979, the quantities of patient information sheets supplied through December of 1979 would be sufficient to provide a patient information sheet with each such prescription for nearly ten months ($13,844,000$ patient information sheets \div $1,400,000$ Rx's/month = 9.89 months).

If pharmacists were to distribute an information sheet for only new prescriptions filled with Darvon and Darvon-N products, the supply of information sheets made available from Lilly through December 31, 1979, for Darvon and Darvon-N prescriptions would last for nearly 17 months ($13,844,000$ information sheets \div $820,000$ new Rx's/month = 16.88 months).

community and hospital pharmacies. Of these, approximately 12,500,000 were sent to community pharmacies. During the period August 1, 1979, through December 31, 1979, approximately 1,344,000 additional patient information sheets were distributed to pharmacies on reorders (1,354,000 distributed through January 10, reduced by approximately 10,000 distributed in early January). Thus, during the five-month period August 1 through December 31, 1979, approximately 13,844,000 patient information sheets were distributed, primarily to community pharmacies.

From August 1, 1979, through December 31, 1979, there were approximately 4.1 million new prescriptions filled with Darvon and Darvon-N products (based on NPA data--after prescription losses due to the substitution of generic brands and the effect of the Maximum Allowable Cost program). Thus, new prescriptions filled with Darvon and Darvon-N products were occurring at the rate of approximately 820,000 per month.

These reorders through January 10, 1980, have resulted in the distribution of an additional 1,354,000 Darvon patient information sheets and 3,500,000 individual Darvon prescription vial stickers to pharmacies.

d) Availability of Darvon Patient Information Sheets to Community Pharmacies

Interest has been expressed in the quantity of patient information sheets available for distribution by community pharmacies. Lilly estimates that the patient information sheets initially distributed to community pharmacies plus sheets reordered by pharmacies would provide nearly a ten-month supply for prescriptions filled with Darvon and Darvon-N products. If patient information sheets were utilized only with those new prescriptions filled with Darvon and Darvon-N products, an estimated 17-month supply has been distributed.

These estimates are based on the following premises:

In August of 1979, approximately 15 million patient information sheets were provided to

Note: The company's October 23, 1979, report indicated that each patient information sheet pad contained 25 individual sheets (see page 2, paragraph 6). This was incorrect. Each such pad contained 50 individual sheets.

c) Reorders

Since early August, 1979, physicians have submitted approximately 5,000 requests for patient information sheets and prescription vial stickers. In response to these requests, approximately 29,000 pads (50 each) of Darvon patient information sheets and 3,800 rolls (500 each) of Darvon prescription vial stickers have been supplied.

During this same period, pharmacists have submitted to Lilly approximately 3,600 requests for Darvon patient information sheets and Darvon prescription vial stickers. (These requests may have been for one or more pharmacies.) Approximately 27,000 pads (50 each) of Darvon patient information sheets and 11,000 rolls (500 each) of prescription vial stickers have been supplied to pharmacies in response to these requests.

and a business reply card to an additional 145,000 physicians in early August, 1979. These same materials were sent to 25,000 psychiatrists.

In summary, Lilly has to date distributed the revised information on Darvon to the 125,000 physicians identified as significant prescribers, to an additional 145,000 physicians, and to approximately 25,000 psychiatrists.

b) Pharmacies

In early August, 1979, the company distributed to approximately 60,000 pharmacies (50,000 community--10,000 hospital) a Darvon information letter, brochure with revised labeling, Darvon patient information sheets (5 pads--50 sheets per pad), Darvon prescription vial stickers (1 roll--500 stickers per roll), and a business reply card to facilitate the reordering of pads and stickers. These shipments thus resulted in the initial distribution to pharmacies of 15 million individual Darvon patient information sheets and 30 million individual Darvon prescription vial stickers.

a) Physicians

The company proposed to distribute revised labeling, a Management of Overdosage booklet, Darvon patient information sheets, prescription vial stickers, and business reply cards to the 125,000 physicians identified by Lilly as significant prescribers of propoxyphene products. By December 1, 1979, company representatives had personally contacted in excess of 75,000 physicians in this group. The physicians in this group whom the company had not contacted personally in a reasonable period of time were to be provided this information by mail.

In mid-November Lilly mailed the items noted above to the approximately 59,000 physicians who had not been personally contacted.

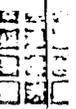
This permitted those physicians who had been identified as key prescribers to have, on a reasonably timely basis, the information then available to other physicians, to pharmacists, and to patients.

In addition, as noted in its report of October 23, Lilly distributed a letter, the brochure with revised physician labeling,

- b. Special planning or effort:
source of lethal drugs.
unusual time and/or place of ingestion.
preparation of wills, notes, warnings.
- c. Drug use-abuse history:
compliance with medical advice.
drug-alcohol abuse, habituation, addiction
previous suicide attempt vs. accidental overdose.
- d. Health factors:
acute and chronic physical illness.
acute and chronic mental illness.
history of depression, confusion, anxiety, hopelessness.
- e. Stress-crisis:
Recent loss or threat of loss (love, health, money, job, etc.)
Recent unusual behavior, perturbation.
- f. Life style:
stable vs. unstable.
conscientious, dependable vs. thrill seeking, irresponsible
no use of alcohol/drugs vs. excessive use of alcohol/drugs
"loner", "implementer" vs "socially involved" "acceptor"

References

- Finkle, B.S. et al-A national assessment of propoxyphene in postmortem medicolegal investigation, 1972-1975. J. Forensic Sc. 21:706-742, 197
- Furman, R.H.-Submission of Eli Lilly and Co. to FDA propoxyphene public hearing, April 6, 1979.
- Nakamura, G.R. et al--Antemortem conversion of codeine to morphine in man. J. Forensic Sc. 21: 518-524, 1976.



Tabulation Design

The data are tabulated in total and by medical specialty within each of the methods employed to submit the warning label.

Data Collection

All interviewing was conducted from the centralized WATS facility of the C/IRS located in suburban Philadelphia.

The interviewing commenced on December 10 and was completed December 20, 1979.

ANALYSIS

The data provided below analyzes the differences, if any, between the methods employed to alert the physicians as well as the differences between medical specialty within each of the campaigns.

Each matrix presents the study's findings in rank order on the left column while the "  " and "  " indicates the difference is significantly higher or lower while the "NS" reveals no significant difference exists.

All statistical testing was performed at the .95 level.

QUESTION 1. DURING THE PAST THREE OR FOUR MONTHS, HAVE YOU BEEN MADE AWARE OF ANY INFORMATION RELATING TO AN ORAL ANALGESIC?

PHYSICIANS MAILED LITERATURE

	<u>PERCENT</u>	<u>IM</u>	<u>GP</u>	<u>ORS</u>	<u>OB/GYN</u>	<u>GENERAL SURGEON</u>
IM	(68.0)	-	NS	NS	NS	NS
GP	(60.0)		-	NS	NS	NS
ORS	(56.0)			-	NS	NS
OB/GYN	(52.0)				-	NS
GENERAL SURGEON	(48.0)					-



PHYSICIANS DETAILED

	<u>PERCENT</u>	<u>ORS</u>	<u>IM</u>	<u>OB/GYN</u>	<u>GP</u>	<u>GENERAL SURGEON</u>
ORS	(76.0)	-	NS	NS	NS	NS
IM	(72.0)		-	NS	NS	NS
OB/GYN	(68.0)			-	NS	NS
GP	(66.0)				-	NS
GENERAL SURGEON	(56.0)					-

<u>SPECIALTY</u>	<u>PHYSICIANS MAILED LITERATURE</u>	<u>PHYSICIANS DETAILED</u>	
TOTAL	57%	67%*	NS
GP	60%	66%	NS
OB/GYN	52%	68%	NS
IM	68%	72%	NS
ORS	56%	76%	NS
GENERAL SURGEON	48%	56%	NS

* Significantly higher when tested at the .90 level



QUESTION 2. FOR WHICH ORAL ANALGESIC WERE YOU GIVEN INFORMATION?

*(Darvon/Darvon Compound/Darvocet)

<u>SPECIALTY</u>	<u>PHYSICIANS MAILED LITERATURE</u>	<u>PHYSICIANS DETAILED</u>	
TOTAL	22%	30%	NS
GP	23%	24%	NS
OB/GYN	8%	47%	NS
IM	35%	33%	NS
ORS	7%	21%	NS
GENERAL SURGEON	33%	29%	NS

QUESTION 2/3. SUMMARY OF DARVON DETAIL AWARENESS. (Unaided plus Aided)

PHYSICIANS MAILED LITERATURE vs. PHYSICIANS DETAILED

TOTAL - 44.7	TOTAL - 48.0	"NS"
GP - 50.0	GP - 52.0	"NS"
OB/GYN - 24.0	OB/GYN - 56.0	"↑"
IM - 68.0	IM - 52.0	"NS"
ORS - 20.0	ORS - 40.0	"NS"
GS - 56.0	GS - 36.0	"NS"

QUESTION 4. HOW DID YOU RECEIVE THIS INFORMATION ABOUT DARVON?

PHYSICIANS MAILED LITERATURE

	<u>PERCENT</u>	<u>MAILINGS</u>	<u>NEWS-PAPER</u>	<u>DETAIL-MAN</u>	<u>TELEVISION</u>	<u>MEDICAL JOURNAL</u>
MAILINGS	(58.2)	-	↑	↑	↑	↑
NEWSPAPER	(25.4)		-	NS	↑	↑
DETAILMAN	(20.9)			-	NS	↑
TELEVISION	(10.4)				-	NS
MED. JOURNAL	(4.5)					-

PHYSICIANS DETAILED

	<u>PERCENT</u>	<u>DETAIL-MAN</u>	<u>MAILINGS</u>	<u>MEDICAL JOURNAL</u>	<u>NEWS-PAPER</u>	<u>TELEVISION</u>
DETAILMAN	(65.3)	-	↑	↑	↑	↑
MAILINGS	(36.1)		-	↑	↑	↑
MED. JOURNAL	(16.7)			-	NS	↑
NEWSPAPER	(6.9)				-	NS
TELEVISION	(1.4)					-

<u>TOTAL</u>			<u>DETAIL-</u>	<u>NEWS-</u>	<u>MEDICAL</u>	<u>TELEVISIO</u>
	<u>PERCENT</u>	<u>MAILINGS</u>	<u>MAN</u>	<u>PAPER</u>	<u>JOURNAL</u>	
MAILINGS	(46.8)	-	NS	↑	↑	↑
DETAILMAN	(43.9)		-	↑	↑	↑
NEWSPAPER	(15.8)			-	NS	↑
MEDICAL JOURNAL	(10.8)				-	NS
TELEVISION	(5.8)					-

QUESTION 5. WHAT DO YOU RECALL ABOUT THE INFORMATION ON DARVON PRODUCTS (Unaided)?

PHYSICIANS MAILED LITERATURE

	<u>PERCENT</u>	<u>CAN'T</u>	<u>1</u>	<u>5</u>	<u>8</u>	<u>6</u>	<u>4</u>	<u>2</u>
		<u>RECALL</u>						
CAN'T RECALL	(50.7)	-	↑	↑	↑	↑	↑	↑
INFO. PT. 1	(11.9)		-	NS	NS	NS	NS	NS
INFO. PT. 5	(11.9)			-	NS	NS	NS	NS
INFO. PT. 8	(9.0)				-	NS	NS	NS
INFO. PT. 6	(7.5)					-	NS	NS
INFO. PT. 4	(7.5)						-	NS
INFO. PT. 2	(6.0)							-

PHYSICIANS DETAILED

	<u>PERCENT</u>	<u>CAN'T RECALL</u>	<u>1</u>	<u>2</u>	<u>8</u>	<u>6</u>	<u>9</u>	<u>5</u>	<u>4</u>	<u>7</u>
RECALL	(38.9)	-	↑	↑	↑	↑	↑	↑	↑	↑
P. 1	(16.7)		-	NS						
P. 2	(12.5)			-	NS	NS	NS	NS	NS	NS
P. 8	(6.9)				-	NS	NS	NS	NS	NS
P. 6	(6.9)					-	NS	NS	NS	NS
P. 9	(6.9)						-	NS	NS	NS
P. 5	(5.6)							-	NS	NS
P. 4	(5.6)								-	NS
P. 7	(5.6)									-

- FO. PT. 1 - Caution should be used when taken with alcohol
 FO. PT. 2 - Caution should be used when taken with CNS depressants
 FO. PT. 3 - Use caution in emotionally disturbed/depressed patients
 FO. PT. 4 - Safe when used as directed
 FO. PT. 5 - Should be taken as directed
 FO. PT. 6 - May be addicting
 FO. PT. 7 - Pain reliever/effective pain reliever
 FO. PT. 8 - Be aware of over-use of drug
 FO. PT. 9 - Government/FDA consider it dangerous/Want it off
 market

QUESTION 5/6. SUMMARY OF AWARENESS - (Unaided plus Aided)

PHYSICIANS MAILED LITERATURE

	<u>PERCENT</u>	<u>1</u>	<u>2</u>	<u>3</u>
When taken with alcohol	(96.7)	-	NS	NS
When taken with CNS depressant drugs	(94.0)	-	-	NS
For emotionally disturbed/depressed patients	(92.0)	-	-	-

PHYSICIANS DETAILED

	<u>PERCENT</u>	<u>1</u>	<u>2</u>	<u>3</u>
When taken with alcohol	(98.0)	-	NS	NS
When taken with CNS depressant drugs	(93.3)	-	-	NS
For emotionally disturbed/depressed patients	(90.0)	-	-	-

QUESTION 8. FOR WHICH TYPE OF PATIENT DO YOU FEEL PHYSICIANS SHOULD UTILIZE GREATER CAUTION WHEN PRESCRIBING DARVON - (Unaided)

PHYSICIANS MAILED LITERATURE

	<u>PERCENT</u>	<u>2</u>	<u>1</u>	<u>3</u>	<u>4</u>	<u>5</u>	<u>10</u>	<u>6</u>	<u>11</u>
TYPE 2*	(24.7)	-	NS	NS	NS	↑	↑	↑	↑
TYPE 1	(24.7)		-	NS	NS	↑	↑	↑	↑
TYPE 3	(17.3)			-	NS	↑	↑	↑	↑
TYPE 4	(16.7)				-	↑	↑	↑	↑
TYPE 5	(5.3)					-	NS	NS	NS
TYPE 10	(5.3)						-	NS	NS
TYPE 6	(4.0)							-	NS
TYPE 11	(4.0)								-

* See last page for definitions.

PHYSICIANS DETAILED

	<u>PERCENT</u>	<u>2</u>	<u>1</u>	<u>3</u>	<u>4</u>	<u>5</u>	<u>6</u>	<u>7</u>	<u>8</u>
TYPE 2*	(32.0)	-	NS	NS	↑	↑	↑	↑	↑
TYPE 1	(26.7)	-	NS	NS	↑	↑	↑	↑	↑
TYPE 3	(24.0)	-	NS	NS	↑	↑	↑	↑	↑
TYPE 4	(20.0)	-	NS	NS	↑	↑	↑	↑	↑
TYPE 5	(8.0)	-	NS						
TYPE 6	(8.0)	-	NS						
TYPE 7	(6.7)	-	NS						
TYPE 8	(6.7)	-	NS						

* See last page for definitions.

- PATIENT TYPE 1 - Those who may use excessive alcohol
- PATIENT TYPE 2 - Are depressed or emotionally disturbed
- PATIENT TYPE 3 - Are taking other CNS depressant drugs
- PATIENT TYPE 4 - Potential/Suspected drug abusers
- PATIENT TYPE 5 - Every patient type/All patients
- PATIENT TYPE 6 - Patients with chronic pain/Illness
- PATIENT TYPE 7 - Younger age groups
- PATIENT TYPE 8 - Elderly patients/Over 65
- PATIENT TYPE 9 - Patients taking other drugs
- PATIENT TYPE 10 - Those asking for specific drugs by name
- PATIENT TYPE 11 - Those with drug addiction history
- PATIENT TYPE 12 - Would not prescribe Darvon at all
- PATIENT TYPE 13 - Patients with liver damage

QUESTION 1. DURING THE PAST THREE OR FOUR MONTHS, HAVE YOU BEEN MADE AWARE OF ANY INFORMATION RELATING TO AN ORAL ANALGESIC

	PHYSICIANS MAILED LITERATURE							PHYSICIANS DETAILED						TOTAL PHYSICIANS				
	TOTAL	GEN	OB/			GEN	TOTAL	GEN	OB/			GEN	GEN	OB/			GEN	
	PHYS	PRACT	GYN	IM'S	OR'S	SURG	PHYS	PRACT	GYN	IM'S	OR'S	SURG	PRACT	GYN	IM'S	OR'S	SURG	
*****	*****	*****	***	****	****	****	*****	*****	***	****	****	****	*****	***	****	****	****	
TOTAL FLIG PHYSICIANS	300	150	50	25	25	25	150	50	25	25	25	25	100	50	50	50	50	
	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	
YES	187	86	30	13	17	14	101	33	17	18	19	14	63	30	35	33	26	
	62.3	57.3	60.0	52.0	68.0	56.0	67.3	66.0	68.0	72.0	76.0	56.0	63.0	60.0	70.0	66.0	52.0	
NO	88	47	16	11	5	8	41	14	8	6	5	8	30	19	11	13	15	
	29.3	31.3	32.0	44.0	20.0	32.0	27.3	28.0	32.0	24.0	20.0	32.0	30.0	38.0	22.0	26.0	30.0	
CAN'T RECA- LL/REFUSED	25	17	4	1	3	3	8	3		1	1	3	7	1	4	4	9	
	8.3	11.3	8.0	4.0	12.0	12.0	5.3	6.0		4.0	4.0	12.0	7.0	2.0	8.0	8.0	18.0	

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(PHYSICIANS WHO HAVE RECENTLY BEEN MADE AWARE OF INFORMATION REGARDING AN ORAL ANALGESIC - 'YES' IN Q.1)
 QUESTION 2. FOR WHICH ORAL ANALGESIC WERE YOU GIVEN INFORMATION

	PHYSICIANS MAILED LITERATURE							PHYSICIANS DETAILED					TOTAL PHYSICIANS				
	TOTAL PHYS *****	GEN TOTAL *****	OB/ PRACT *****	GYN ***	IM'S ****	OR'S ****	GEN SURG ****	TOTAL *****	GEN PRACT *****	OB/ GYN ***	IM'S ****	OR'S ****	GEN SURG ****	GEN PRACT *****	OB/ GYN ***	IM'S ****	OR'S ****
TOTAL ELIG PHYSICIANS	187 100.0	86 100.0	30 100.0	13 100.0	17 100.0	14 100.0	12 100.0	101 100.0	33 100.0	17 100.0	18 100.0	19 100.0	14 100.0	63 100.0	30 100.0	35 100.0	33 100.0
DARVON (COM) /DARVOCET	49 26.2	19 22.1	7 23.3	1 7.7	6 35.3	1 7.1	4 33.3	30 29.7	8 24.2	8 47.1	6 33.3	4 21.1	4 28.6	15 23.8	9 30.0	12 34.3	5 15.2
CODEINE	32 17.1	14 16.3	6 20.0	2 15.4	2 11.8	2 14.3	2 16.7	18 17.8	6 18.2	1 5.9	5 27.8	4 21.1	2 14.3	12 19.0	3 10.0	7 20.0	6 18.2
MOTRIN	18 9.6	6 7.0	1 3.3	5 38.5				12 11.9	5 15.2	1 5.9	4 22.2	1 5.3	1 7.1	6 9.5	6 20.0	4 11.4	1 3.0
TYLENOL	18 9.6	8 9.3	5 16.7	1 7.7	1 5.9	1 7.1		10 9.9	2 6.1	2 11.8	2 11.1	2 10.5	2 14.3	7 11.1	3 10.0	3 8.6	3 9.1
TALWIN	17 9.1	10 11.6		2 15.4	4 23.5	4 28.6		7 6.9	1 3.0	2 11.8		1 5.3	3 21.4	1 1.6	4 13.3	4 11.4	5 15.2
PERCODAN	14 7.5	7 8.1	1 3.3	1 7.7	2 11.8	1 7.1	2 16.7	7 6.9		1 5.9	3 16.7	1 5.3	2 14.3	1 1.6	2 6.7	5 14.3	2 6.1
EMPIRIN	14 7.5	8 9.3	2 6.7		1 5.9	2 14.3	3 25.0	6 5.9	3 9.1	1 5.9	1 5.6		1 7.1	5 7.9	1 3.3	2 5.7	2 6.1
EMPIRIN W/ CODEINE	13 7.0	5 5.8	1 3.3	1 7.7	2 11.8		1 8.3	8 7.9	1 3.0	1 5.9	2 11.1	2 10.5	2 14.3	2 3.2	2 6.7	4 11.4	2 6.1
PONSTEL	7 3.7	3 3.5	1 3.3	2 15.4				4 4.0		3 17.6			1 7.1	1 1.6	5 16.7		
NAPROSYN	6 3.2	2 2.3		2 15.4				4 4.0		1 5.9	1 5.6	2 10.5		3 10.0	1 2.9	2 6.1	
VICODIN	6 3.2	1 1.2				1 7.1		5 5.0				5 26.3					6 18.2
OTHER	46 24.6	24 27.9	11 36.7	2 15.4	3 17.6	5 35.7	3 25.0	22 21.8	13 39.4		3 16.7	5 26.3	1 7.1	24 38.1	2 6.7	6 17.1	10 30.3
CAN'T RECA- LL/REFUSED	6 3.2	4 4.7	2 6.7		1 5.9	1 7.1		2 2.0	1 3.0	1 5.9				3 4.8	1 3.3	1 2.9	1 3.0

(PHYSICIANS NOT MENTIONING DARVON/DARVOCET IN Q.2, OR 'CAN'T RECALL' INFORMATION REGARDING AN ORAL ANALGESIC IN Q.1) QUESTION 3, HAVE YOU RECEIVED ANY INFORMATION RELATING TO THE ANALGESIC DARVON OR DARVOCET

	PHYSICIANS MAILED LITERATURE							PHYSICIANS DETAILED						TOTAL PHYSICIANS				
	TOTAL PHYS *****	GEN TOTAL *****	OB/ PRACT *****	OB/ GYN ***	IM'S ****	OR'S ****	GEN SURG *****	TOTAL *****	GEN PRACT *****	OB/ GYN ***	IM'S ****	OR'S ****	GEN SURG *****	GEN PRACT *****	OB/ GYN ***	IM'S ****	OR'S ****	GEN SURG *****
TOTAL ELIG PHYSICIANS	163 100.0	84 100.0	27 100.0	13 100.0	14 100.0	16 100.0	14 100.0	79 100.0	28 100.0	9 100.0	13 100.0	16 100.0	13 100.0	55 100.0	22 100.0	27 100.0	32 100.0	27 100.0
YES	90 55.2	48 57.1	18 66.7	5 38.5	11 78.6	4 25.0	10 71.4	42 53.2	18 64.3	6 66.7	7 53.8	6 37.5	5 38.5	36 65.5	11 50.0	18 66.7	10 31.3	15 55.6
NO	60 36.8	30 35.7	8 29.6	6 46.2	2 14.3	11 68.8	3 21.4	30 38.0	6 21.4	3 33.3	4 30.8	9 56.3	8 61.5	14 25.5	9 40.9	6 22.2	20 62.5	11 40.7
CAN'T RECA- LL/REFUSED	13 8.0	6 7.1	1 3.7	2 15.4	1 7.1	1 6.3	1 7.1	7 8.9	4 14.3		2 15.4	1 6.3		5 9.1	2 9.1	3 11.1	2 6.3	1 3.7

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(PHYSICIANS HAVING REC'D INFO RELATING TO DARVON - 'YES' IN Q.1 OR 'DARVON (COMPOUND)'/ 'DARVOCET' MENTIONED IN Q.2)
 QUESTION 4. HOW DID YOU RECEIVE THIS INFORMATION ABOUT DARVON

	PHYSICIANS MAILED LITERATURE							PHYSICIANS DETAILED						TOTAL PHYSICIANS				
	TOTAL PHYS	GEN PRACT	OB/ GYN	IM'S	OR'S	GEN SURG	TOTAL	GEN PRACT	OB/ GYN	IM'S	OR'S	GEN SURG	GEN PRACT	OB/ GYN	IM'S	OR'S	GEN SURG	
	*****	*****	***	****	****	****	*****	*****	***	****	****	****	*****	***	****	****	****	
TOTAL ELIG PHYSICIANS	139 100.0	67 100.0	25 100.0	6 100.0	17 100.0	5 100.0	14 100.0	72 100.0	26 100.0	14 100.0	13 100.0	10 100.0	9 100.0	51 100.0	20 100.0	30 100.0	15 100.0	23 100.0
MAILINGS	65 46.8	39 58.2	13 52.0	1 16.7	11 64.7	3 60.0	11 78.6	26 36.1	12 46.2	5 35.7	4 30.8	2 20.0	3 33.3	25 49.0	6 30.0	15 50.0	5 33.3	14 60.9
DETAILMAN/ REP	61 43.9	14 20.9	8 32.0		2 11.8	1 20.0	3 21.4	47 65.3	15 57.7	10 71.4	7 53.8	8 80.0	7 77.8	23 45.1	10 50.0	9 30.0	9 60.0	10 43.5
NEWSPAPER	22 15.8	17 25.4	10 40.0	3 50.0	3 17.6		1 7.1	5 6.9	3 11.5	1 7.1			1 11.1	13 25.5	4 20.0	3 10.0		2 8.7
MED JOURNAL /MAGAZINES	15 10.8	3 4.5	1 4.0	1 16.7			1 7.1	12 16.7	6 23.1	3 21.4	2 15.4	1 10.0		7 13.7	4 20.0	2 6.7	1 6.7	1 4.3
TELEVISION	8 5.8	7 10.4	4 16.0		2 11.8		1 7.1	1 1.4		1 7.1				4 7.8	1 5.0	2 6.7		1 4.3
OTHER	7 5.0	4 6.0	3 12.0		1 5.9			3 4.2	1 3.8	1 7.1		1 10.0		4 7.8	1 5.0	1 3.3	1 6.7	
CAN'T RECA- LL/REFUSED	11 7.9	7 10.4	2 8.0	1 16.7	2 11.8	1 20.0	1 7.1	4 5.6		2 14.3	1 7.7	1 10.0		2 3.9	3 15.0	3 10.0	2 13.3	1 4.3

(PHYSICIANS HAVING REC'D INFO RELATING TO DARVON)
 QUESTION 5. WHAT DO YOU RECALL ABOUT THE INFORMATION ON DARVON PRODUCTS

--- INFO PT. DEFINITIONS AT BOTTOM OF PAGE ---

	PHYSICIANS MAILED LITERATURE						PHYSICIANS DETAILED						TOTAL PHYSICIANS					
	TOTAL PHYS	GEN PRACT	OB/ GYN	IM'S	OR'S	GEN SURG	TOTAL PHYS	GEN PRACT	OB/ GYN	IM'S	OR'S	GEN SURG	GEN PRACT	OB/ GYN	IM'S	OR'S	GEN SURG	
TOTAL FLIG PHYSICIANS	139	67	25	6	17	5	14	72	26	14	13	10	9	51	20	30	15	23
	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
INFO PT. 1	20	8	5	1		1	1	12	4	4	2	1	1	9	5	2	2	2
	14.4	11.9	20.0	16.7		20.0	7.1	16.7	15.4	28.6	15.4	10.0	11.1	17.6	25.0	6.7	13.3	8.7
INFO PT. 2	13	4	1	2		1		9	2	4		1	2	3	6		2	2
	9.4	6.0	4.0	33.3		20.0		12.5	7.7	28.6		10.0	22.2	5.9	30.0		13.3	8.7
INFO PT. 5	12	8	4	1	3			4	2		1		1	6	1	4		1
	8.6	11.9	16.0	16.7	17.6			5.6	7.7		7.7		11.1	11.8	5.0	13.3		4.3
INFO PT. 8	11	6	3	1		2		5	1	1	1	1	1	4	2	1	1	3
	7.9	9.0	12.0	16.7		14.3		6.9	3.8	7.1	7.7	10.0	11.1	7.0	10.0	3.3	6.7	13.0
INFO PT. 6	10	5	1	1	1	2		5	1	1	3		2	2	4		2	2
	7.2	7.5	4.0	16.7	5.9	14.3		6.9	3.8	7.1	23.1		3.9	10.0	13.3		8.7	
INFO PT. 4	9	5		1	2	2		4		1	1	1	1	2	3	1	1	3
	6.5	7.5		16.7	11.8	14.3		5.6		7.1	7.7	10.0	11.1	10.0	10.0	6.7	13.0	
INFO PT. 7	5	1	1			4		1	1		1	1	1	2		1	1	1
	3.6	1.5	4.0			5.6		3.8			7.7	10.0	11.1	3.9		3.3	6.7	4.3
INFO PT. 9	5					5		3	1	1				3	1	1		
	3.6					6.9		11.5	7.1	7.7				5.9	5.0	3.3		
INFO PT. 3	1					1		1		1						1		
	.7					1.4				7.7						3.3		
OTHER	13	5	2	1	1	1		8	3	2	1	2		5	3	2	3	
	9.4	7.5	8.0	16.7	5.9	20.0		11.1	11.5	14.3	7.7	20.0		9.8	15.0	6.7	20.0	
NOTHING	2					2		1			1			1			1	
	1.4					2.8		3.8			10.0			2.0			6.7	
CAN'T RECA- LL/REFUSED	62	34	10	1	10	4	9	28	14	3	2	5	3	24	4	13	9	12
	44.6	50.7	40.0	16.7	58.3	80.0	64.3	38.9	55.8	21.4	23.1	50.0	33.3	47.1	20.0	43.3	60.0	52.2

1. CAUTION SHLD BE USED WHEN TAKEN W/ALCOHOL
2. CAUTION SHD BE USED WHEN TAKEN W/ CNS DEPRESSANTS
3. USE CAUTION IN EMOTIONALLY DIST/DEPRESSED PATIENTS
4. SAFE WHEN USED AS DIRECTED
5. SHOULD BE TAKEN AS DIRECTED

6. MAY BE ADDICTING
7. PAIN RELIEVER/EFFECTIVE PAIN RELIEVER
8. BE AWARE OF OVER-USE OF DRUG
9. GOV'T/FDA CONSIDER IT DANGEROUS/WANT IT OFF MARKET

(PHYSICIANS NOT MENTIONING (*) IN Q.5, INCLUDING THOSE NOT ANSWERING Q.5)
 QUESTION 6. THINKING OF THE VARIOUS DARVON PRODUCTS, ARE YOU AWARE THAT...

	PHYSICIANS MAILED LITERATURE							PHYSICIANS DETAILED						TOTAL PHYSICIANS				
	TOTAL PHYS	GEN TOTAL	OB/ PRACT	IM'S GYN	OR'S SURG	GEN SURG	TOTAL	GEN PRACT	OB/ GYN	IM'S	OR'S SURG	GEN SURG	GEN PRACT	OB/ GYN	IM'S	OR'S SURG	GEN SURG	
INFO PT. 1	280	142	45	24	25	24	24	138	46	21	23	24	24	91	45	48	48	48
*****	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
YES	272	137	43	24	22	24	24	135	45	21	23	23	23	86	45	45	47	47
	97.1	96.5	95.6	100.0	88.0	100.0	100.0	97.8	97.8	100.0	100.0	95.8	95.8	96.7	100.0	93.8	97.9	97.9
NO	8	5	2		3			3	1			1	1	3		3	1	1
	2.9	3.5	4.4		12.0			2.2	2.2			4.2	4.2	3.3		6.3	2.1	2.1
INFO PT. 2	287	146	49	23	25	24	25	141	48	21	25	24	23	97	44	50	48	48
*****	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
YES	268	137	46	21	22	24	24	131	45	21	23	21	21	91	42	45	45	45
	93.4	93.8	93.9	91.3	88.0	100.0	96.0	92.9	93.8	100.0	92.0	87.5	91.3	93.8	95.5	90.0	93.8	93.8
NO	19	9	3	2	3		1	10	3		2	3	2	6	2	5	3	3
	6.6	6.2	6.1	8.7	12.0		4.0	7.1	6.3		8.0	12.5	8.7	6.2	4.5	10.0	6.3	6.3
INFO PT. 3	299	150	50	25	25	25	25	149	50	25	24	25	25	100	50	49	50	50
*****	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
YES	272	138	47	22	23	24	22	134	45	24	23	20	22	92	46	46	44	44
	91.0	92.0	94.0	88.0	92.0	96.0	88.0	89.9	90.0	96.0	95.8	80.0	88.0	92.0	92.0	93.9	88.0	88.0
NO	27	12	3	3	2	1	3	15	5	1	1	5	3	8	4	3	6	6
	9.0	8.0	6.0	12.0	8.0	4.0	12.0	10.1	10.0	4.0	4.2	20.0	12.0	8.0	8.0	6.1	12.0	12.0

--- SUMMARY --- PHYSICIANS FEELING 'GREATER CAUTION' IS NECESSARY IN PATIENT TYPES 1, 2 AND 3 (O.B./UNAIDED & O.9/AIDED)

	PHYSICIANS MAILED LITERATURE							PHYSICIANS DETAILED						TOTAL PHYSICIANS				
	TOTAL PHYS *****	TOTAL *****	GEN PRACT *****	OB/ GYN ***	IM'S ****	OR'S ****	GEN SURG ****	TOTAL *****	GEN PRACT *****	OB/ GYN ***	IM'S ****	OR'S ****	GEN SURG ****	GEN PRACT *****	OB/ GYN ***	IM'S ****	OR'S ****	GEN SURG ****
TOTAL ELIG PHYSICIANS	300 100.0	150 100.0	50 100.0	25 100.0	25 100.0	25 100.0	25 100.0	150 100.0	50 100.0	25 100.0	25 100.0	25 100.0	25 100.0	100 100.0	50 100.0	50 100.0	50 100.0	50 100.0
* TYPE 1 * **TOTAL**	286 95.3	142 94.7	48 96.0	25 100.0	21 84.0	24 96.0	24 96.0	144 96.0	48 96.0	25 100.0	25 100.0	21 84.0	25 100.0	96 96.0	50 100.0	46 92.0	45 90.0	49 98.0
UNAIDED	77 25.7	37 24.7	14 28.0	5 20.0	5 20.0	5 20.0	8 32.0	40 26.7	10 20.0	6 24.0	9 36.0	7 28.0	8 32.0	24 24.0	11 22.0	14 28.0	12 24.0	16 32.0
AIDED	209 69.7	105 70.0	34 68.0	20 80.0	16 64.0	19 76.0	16 64.0	104 69.3	38 76.0	19 76.0	16 64.0	14 56.0	17 68.0	72 72.0	39 78.0	32 64.0	33 66.0	33 66.0
* TYPE 2 * **TOTAL**	280 93.3	143 95.3	49 98.0	24 96.0	24 96.0	23 92.0	23 92.0	137 91.3	43 90.0	25 100.0	24 96.0	19 76.0	24 96.0	94 94.0	49 98.0	48 96.0	42 84.0	47 94.0
UNAIDED	85 28.3	37 24.7	12 24.0	4 16.0	8 32.0	8 32.0	5 20.0	48 31.0	16 32.0	8 32.0	10 40.0	7 28.0	7 28.0	28 28.0	12 24.0	15 30.0	15 30.0	18 36.0
AIDED	195 68.0	106 70.7	37 74.0	20 80.0	16 64.0	15 60.0	18 72.0	89 60.7	27 54.0	17 68.0	14 56.0	12 48.0	17 68.0	66 66.0	37 74.0	30 60.0	27 54.0	29 58.0
* TYPE 3 * **TOTAL**	285 95.0	143 95.3	49 98.0	25 100.0	21 84.0	24 96.0	24 96.0	142 94.7	46 92.0	25 100.0	25 100.0	22 88.0	24 96.0	95 95.0	50 100.0	46 92.0	46 92.0	48 96.0
UNAIDED	62 20.7	26 17.3	10 20.0	2 8.0	3 12.0	5 20.0	6 24.0	36 24.0	9 18.0	7 28.0	7 28.0	5 20.0	8 32.0	19 19.0	9 18.0	10 20.0	10 20.0	14 28.0
AIDED	195 65.0	106 70.7	37 74.0	20 80.0	16 64.0	15 60.0	18 72.0	89 60.3	29 58.0	17 68.0	14 56.0	12 48.0	17 68.0	66 66.0	37 74.0	30 60.0	27 54.0	29 58.0

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* NOTE * PATIENT TYPES DEFINED IN QUESTION 8

QUESTION 7. DO YOU FEEL IT IS IMPORTANT FOR PHYSICIANS TO SCREEN THE PATIENTS WHO MAY BE OR ARE POTENTIAL DRUG ABUSERS PRIOR TO PRESCRIBING DARVON

	PHYSICIANS MAILED LITERATURE							PHYSICIANS DETAILED						TOTAL PHYSICIANS					
	TOTAL PHYS *****	GEN TOTAL *****	OB/ PRACT ***	GYN ***	IM'S ****	OR'S ****	GEN SURG ****	TOTAL *****	GEN PRACT *****	OB/ GYN ***	IM'S ****	OR'S ****	GEN SURG ****	GEN PRACT *****	OB/ GYN ***	IM'S ****	OR'S ****	GEN SURG ****	
TOTAL FLIG PHYSICIANS	300 100.0	150 100.0	50 100.0	25 100.0	25 100.0	25 100.0	25 100.0	150 100.0	50 100.0	25 100.0	25 100.0	25 100.0	25 100.0	100 100.0	50 100.0	50 100.0	50 100.0	50 100.0	
YES	269 89.7	131 87.3	46 92.0	24 96.0	23 92.0	18 72.0	20 80.0	138 92.0	45 90.0	25 100.0	25 100.0	21 84.0	22 88.0	91 91.0	49 98.0	48 96.0	39 78.0	42 84.0	
NO	20 6.7	13 8.7	2 4.0	1 4.0	2 8.0	5 20.0	3 12.0	7 4.7	3 6.0			1 4.0	3 12.0	5 5.0	1 2.0	2 4.0	6 12.0	6 12.0	
DON'T KNOW /REFUSED	11 3.7	6 4.0	2 4.0					2 8.0	2 8.0			3 12.0		4 4.0				5 10.0	2 4.0

QUESTION 8. FOR WHICH TYPE OF PATIENT DO YOU FEEL PHYSICIANS SHOULD UTILIZE GREATER CAUTION WHEN PRESCRIBING DARVON

--- PATIENT TYPE DEFINITIONS AT BOTTOM OF PAGE ---

	PHYSICIANS MAILED LITERATURE							PHYSICIANS DETAILED						TOTAL PHYSICIANS				
	TOTAL PHYS *****	GEN TOTAL *****	OB/ PRACT ****	OB/ GYN ***	IM'S ****	OR'S ****	GEN SURG ****	TOTAL *****	GEN PRACT *****	OB/ GYN ***	IM'S ****	OR'S ****	GEN SURG ****	GEN PRACT *****	OB/ GYN ***	IM'S ****	OR'S ****	GEN SURG ****
TOTAL ELIG PHYSICIANS	300 100.0	150 100.0	50 100.0	25 100.0	25 100.0	25 100.0	25 100.0	150 100.0	50 100.0	25 100.0	25 100.0	25 100.0	25 100.0	100 100.0	50 100.0	50 100.0	50 100.0	50 100.0
TYPE 2	85 28.3	37 24.7	12 24.0	4 16.0	8 32.0	8 32.0	5 20.0	48 32.0	16 32.0	8 32.0	10 40.0	7 28.0	7 28.0	28 28.0	12 24.0	18 36.0	15 30.0	12 24.0
TYPE 1	77 25.7	37 24.7	14 28.0	5 20.0	5 20.0	5 20.0	8 32.0	40 26.7	10 20.0	6 24.0	9 36.0	7 28.0	8 32.0	24 24.0	11 22.0	14 28.0	12 24.0	16 32.0
TYPE 3	62 20.7	26 17.3	10 20.0	2 8.0	3 12.0	5 20.0	6 24.0	36 24.0	9 18.0	7 28.0	7 28.0	5 20.0	8 32.0	19 19.0	9 18.0	10 20.0	10 20.0	14 28.0
TYPE 4	55 18.3	25 16.7	9 18.0	7 20.0	3 12.0	3 12.0	3 12.0	30 20.0	11 22.0	6 24.0	7 28.0	3 12.0	3 12.0	20 20.0	13 26.0	10 20.0	6 12.0	6 12.0
TYPE 5	20 6.7	8 5.3	1 2.0	2 8.0	1 4.0		4 16.0	12 8.0	3 6.0	4 16.0	1 4.0	2 8.0	2 8.0	4 4.0	6 12.0	2 4.0	2 4.0	6 12.0
TYPE 6	18 6.0	6 4.0	3 6.0	1 4.0	1 4.0	1 4.0		12 8.0	3 6.0	2 8.0	4 16.0	1 4.0	2 8.0	6 6.0	3 6.0	5 10.0	2 4.0	2 4.0
TYPE 7	15 5.0	5 3.3	3 6.0	1 4.0			1 4.0	10 6.7	4 8.0	1 4.0	4 16.0		1 4.0	7 7.0	2 4.0	4 8.0		2 4.0
TYPE 8	13 4.3	3 2.0	2 4.0		1 4.0			10 6.7	8 16.0		1 4.0	1 4.0		10 10.0		2 4.0	1 2.0	
TYPE 10	13 4.3	8 5.3	4 8.0	1 4.0	1 4.0	1 4.0	1 4.0	5 3.3	1 2.0		2 8.0	2 8.0		5 5.0	1 2.0	3 6.0	3 6.0	1 2.0
TYPE 9	9 3.0	5 3.3	1 2.0	1 4.0	1 4.0		2 8.0	4 2.7	2 4.0		1 4.0		1 4.0	3 3.0	1 2.0	2 4.0		3 6.0
TYPE 11	7 2.3	6 4.0	1 2.0	3 12.0	1 4.0	1 4.0		1 .7	1 2.0					2 2.0	3 6.0	1 2.0	1 2.0	
TYPE 13	5 1.7	3 2.0	1 2.0	1 4.0		1 4.0		2 1.3	1 2.0		1 4.0			2 2.0	1 2.0	1 2.0	1 2.0	
TYPE 12	4 1.3	4 2.7	3 6.0			1 4.0								3 3.0			1 2.0	

QUESTION 9. FOR WHICH TYPE OF PATIENT DO YOU FEEL PHYSICIANS SHOULD UTILIZE GREATER CAUTION WHEN PRESCRIBING DARVON

--- PATIENT TYPE DEFINITIONS AT BOTTOM OF PAGE ---

	PHYSICIANS MAILED LITERATURE						PHYSICIANS DETAILED						TOTAL PHYSICIANS					
	TOTAL PHYS *****	GEN TOTAL *****	OB/ PRACT *****	GYN ***	IM'S ****	OR'S ****	GEN SURG ****	TOTAL *****	GEN PRACT *****	OB/ GYN ***	IM'S ****	OR'S ****	GEN SURG ****	GEN PRACT *****	OB/ GYN ***	IM'S ****	OR'S ****	GEN SURG ****
OTHER TYPE	39 13.0	18 12.0	7 14.0	5 20.0	2 8.0	4 16.0	21 14.0	6 12.0	3 12.0	6 24.0	3 12.0	3 12.0	13 13.0	8 16.0	8 16.0	7 14.0	3 6.0	
NONE	1 .3						1 .7					1 4.0					1 2.0	
DON'T KNOW /REFUSED	41 13.7	26 17.3	3 6.0	3 12.0	6 24.0	9 36.0	5 20.0	15 10.0	6 12.0	1 4.0	2 8.0	5 20.0	1 4.0	9 9.0	4 8.0	8 16.0	14 20.0	6 12.0

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|---|--|---------------------------------------|
| 1. THOSE WHO MAY USE EXCESSIVE ALCOHOL | 6. PATIENTS W/ CHRONIC PAIN/ILLNESS | 11. THOSE W/ DRUG ADDICTION HISTORY |
| 2. ARE DEPRESSED OR EMOTIONALLY DISTURBED | 7. YOUNGER AGE GROUPS | 12. WOULD NOT PRESCRIBE DARVON AT ALL |
| 3. ARE TAKING OTHER CNS DEPRESSANT DRUGS | 8. ELDERLY PATIENTS/OVER 65 | 13. PATIENTS WITH LIVER DAMAGE |
| 4. POTENTIAL/SUSPECTED DRUG ABUSERS | 9. PATIENTS TAKING OTHER DRUGS | |
| 5. EVERY PATIENT TYPE/ALL PATIENTS | 10. THOSE ASK'G FOR SPEC DRUGS BY NAME | |

(PHYSICIANS NOT MENTIONING (TYPE) IN Q.8)
 QUESTION 9. DO YOU FEEL GREATER CAUTION SHOULD BE UTILIZED FOR...

	PHYSICIANS MAILED LITERATURE							PHYSICIANS DETAILED					TOTAL PHYSICIANS					
	TOTAL PHYS *****	TOTAL *****	GEN PRACT *****	OB/ GYN ***	IM'S ****	OR'S ****	GEN SURG ****	TOTAL *****	GEN PRACT *****	OB/ GYN ***	IM'S ****	OR'S ****	GEN SURG ****	GEN PRACT *****	OB/ GYN ***	IM'S ****	OR'S ****	GEN SURG ****
TYPE 1 *****	223 100.0	113 100.0	36 100.0	20 100.0	20 100.0	20 100.0	17 100.0	110 100.0	40 100.0	19 100.0	16 100.0	18 100.0	17 100.0	76 100.0	39 100.0	36 100.0	38 100.0	34 100.0
YES	209 93.7	105 92.9	34 94.4	20 100.0	16 80.0	19 95.0	16 94.1	104 94.5	38 95.0	19 100.0	16 100.0	14 77.8	17 100.0	72 94.7	39 100.0	32 88.9	33 86.8	33 97.1
NO	4 1.8	2 1.8			2 10.0			2 1.8	1 2.5			1 5.6	1 1.3		2 5.6	1 2.6		
DON'T KNOW	10 4.5	6 5.3	2 5.6		2 10.0	1 5.0	1 5.9	4 3.6	1 2.5			3 16.7	3 3.9		2 5.6	4 10.5	1 2.9	
TYPE 2 *****	215 100.0	113 100.0	38 100.0	21 100.0	17 100.0	17 100.0	20 100.0	102 100.0	34 100.0	17 100.0	15 100.0	18 100.0	18 100.0	72 100.0	38 100.0	32 100.0	35 100.0	33 100.0
YES	195 90.7	106 93.8	37 97.4	20 95.2	16 94.1	15 88.2	18 90.0	89 87.3	29 85.3	17 100.0	14 93.3	12 66.7	17 94.4	66 91.7	37 97.4	30 93.8	27 77.1	35 92.1
NO	6 2.8	1 .9			1 5.9			5 4.9	3 8.8			1 5.6	1 5.6	3 4.2		1 3.1	1 2.9	1 2.6
DON'T KNOW	14 6.5	6 5.3	1 2.6	1 4.8		2 11.8	2 10.0	8 7.9	2 5.9		1 6.7	5 27.8	3 4.2	1 2.6	1 3.1	7 20.0	2 5.3	
TYPE 3 *****	238 100.0	124 100.0	40 100.0	23 100.0	22 100.0	20 100.0	19 100.0	114 100.0	41 100.0	18 100.0	18 100.0	20 100.0	17 100.0	81 100.0	41 100.0	40 100.0	40 100.0	36 100.0
YES	223 93.7	117 94.4	39 97.5	23 100.0	18 81.8	19 95.0	18 94.7	106 93.0	37 90.2	18 100.0	18 100.0	17 85.0	16 94.1	76 93.8	41 100.0	36 90.0	36 90.0	34 94.4
NO	4 1.7	2 1.6			2 9.1			2 1.8	2 4.9					2 2.5		2 5.0		
DON'T KNOW	11 4.6	5 4.0	1 2.5		2 9.1	1 5.0	1 5.3	6 5.3	2 4.9			3 15.0	1 5.9	3 3.7		2 5.0	4 10.0	2 5.6

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* NOTE * PATIENT TYPES DEFINED IN QUESTION 8

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NDA Quarterly Report--Jan. 1

--- SUMMARY --- PHYSICIANS 'AWARE OF' INFORMATION POINTS 1, 2 AND 3 (Q.5/UNAIDED AND Q.6/AIDED)

	PHYSICIANS MAILED LITERATURE							PHYSICIANS DETAILED						TOTAL PHYSICIANS				
	TOTAL PHYS *****	GEN TOTAL *****	OB/ PRACT ****	OB/ GYN ***	IM'S ****	OR'S ****	GEN SURG ****	TOTAL *****	GEN PRACT *****	OB/ GYN ***	IM'S ****	OR'S ****	GEN SURG ****	GEN PRACT *****	OB/ GYN ***	IM'S ****	OR'S ****	GEN SURG ****
TOTAL ELIG PHYSICIANS	300 100.0	150 100.0	50 100.0	25 100.0	25 100.0	25 100.0	25 100.0	150 100.0	50 100.0	25 100.0	25 100.0	25 100.0	25 100.0	100 100.0	50 100.0	50 100.0	50 100.0	50 100.0
INFO PT 1 ==TOTAL==	292 97.3	145 96.7	48 96.0	25 100.0	22 88.0	25 100.0	25 100.0	147 98.0	49 98.0	25 100.0	25 100.0	24 96.0	24 96.0	97 97.0	50 100.0	47 94.0	49 98.0	49 98.0
UNAIDED	20 6.7	8 5.3	5 10.0	1 4.0		1 4.0	1 4.0	12 8.0	4 8.0	4 16.0	2 8.0	1 4.0	1 4.0	9 9.0	5 10.0	2 4.0	2 4.0	2 4.0
AIDED	272 90.7	137 91.3	43 86.0	24 96.0	22 88.0	24 96.0	24 96.0	135 90.0	45 90.0	21 84.0	23 92.0	23 92.0	23 92.0	88 88.0	45 90.0	45 90.0	47 94.0	47 94.0
INFO PT 2 ==TOTAL==	281 93.7	141 94.0	47 94.0	23 92.0	22 88.0	25 100.0	24 96.0	140 93.3	47 94.0	25 100.0	23 92.0	22 88.0	23 92.0	94 94.0	48 96.0	45 90.0	47 94.0	47 94.0
UNAIDED	13 4.3	4 2.7	1 2.0	2 8.0		1 4.0		9 6.0	2 4.0	4 16.0		1 4.0	2 8.0	3 3.0	6 12.0		2 4.0	2 4.0
AIDED	268 89.3	137 91.3	46 92.0	21 84.0	22 88.0	24 96.0	24 96.0	131 87.3	45 90.0	21 84.0	23 92.0	21 84.0	21 84.0	91 91.0	42 84.0	45 90.0	45 90.0	45 90.0
INFO PT 3 ==TOTAL==	273 91.0	138 92.0	47 94.0	22 88.0	23 92.0	24 96.0	22 88.0	135 90.0	45 90.0	24 96.0	24 96.0	20 80.0	22 88.0	92 92.0	46 92.0	47 94.0	44 88.0	44 88.0
UNAIDED	1 .3							1 .7			1 4.0					1 2.0		
AIDED	272 90.7	138 92.0	47 94.0	22 88.0	23 92.0	24 96.0	22 88.0	134 89.3	45 90.0	24 96.0	23 92.0	20 80.0	22 88.0	92 92.0	46 92.0	46 92.0	44 88.0	44 88.0

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* NOTE * INFORMATION POINTS DEFINED IN QUESTION 5

WISCONSIN CRIME LABORATORY REPORTS

<u>Month</u>	<u>Total No. Drugs Analyzed</u>	<u>Madison Lab</u>	<u>New Berlin Lab</u>	<u>Total No. Identified As Containing Propoxyphene</u>	<u>Madison Lab</u>	<u>New Berlin Lab</u>
<u>1979</u>						
January	562	247	315	4	1	3
February	455	133	322	1	0	1
March	561	234	327	2	1	1
April	480	222	258	2	1	1
May	550	208	342	1	1	0
June	530	221	309	2	2	0
July	547	195	352	3	1	2
August	504	125	379	0	0	0
September	480	132	348	1	0	1
October	504	185	319	2	0	2
November	375	177	198	1	1	0
December	257	142	115	1	1	0
Totals	<u>5,805</u>	<u>2,221</u>	<u>3,584</u>	<u>20</u>	<u>9</u>	<u>11</u>

WISCONSIN CRIME LABORATORY REPORTS

Crime Laboratory Bureau, Division of Law Enforcement Services
Department of Justice, State of Wisconsin

Before July, 1975, all data came from the Crime Laboratory—Madison. From July, 1975, on, data were supplied by both the Crime Laboratory—Madison and the Crime Laboratory—New Berlin.

<u>Month</u>	<u>Total No. Drugs Analyzed</u>	<u>Madison Lab</u>	<u>New Berlin Lab</u>	<u>Total No. Identified as Containing Propoxyphene</u>	<u>Madison Lab</u>	<u>New Berlin Lab</u>
<u>1975</u>						
April	344			0		
May	305			0		
June	276			1		
July	636	395	241	0	0	0
August	800	267	533	2	1	1
September	631	245	386	2	1	1
October	642	257	385	2	0	2
November	699	342	357	1	0	1
December	519	178	341	4	2	2
Totals	4,852	1,684	2,243	12	4	7
<u>1976</u>						
January	547	172	375	2	1	1
February	815	245	570	5	1	4
March	575	167	408	1	0	1
April	459	197	262	3	1	2
May	475	173	302	1	0	1
June	613	264	349	0	0	0
July	665	138	527	1	0	1
August	661	283	378	7	4	3
September	523	161	362	0	0	0
October	744	178	566	3	0	3
November	752	158	594	4	0	4
December	626	174	462	4	1	3
Totals	7,465	2,310	5,155	31	8	23
<u>1977</u>						
January	664	271	393	2	0	2
February	683	211	472	2	0	2
March	787	220	567	3	0	3
April	613	129	484	3	0	3
May	675	217	458	7	1	6
June	510	175	335	2	0	2
July	667	236	431	2	0	2
August	1,027	260	767	6	2	4
September	766	326	440	4	0	4
October	666	292	574	4	1	3
November	722	208	514	9	2	7
December	667	320	347	6	1	5
Totals	8,647	2,865	5,782	50	7	43
<u>1978</u>						
January	1,019	364	655	0	0	0
February	665	263	402	3	0	3
March	779	313	466	4	0	4
April	646	234	412	3	0	3
May	729	309	420	1	0	1
June	580	230	350	3	0	3
July	604	233	371	0	0	0
August	752	298	454	6	4	2
September	549	225	324	3	0	3
October	741	300	441	2	1	1
November	474	198	276	4	0	4
December	438	203	235	1	1	0
Totals	7,976	3,170	4,806	30	6	24

7. Doctor, do you feel it is important for physicians to screen the patients who may be or are potential drug abusers prior to prescribing DARVON products?

- Yes
 (21) No
 Don't Know

8. For which type of patient do you feel physicians should utilize greater caution when prescribing DARVON? DO NOT READ LIST

FOR EACH PRELISTED TYPE NOT MENTIONED, ASK

9. Do you feel greater caution should be utilized for . . . READ LIST

PATIENT TYPE	Q.8 <u>UNAIDED</u>	Q.9 <u>AIDED</u>		DON'T <u>KNOW</u>
		<u>YES</u>	<u>NO</u>	
Those who may use excessive alcohol	1 (22)	(24) 1	2	3
Those who are either depressed or emotionally disturbed	2	(25) 1	2	3
Those taking other CNS (central nervous system) depressant drugs (see list)	3	(26) 1	2	3
OTHER: _____	0			

(specify)				

Don't Know
 (23) _____

THANK YOU VER MUCH, DOCTOR. WE APPRECIATE YOUR TIME AND COOPERATION

5. Can you tell me what you recall about the information on DARVON products?

DO NOT READ LIST

FOR EACH OF THE FIRST THREE PRELISTED STATEMENTS NOT MENTIONED, ASK:

6. Thinking of the various DARVON products, are you aware that . . .

READ LIST

INFORMATION POINTS	<u>Q.5</u> <u>UNAIDED</u>	<u>Q.6</u> <u>AIDED</u>	<u>YES</u>	<u>NO</u>
Caution should be used when taken with alcohol	<input type="checkbox"/>	(18)	<input type="checkbox"/>	<input type="checkbox"/>
Caution should be used when taken with CNS depressant drugs (central nervous system - see list)	<input type="checkbox"/>	(19)	<input type="checkbox"/>	<input type="checkbox"/>
Caution should be used in emotionally disturbed or depressed patients	<input type="checkbox"/>	(20)	<input type="checkbox"/>	<input type="checkbox"/>
Safe when used as directed	<input type="checkbox"/>			
Should be taken as directed	<input type="checkbox"/>			
OTHER: _____ _____ _____	<input type="checkbox"/>			
(specify)				
Can't Recall	(17)	_____	<input type="checkbox"/>	

2. Can you tell me for which analgesic you were given information?

1 Darvon, Darvon Compound, Darvocet . . . SKIP TO Q.4

(13) C Other: _____

(specify)

& Can't Recall

3. Have you received any information relating to the analgesic, DARVON or DARVO CET?

1 Yes

(14)

2 No

SKIP TO Q.6

& Can't Recall

4. How did you receive this information about DARVON?

DO NOT READ LIST

1 Detailman/rep

2 Mailings

(15)

3 Newspaper

4 Television

C Other: _____

(specify)

& Can't Recall

STUDY # (4-6) 8 2

STATE (7-8) _____

SAMPLE TYPE (9) _____

SPECIALTY (10) _____

(11) B L A N

DARVON AWARENESS STUDY

Good morning/afternoon, Dr. _____. This is Mrs. Stewart calling long distance from Philadelphia for the Professional Services Department of the Consumer/Industrial Research Service.

Doctor, we are conducting a national study among physicians like yourself regarding ORAL analgesics, and I would like to ask you just a couple of brief questions if I may.

Doctor, before we begin, I would like to mention that this data will remain anonymous.

1. During the past three or four months, have you been made aware of any information relating to an ORAL analgesic?

Yes

(12)

No . . . SKIP TO Q.6

Can't Recall . . . SKIP TO Q.3

A copy of the interviewing document can be found in the Appendix.

Sample Design

A total of 300 interviews was requested to be distributed among five medical specialties as follows:

	<u>QUOTA</u>
General Practitioners	50
Obstetricians/Gynecologists	25
Internists	25
Orthopedic Surgeons	25
General Surgeons	25

The quota samples were equally distributed among those physicians alerted by the mail and detail campaigns.

The physician listings were provided by Eli Lilly and Company.

INTRODUCTION

Study Objective

The primary objective of this research investigation was to evaluate the level of awareness of a recent DARVON caution issued by Eli Lilly and Company.

The caution indications were submitted to physicians via a mail campaign in August, 1979 or by a visit from the company detailperson during September, 1979.

The key messages outlined for analysis were:

- ... Caution should be used when taken with alcohol.
- Caution should be used when taken with CNS depressant drugs.
- ... Caution should be used in emotionally disturbed or depressed patients.

CNS DEPRESSANT DRUGS (4 major categories)

1. MINOR TRANQUILIZERS:

Valium
Librium
Meprobamate
Equanil

Serax
Azene
Tranxene

2. MAJOR TRANQUILIZERS:

Thorazine
Compazine
Mellaril
Vistaril

Quaalude
Sinequan
Atarax
Dalmane

3. SLEEPING PILLS:

Seconal
Tuinal
Phenobarbital
Placidyl

Nembutal
Chloral Hydrate
Noctec

4. ANALGESICS:

Talwin
Percodan
Morphine
Codeine (codeine products)

FDA Comments on Eli-Lilly Report

I. Summary

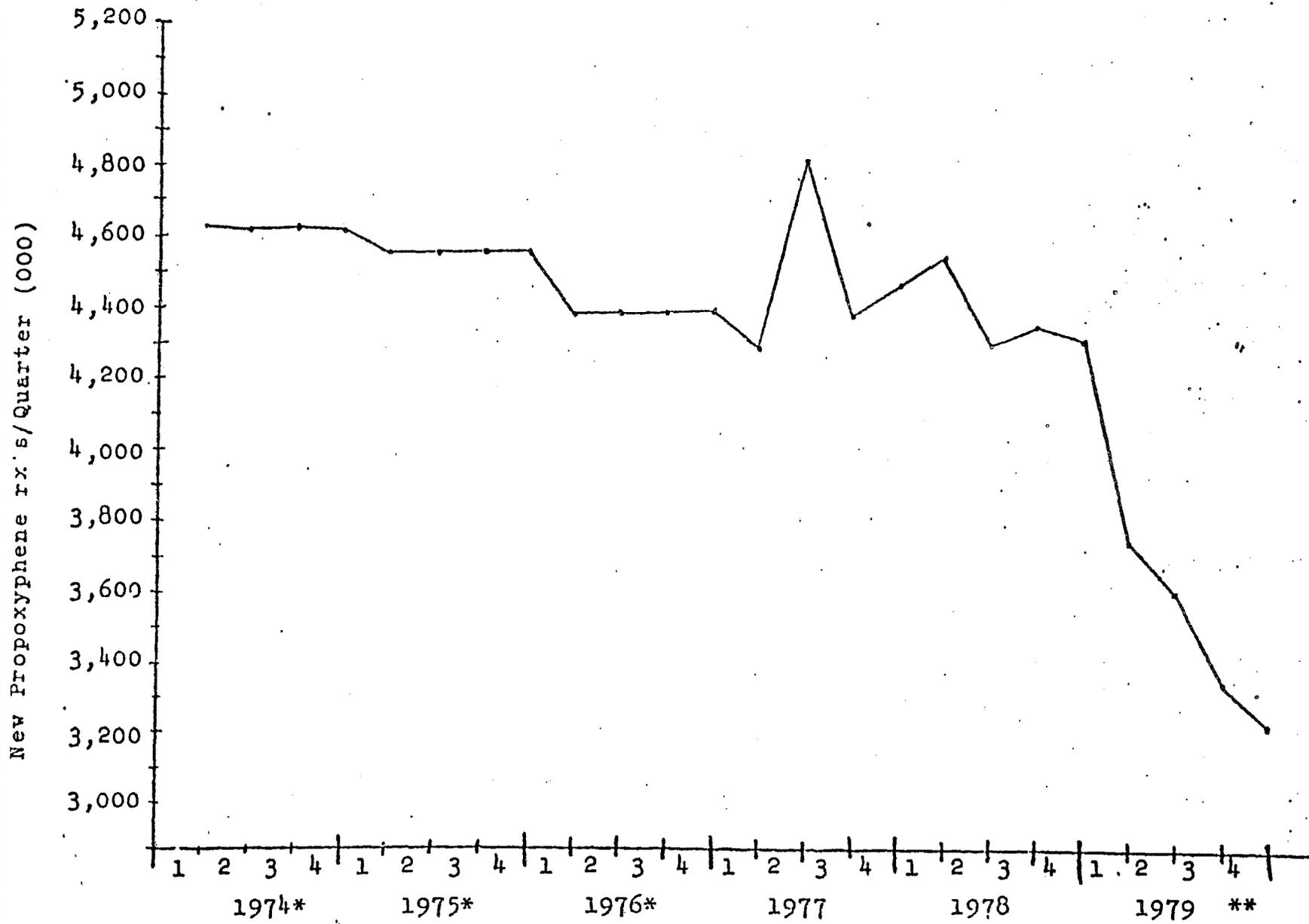
As agreed in previous conversations with Eli Lilly, the firm provided a report of its progress on its educational programs as well as its surveys of physician and patient attitudes and surveys of outcomes including abuse and death. A copy of this report is attached.

Several members of the FDA staff representing several disciplines reviewed the Eli Lilly report in detail. Previous discussions in October of 1979 established the date of January 20 as the date for receipt of a number of efforts by Lilly. It was the consensus of the FDA reviewers' of this report that Lilly had failed to meet its proposed program in several respects. Some of these problem areas include the following:

1. Studies of Prescription Data, DAWN Data and Prescription Data Services and Drug Utilization Data. The Drug Use Analysis Branch in the Division of Drug Experience reviewed the data carefully. In general, there were several discrepancies between information provided in the Lilly Report and information summarized in the early part of this Quarterly Report (Appendix II).
2. Eli Lilly had promised in early conversations a general summary of deaths reported in 18 coroner's offices throughout the country. This survey as indicated was not completed by the time of the report.
3. The remaining materials provided including reports from the Wisconsin Crime Laboratory Reports, the proposed study by Dr. Dorsey and the proposed material from Dr. Lietman were of interest but did not allow for adequate evaluation of the overall magnitude of the problem. It is possible that in future reports these data may be helpful.
4. Although Lilly indicated that the audiovisual film prepared was available in 57 Lilly offices, no information was provided as to how these films were being used so the meaning of this particular item in the report was unknown.

The substance of these comments are also being communicated to Eli Lilly.

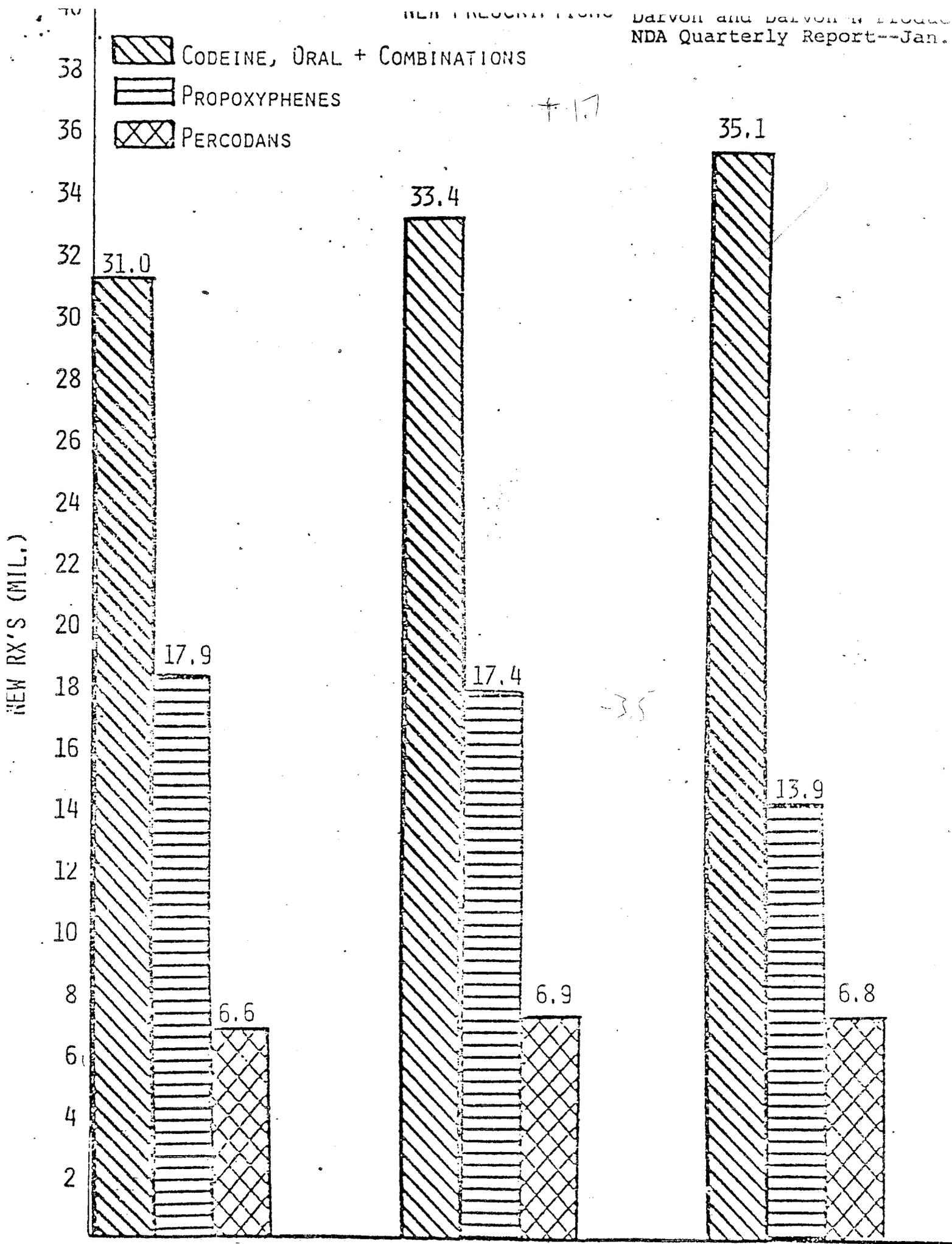
New Rx's - Propoxyphene



*Quarterly data for 1974, 1975 and 1976 not available
 **Preliminary data (1979, 4th quarter)

Source: National Prescription Audit (NPA)

DARVON-N Products
 NDA Quarterly Report--Jan. 1



Lilly Propoxyphene Products, August 1 - December 31, 1979

	NPA-Assuming Prescriptions Dispensed as Written	Lilly Estimates-Adjusted Prescriptions Dispensed
New Rx's (million)	4.8	4.1
Refill Rx's (million)	3.7	2.9
Monthly New Rx's	960,000	820,000
Monthly Refill Rx's	740,000	580,000
Total Monthly Rx's	1,700,000	1,400,000
Patient Info. Sheet Supply if given with All Lilly Rx's	8.14 months	9.89 months
Patient Info. Sheet Supply if given with New Lilly Rx's Only	14.42 months	16.88 months

The manufacturer used new prescriptions, rather than total prescriptions throughout their report. . . . When comparing DPX with codeine or oxycodone (both Schedule II drugs), total DPX prescriptions should be used, since new Rx's for codeine and oxycodone represent total Rx's dispensed. More significantly, DAWN data, which is one measure of misuse or abuse, should be compared to total exposure, ie, total Rx's or total kilograms.

4) Patient-Profile Study

Lilly has purchased data from Prescription Data Services for the study of propoxyphene. These data would be most useful if compared with the study done previously by FDA. However, because of the time frame selected, by Lilly, the two studies will not be comparable. Furthermore, new users in 1979, will be excluded because selection for Lilly's study will be based on 1978 users only, even though their profiles extend through June 1979.

inflated estimate of the months supply of patient information sheets. See Table 18. Although it is desirable for all producers to supply patient information sheets, Lilly propoxyphene products accounted for 88% of the unadjusted new prescription market for the year 1979. Thus, these products probably play the predominant role in the public health problem which results from the misuse of propoxyphene.

3) Propoxyphene Prescription Volume

Although new prescriptions are the first values to reflect changes in prescribing behavior, total prescriptions or total kilograms provide a better estimate of the extent of drug prescribing. In the case of propoxyphene (DPX) both prescriptions and kilograms dispensed have decreased markedly over the past year. As noted on Tables 1 & 2, comparison of 4th quarter 79 with 4th quarter 78 indicated a 25% decrease in new DPX prescriptions but only a 20% decrease in refill DPX prescriptions. Since total kilograms also reflect prescription size and product strength, kilogram estimates are perhaps the best estimate of exposure. Total DPX kilograms decreased 21% for the same time period.

Comments on Lilly's Second Quarterly Darvon Report

Submitted to FDA January 24, 1980

Several concerns, with respect to this report, have been raised by members of the Drug Use Analysis Branch of the Division of Drug Experience. These include use of imprecise terminology, adjustment factors which lack clear definition and the consistent use of new rather than total prescription estimates. In addition, we are concerned with the design of the proposed PDS study.

1) Terminology

We have assumed that "Darvon and Darvon-N products" includes all strengths of the following products: Darvon, Darvon w/ASA, Darvon Compound, Darvon N, Darvocet N, Darvon N w/ASA, Propoxyphene N, Propoxyphene N w/ASA and Propoxyphene (Comp) - Lilly. This definition of products is a prerequisite for data comparison.

2) Adjustment Factors

According to our calculations, based on NPA data, 4.8 million new prescriptions were dispensed for prescriptions written for Lilly propoxyphene products during the period August 1979 - December 1979. In the same time period 3.7 million prescriptions originally written for Lilly propoxyphene products were refilled. The manufacturer has adjusted these estimates for prescription losses due to substitution and MAC effects, with resultant estimates of 4.1 and 2.9 million for new and refill prescriptions filled with Lilly products respectively. The factors used for these adjustments were not included in the Lilly report. The adjustments result in a substantially lower monthly prescription volume for Lilly products, with a resultant

LILLY RESEARCH LABORATORIES

DIVISION OF ELI LILLY AND COMPANY • INDIANAPOLIS, INDIANA 46206 • TELEPHONE (317) 231-2000

January 24, 1980

Judith K. Jones, M.D., Ph.D., Director
Division of Drug Experience (HFD-210)
Office of Biometrics and Epidemiology
Bureau of Drugs
Department of Health, Education,
and Welfare
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Re: Report to NDA Nos. 10-996, 10-997, 16-827, 16-829,
16-844, 16-861, 16-862, 16-863, 16-864, 17-122,
17-507

Dear Dr. Jones:

In October of 1979 you requested information on a quarterly basis on the status of various programs for the dissemination of information on Darvon and Darvon-N products. We submit herewith Lilly's second quarterly report on these items. This report will supplement in part the company's report of October 23, 1979.

1) Preparation and Dissemination of Revised Information Regarding Darvon and Darvon-N Products

As noted in the company's October 23 report, following consultation with FDA, Lilly initiated a program on August 1, 1979, to provide physicians, pharmacists, and patients with additional information on Darvon products. This program included the following elements:



13. Harell, M., Shea, J.J., Emmett, J.R. Total deafness with chronic propoxyphene abuse. Laryngoscope. 1978; 88 (Sep.); 1518-21.

14. Schuckit, M.D., Morrissey, E.R. Propoxyphene and phencyclidine (PCP) use in adolescents. J Clin Psychiatr. 1978; 39 (Jan.):7-13.

Use of these is more likely to occur in people with more antisocial, drug, and alcohol problems.

DEATHS RELATIVE TO PRESCRIPTION (Rx) USE

January - March 1979

Comparison of Propoxyphene with Other Drugs (DAWN, NPA)

<u>Drug Group</u>	<u>Total Rx's*</u> (in millions)	All Reported Deaths** (Coroner Mentions)	<u>Deaths</u> <u>Million</u> <u>Rx's</u>	<u>Group</u> <u>Rank</u>
I. Barbiturates (excluding phenobarbital)	1.5	221	147	1
II. Other Sedative/Hypnotics flurazepam methaqualone glutethimide ethchlorvynol	4.4	115	26	2
III. Benzodiazepines (excluding flurazepam)	15.9	117	7	6
IV. Major tranquilizers Chlorpromazine Thioridazine Amitriptyline/Perphenazine	3.9	36	9	4
V. Analgesics Pentazocine Codeine	0.9 13.0	7 81	8 6	5 7
VI. Propoxyphene	6.6	112	17	3

*Data from National Prescription Audit, IMS America

**Data from Drug Abuse Warning Network, NIDA, unpublished data.

Table 17
MEDLINE JOURNAL SEARCH

The following propoxyphene citations were found for the period January 1978 through February 1980 which relate to abuse, death, and toxicity: (This search only included human studies in the English language.)

1. Vorhees, C.V., Brunner, R.L., Butcher, R.E., Psychotropic Drugs as Behavioral Teratogens. Science. 1979; 205 (Sep): 1220-5.

Propoxyphene had no apparent effects on reproduction or growth, but produced a variety of behavioral changes.

- ✓ 2. Jasinski, D.R. Human pharmacology of narcotic antagonists. Br J Clin Pharmacol. 1979; 7 Suppl 3: 287~~8~~-290~~8~~.
5 5

Six narcotic antagonists developed in recent years appear to have a lesser abuse potential than codeine or propoxyphene. Pentazocine appears to be abused less than codeine or propoxyphene in the U.S.

3. Acute poisoning with Distalgesic (letter). Br Med J. 1979; 1 (Feb. 3): 342-3.
4. Farrell, J, Brown A.W., Sturrock, R.D.. The use and abuse of Distalgesic (letter). Br Med J. 1979; 1 (May 12): 1284.
5. Gumpel, J.M., Acute poisoning with Distalgesic (letter). Br Med J. 1979; 1 (Feb. 24): 551.
6. Hails F.G., Whittington, R.M., Distalgesic and paracetamol poisoning (letter). Br Med J, 1978; 2 (Dec 2): 1569-70.
7. Starkey, I.R., Lawson, A.A. Acute poisoning with Distalgesic. Br Med J. 1978; 2 (Nov. 25): 1468.
8. Gennery, B., Lucas, R., Distalgesic and paracetamol poisoning (letter) Br Med J. 1978; 2 (Oct. 28): 1226.
9. Maruta, T., Swanson, D.W., Finlayson, R.E., Drug abuse and dependency in patients with chronic pain. Mayo Clin Proc. 1979; 54 (Apr.):241-4.

144 patients with chronic pain of nonmalignant cause. Codeine and oxycodone were most frequently abused.

10. Jain, N.C., Budd, R.D., Sneath, T.C., et al. A survey of drug use among probationers in the Los Angeles area in 1976. Int J Addict. 1978; 13 (Nov.):1319-25.

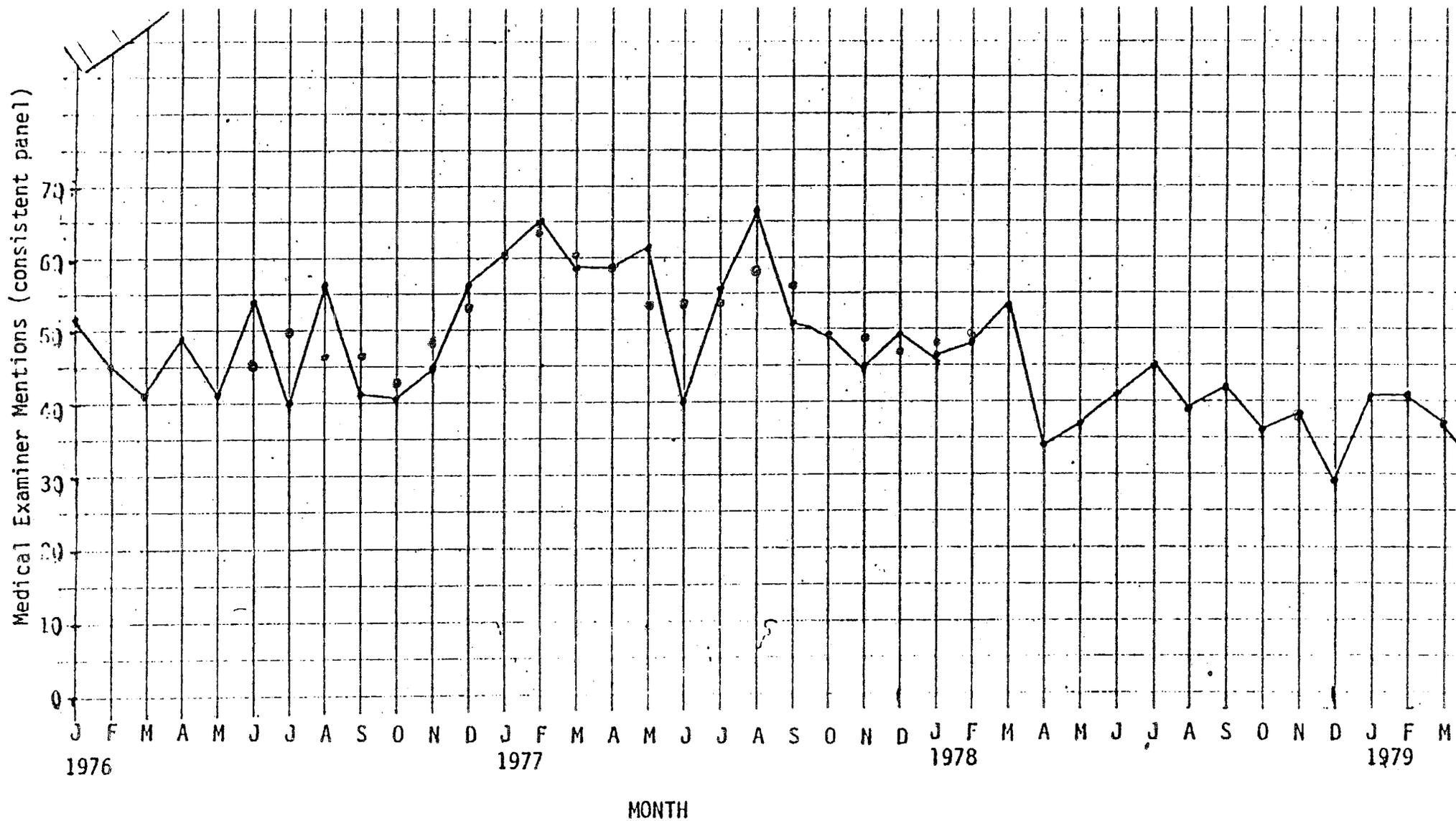
11. Ente, G., Mehra, M.C., Neonatal withdrawal from propoxyphene hydrochloride. NY State J Med. 1978; 13(Nov.): 2084-5.

12. Fraser, H.F., Kay, D.C., Yeh, S.Y., et al. Possible effects of nonmetabolites on the subjective and reinforcing characteristics of opioids in animals and man. Drug Alcohol Depend. 1978; 3(Sep): 301-18.

The summation of all DPX-related deaths as reported to DAWN is displayed in Figure 7 and the data for both Figures 6 and 7 are tabulated in Table 15. A continued trendline through 1979 is necessary before a final conclusion can be reached as to the effect of the 1979 proceedings. However, there was a 50% decrease in DPX-related deaths as reported to DAWN between the second quarter of 1977 and the second quarter of 1979 with 30% of this decrease between the second quarters of 1978 and 1979.

Figure 7

PROPOXYPHENE DEATHS
DAWN-Consistently Reporting
Medical Examiners
1976-1979 Monthly



DAWN DEATHS AS A PROPORTION OF USE

Deaths relative to prescription use for the first quarter of 1979 are listed in Table 16. A comparison is made of DPX with other drugs that are major causes of death per DAWN. This table updates the similar table which appeared in previous DPX surveillance reports. The rankings have remained the same. Barbiturates still rank first. The sedative/hypnotics, as a group, are next, and DPX falls third. The other analgesics, pentazocine and codeine fall below DPX in this ranking by the ratio of deaths per million Rx's dispensed.

V. REVIEW OF LITERATURE

A medline journal search was done for DPX literature published between January 1978 and February 1980 in the English language. The articles pertaining to abuse, dependence, and cardiotoxicity are listed in Table 17.

Table 15
PROPOXYPHENE

DAWN - Consistent Reporting Medical Examiners
January 1976 - June 1979 - Monthly

	1976			1977			1978			1979		
	Suicide	Other	Total									
January	16	36	52	30	31	61	16	31	47	17	24	41
February	19	26	45	35	30	65	20	28	48	17	24	41
March	13	29	42	27	31	58	25	28	53	14	23	37
April	17	31	48	24	34	58	16	18	34	15	15	30
May	16	26	42	27	35	62	22	15	37	15	8	23
June	28	26	54	16	24	40	27	14	41	12	13	25
July	16	24	40	28	28	56	20	25	45			
August	26	30	56	29	38	67	21	18	39			
September	23	19	42	24	27	51	15	27	42			
October	17	24	41	26	23	49	15	21	36			
November	21	24	45	24	21	45	16	22	38			
December	19	38	57	23	26	49	9	20	29			

Handwritten notes and calculations:

- 2/16/77
- 15
- 13
- 3/14/77
- 2/16/77
- 15
- 13
- 126
- 58
- 184

Table 14

Propoxyphene Products
Overdose Reports
Received at FDA During 1979

<u>OD/Fatal</u>	<u>Propoxyphene Product Only</u>	<u>With Alcohol</u>	<u>With Other Drugs Only</u>	<u>With Other Drugs and Alcohol</u>
Napsylate	-	-	1	1
HCl Combination	-	-	1(1)	-
Napsylate Combination	1(1) ^a	-	-	-
HCl Single Entity	5(1)	3(1)	5	2
 <u>OD/Recovered</u>				
Napsylate Single Entity	-	1	-	-
HCl Single Entity	1(1) ^b	-	-	-
HCl Combination	1	-	-	-

() indicates the subset of total cases that involved a suicide attempt or success

a - second propoxyphene product used (DPX and acetaminophen)

b - severe sequelae

FIGURE 6
PROPOXYPHENE DEATHS
DRUG ABUSE WARNING NETWORK
CONSISTENTLY REPORTING MEDICAL EXAMINERS
1976-1979-MONTHLY

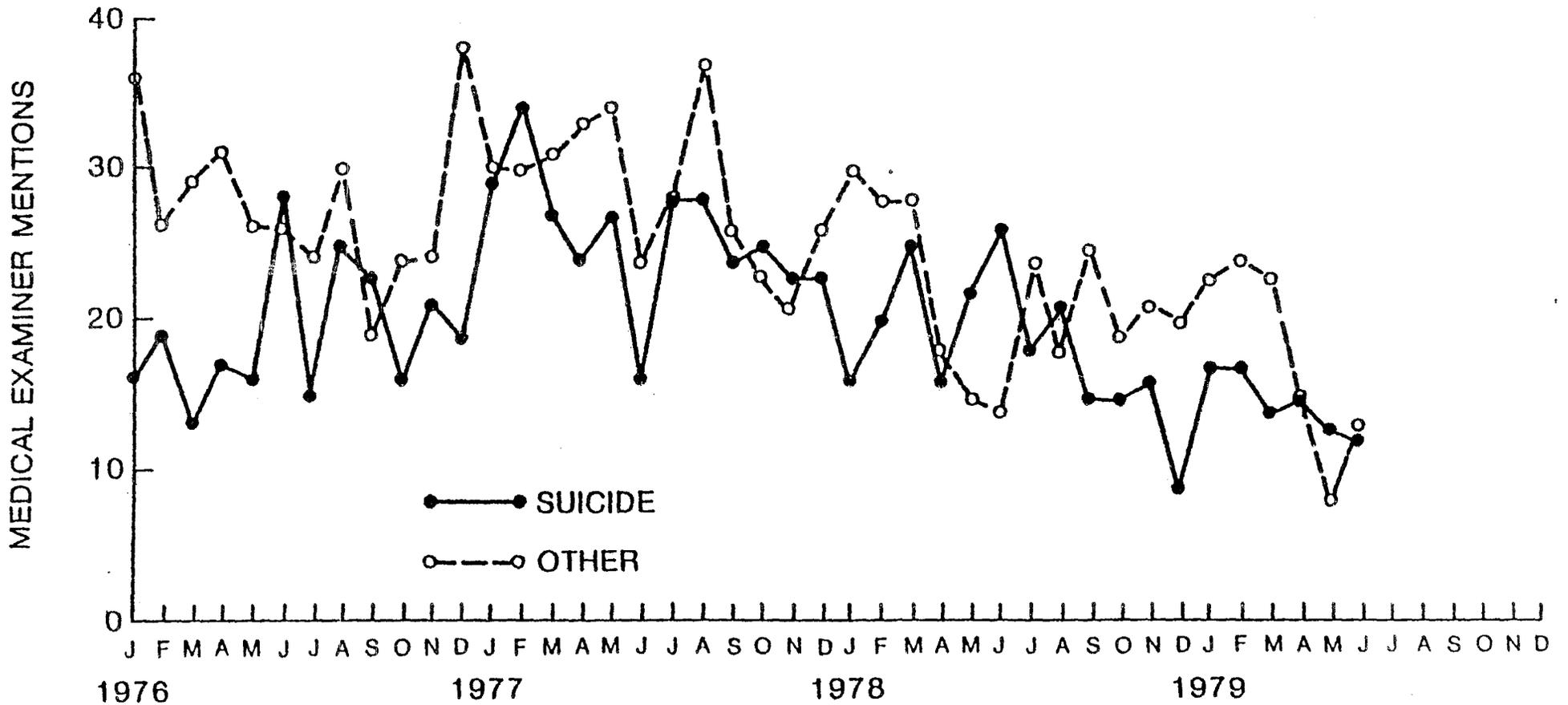


Table 13

PROPOXYPHENE

DAWN-ER's Consistent Panel

	<u>1976</u>	<u>1977</u>	<u>1978</u>	<u>1979</u>
January	328	300	281	330
February	276 (912)	298 968	276 870	251 846 (9)
March	308	370	323	265
April	306	312	311	236
May	348 (972)	338 975	261 821	241 674 (5)
June	318	325	249	197
July	347	297	272 861 (2)	212 658 (675)
August	364 (1024)	321 906	287	221
September	313	288	302	225
October	339	301	265	209
November	368 1035	309 909	267 790	217 595 618
December	328	299	258	169 313/80

524
 3700 / 1211
 111
 90
 74
 160
 185

225
 3941 / 11240
 1882
 33580
 31528
 20520

IV. FATAL MEDICAL PROBLEMS

Deaths Reported to FDA

There were three reports of non-fatal DPX overdoses and 19 cases of fatal overdoses reported to the FDA in 1979. (Table 14). Only 5 of these specifically indicated a suicide attempt but some other cases were poorly documented. Eight of the 22 cases involved DPX alone; the remainder were associated with other drugs and/or alcohol.

Deaths Recorded by DAWN Medical Examiners

Deaths as reported by consistently reporting medical examiners to the DAWN data base are depicted in Figure 6 for all DPX products. These data are displayed monthly from January 1976 through June 1979, the last month for which complete data are available. Deaths which were specifically reported as suicide are graphed separately from other deaths. At first glance, it appears that there has been a precipitous drop in non-suicide deaths associated with DPX from March to May 1979. However, a similar decline occurred in 1978 during the same months. Therefore, this trend may be indicative of seasonal variation rather than a reaction to DPX publicity and warnings. Deaths associated with DPX (both suicidal and non-suicidal) seem to have decreased since 1977. The deaths are approximately equally distributed between suicide and non-suicide.

It is important to emphasize that the designation of suicide may vary between reportors and the diagnosis of suicide is often difficult to make in obscure cases. Accordingly these may represent underestimates of actual proportion of suicides.

Fig 6

FIGURE 5
PROPOXYPHENE
DRUG ABUSE WARNING NETWORK CONSISTENTLY
REPORTING EMERGENCY ROOMS
MONTHLY 1976 thru 1979

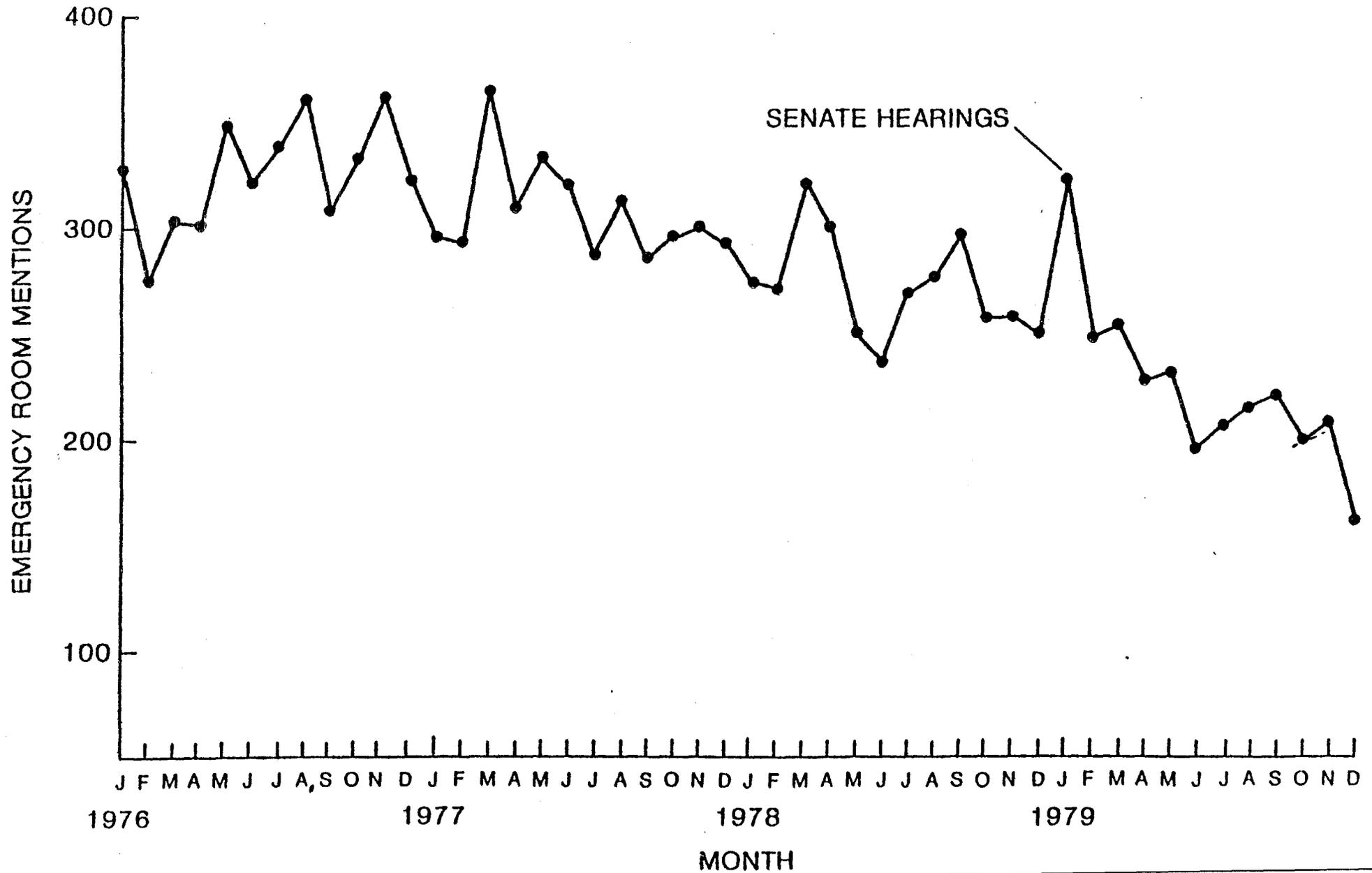


Table 12

Propoxyphene Products

Reports of Addiction and Dependence
Received at FDA During 1979

<u>Addict/Dependence</u>	<u>propoxyphene product only</u>	<u>with alcohol</u>	<u>with other drugs only</u>	<u>with other drugs and alcohol.</u>
Napsylate Single Entity	4(1)	-	1	-
HCl Combination	6 ^a	1	-	-
HCl Single Entity	11	2	2	-

() indicates the subset of total cases that involved a suicide attempt or success

a - mild neonatal withdrawal (mother - chronic user) for one case

III. ACUTE, NONFATAL MEDICAL PROBLEMS

Drug Abuse or Addiction

There were 27 cases of addiction or dependence reported to the FDA in 1979. Twenty-one of the 27 involved DPX only. There was one case of mild neonatal withdrawal reported where the mother was a chronic user of DPX. These cases are tabulated in Table 12.

The DAWN emergency room (ER) panel estimates trends in drug abuse medical problems severe enough to bring the patient to the ER. Figure 5 displays the monthly trend in consistently reporting ER mentions for DPX from January 1976 through December 1979. A fairly substantial decrease in ER mentions is seen beginning in 1978 and continuing through the end of 1979. It is interesting to note the peak of ER reports which occurred in January 1979, the month of initial DPX publicity and Senate hearings. It cannot be ascertained whether this peak in drug abuse reporting can be attributed to these events, however. There was a 35% decrease in DPX ER mentions between the fourth quarter of 1977 and the fourth quarter of 1979. Twenty-five percent of this decrease has occurred since the fourth quarter of 1978. The monthly data are displayed in Table 13.

Table 11
(R)
Darvocet N

Rank Among Drug Mentions
Percent of Use in Females
Major Diagnoses By Age Group

October 1978 - September 1979

Age Group	Rank	%Female	Major Diagnoses at Time of Mention						
			Surgical Aftercare	Arthritis	Contusions, Fractures, Displaced Disc	Post-Partum	Acute Infection	Dysmenorrhea	Neuroses, Psychoses
10-14	#19	50%	-	-	50%	-	33%	-	-
15-24	14	69	31%	-	-	18%	-	17%	-
25-34	13	73	19	20%	-	13	-	-	23%
35-44	15	61	32	-	35	-	-	-	-
45-54	22	65	21	18	10	-	-	-	-
55-64	22	60	27	14	11	-	-	-	-
65-74	22	70	13	30	-	-	-	-	-
75+	20	71	21	27	-	-	-	-	-

absent doctor Major Dx

Data from National Disease & Therapeutic Index, IMS America

Table 10
PROPOXYPHENE (DPX) MENTIONS

PRIMARY DIAGNOSES

	<u>July 1977- June 1978</u>	<u>October 1978- September 1979</u>
Surgical Aftercare	24%	20%
Bone and Movement Diseases	18	23
Sprains, Strains, Fractures	12	12
Obstetrics, Post-partum	3	6

Data from National Disease and Therapeutic Index, IMS America

Table 9
 PROPOXYPHENE MENTIONS
 AGE AND SEX DEMOGRAPHICS OF USERS

<u>AGE</u>	<u>July 1977- June 1978</u>	<u>October 1978- September 1979</u>
0-19	10%	5%
20-39	31	32
40-59	28	26
60+	31	37
 <u>SEX</u>		
Male		34
Female		66

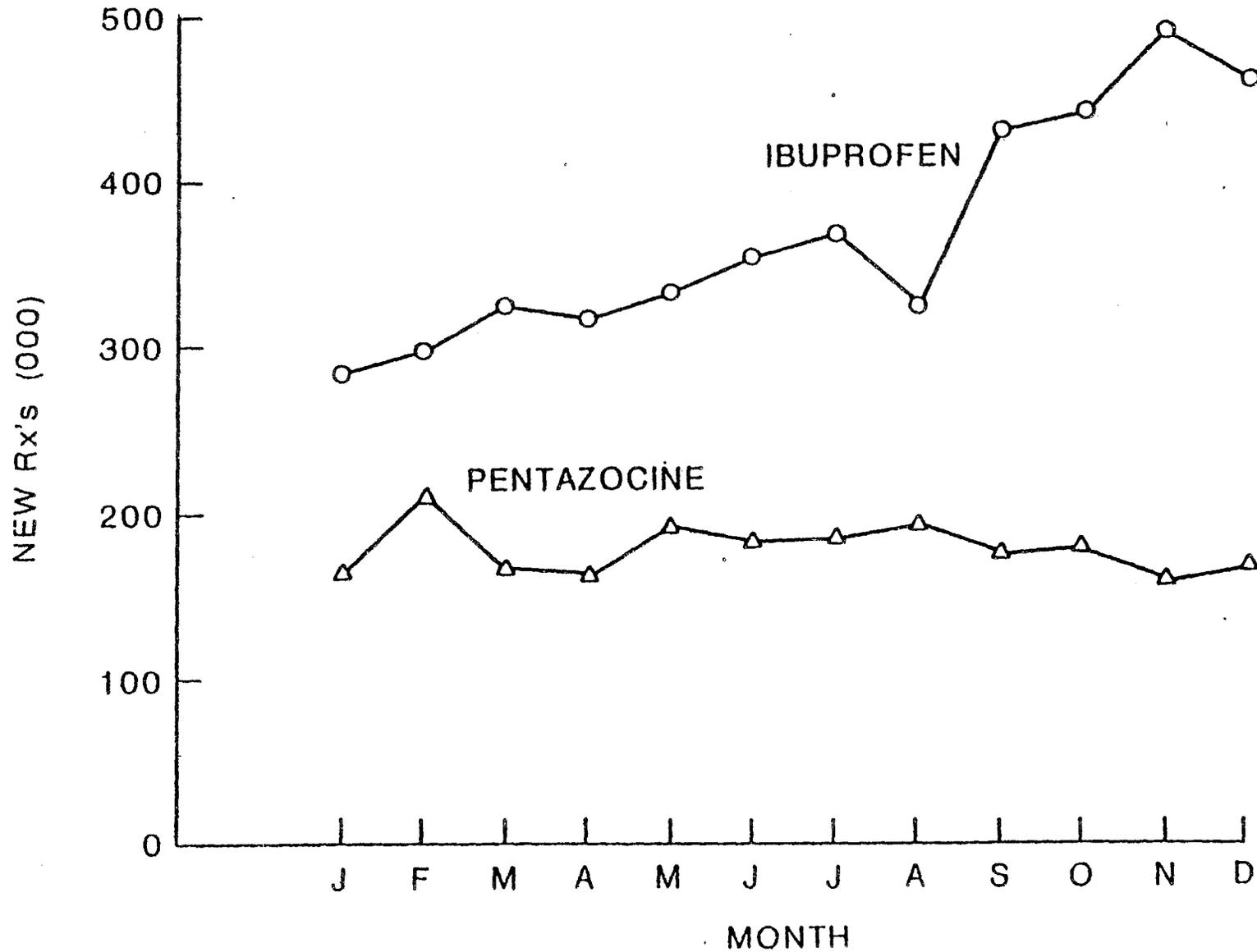
Data from National Disease and Therapeutic Index, IMS America

in the over 64 age groups, which can be ascribed in part to the sex characteristics of the general population in this age group. The most often mentioned diagnosis for the over 64 age groups was arthritis.

J. PHYSICIAN SPECIALTY

Prescribing of DPX by physician specialty has not changed appreciably since 1978, according to the NDTI. Over half of DPX use is in general practitioners, family practitioners, and internists. A substantial amount of use is also seen in general surgery, obstetrics, and orthopedics.

IBUPROFEN AND PENTAZOCINE NEW PRESCRIPTIONS DISPENSED 1979, MONTHLY



Data from National Prescription Audit IMS America

Pentazocine is another Schedule IV analgesic. Monthly new Rx's were graphed for these drugs in Figure 4. Ibuprofen has seen over 50% increase in sales over 1979 while pentazocine has remained fairly constant in new Rx use.

H. DEMOGRAPHICS OF DPX USERS

Table 9 gives the age and sex demographics of DPX users for the year October 1978 through September 1979 compared to the year July 1977 through June 1978, the latter representing a time period before the DPX controversy began. There has been a slight increase in DPX use in the 60-and-over age group with a concomitant decrease in the under-20 age group. This decreased use in the younger age group may be a favorable indicator of decreased abuse potential.

I. INDICATION FOR USE

Table 10 compares primary diagnoses for the same time periods. This indicates a slight decrease in DPX use for surgical aftercare and an increase in DPX use for bone and movement diseases and in obstetrics (postpartum). However, the significance of these changes is not known.

Because Darvocet-N is the most extensively prescribed DPX product, it was possible to rank its use among the most often mentioned drugs by age group. Then, the sex breakdown of this use, and the associated major diagnoses for each age group was examined. Table 11 demonstrates these data for the year October 1978 through September 1979. The age groups in which a high proportion of use was in women were 15-24 and 25-34, where 18% and 13% of use, respectively, was postpartum. A high ratio of female users also occurred

PROPOXYPHENE

Total Kgs (000) Dispensed-1979 in HCl Equivalents

	<u>Lilly</u>	<u>Non-Lilly</u>
January	4.85	.66
February	4.47	.77
March	4.32	.75
April	4.45	.67
May	4.40	.62
June	4.70	.82
July	4.20	.67
August	4.09	.54
September	4.13	.62
October	4.00	.74
November	3.96	.71
December	3.94	.73

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PROPOXYPHENE TOTAL KILOGRAMS DISPENSED
(CONVERTED TO HYDROCHLORIDE EQUIVALENTS)
LILLY vs. NON-LILLY PRODUCTS
1979-MONTHLY

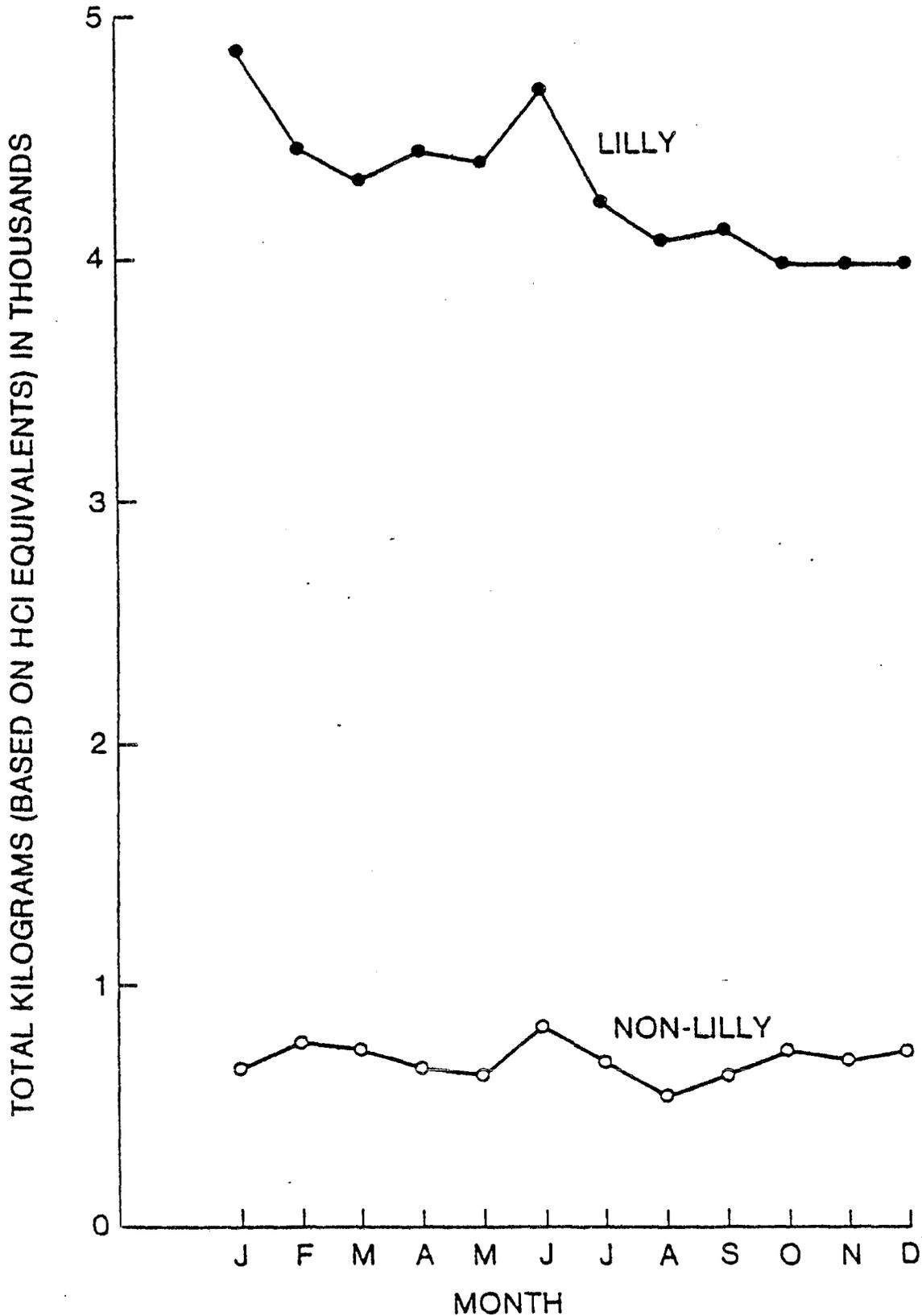


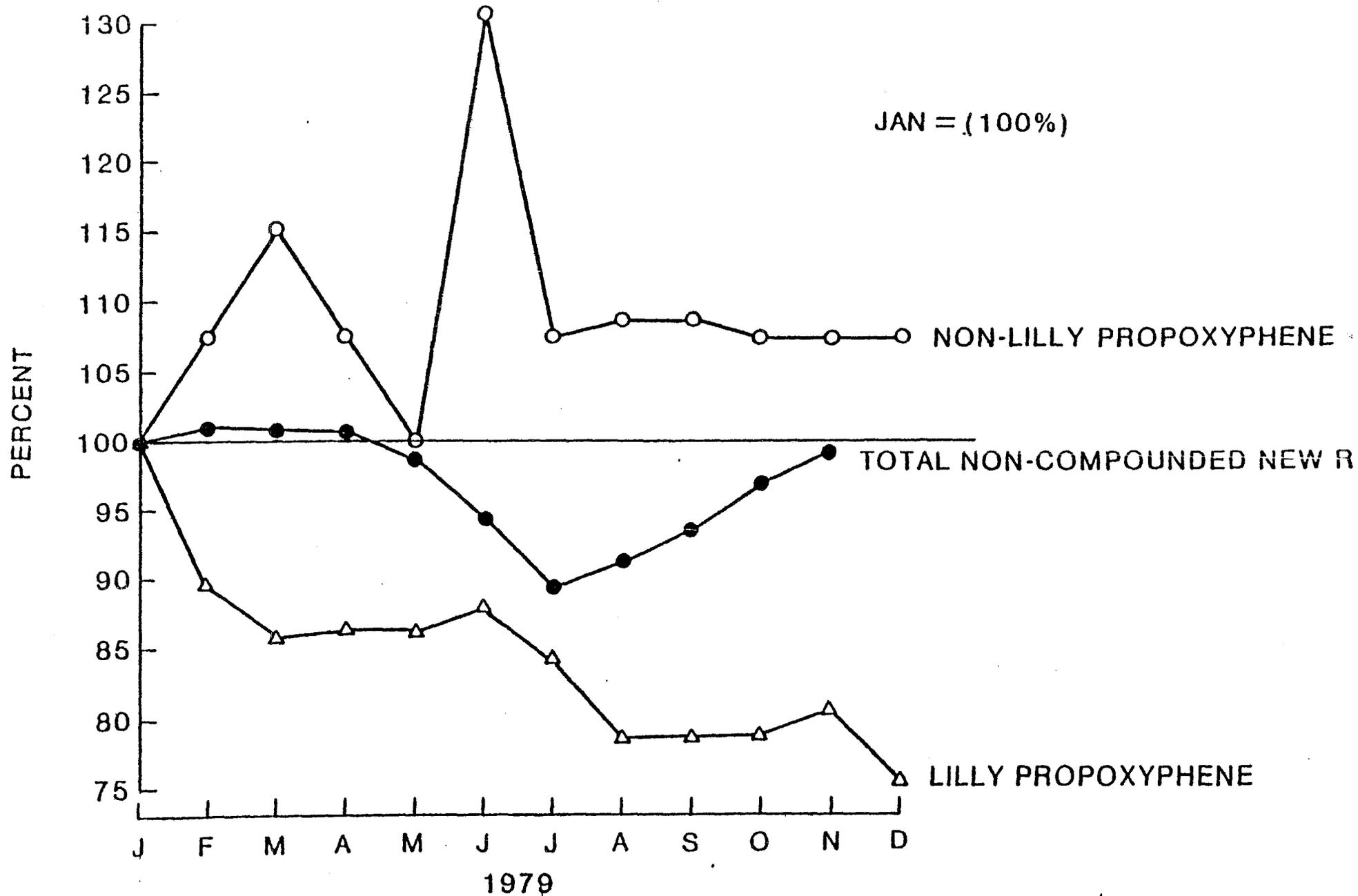
Table 7

Propoxyphene Prescriptions Dispensed-1979
 (New Rx's Only)
 and Percent Changes by Months

	<u>Total Non-Compounded New Rx's (millions)</u>		<u>Lilly Propoxyphene New Rx's (million)</u>		<u>Non-Lilly Propoxyphe New Rx's (million)</u>	
January	63.00	100%	1.21	100%	.13	100%
February	63.59	100.9	1.08	89.3	.14	107.7
March	63.51	101.8	1.04	86.0	.15	115.4
April	63.44	101.6	1.05	86.8	.14	107.7
May	61.50	97.6	1.05	86.8	.13	100
June	59.38	94.3	1.06	87.6	.17	130.8
July	56.54	89.7	1.02	84.3	.14	107.7
August	57.68	91.6	.95	78.5	.12	108.7
September	58.88	93.5	.95	78.5	.12	108.7
October	60.99	96.8	.95	78.5	.14	107.7
November	61.89	98.2	.97	80.2	.14	107.7
December	NA	-	.91	75.1	.14	107.7

FIGURE 2

PROPOXYPHENE (LILLY vs. NON-LILLY) vs. TOTAL Rx MARKET
 PERCENT CHANGE IN NEW PRESCRIPTIONS DISPENSED
 1979-MONTHLY



Using new Rx's, the trend in Lilly vs. non-Lilly DPX Rx's dispensed versus new prescriptions dispensed for all drugs was compared over the same time period. January 1979 was arbitrarily assigned the value of 100% and the percent deviation from the January level was graphed by month. (Figure 2) The absolute January 1979 values for (1) all new Rx's, (2) Lilly DPX new Rx's and (3) non-Lilly new Rx's were 63 million, 1.21 million, and .13 million respectively. (See also Table 7.) Further, Figure 2 demonstrates that the decrease in the Lilly DPX market is not artifactual since the decrease is much greater than prescribing in general. Whereas overall prescribing decreased by less than 2%, Lilly DPX prescribing fell by nearly 25%. On the other hand, non-Lilly DPX prescribing actually increased by about 7%. (The huge jumps seen in April through July of 1979 for non-Lilly DPX is probably not significant due to the thinness of the data.)

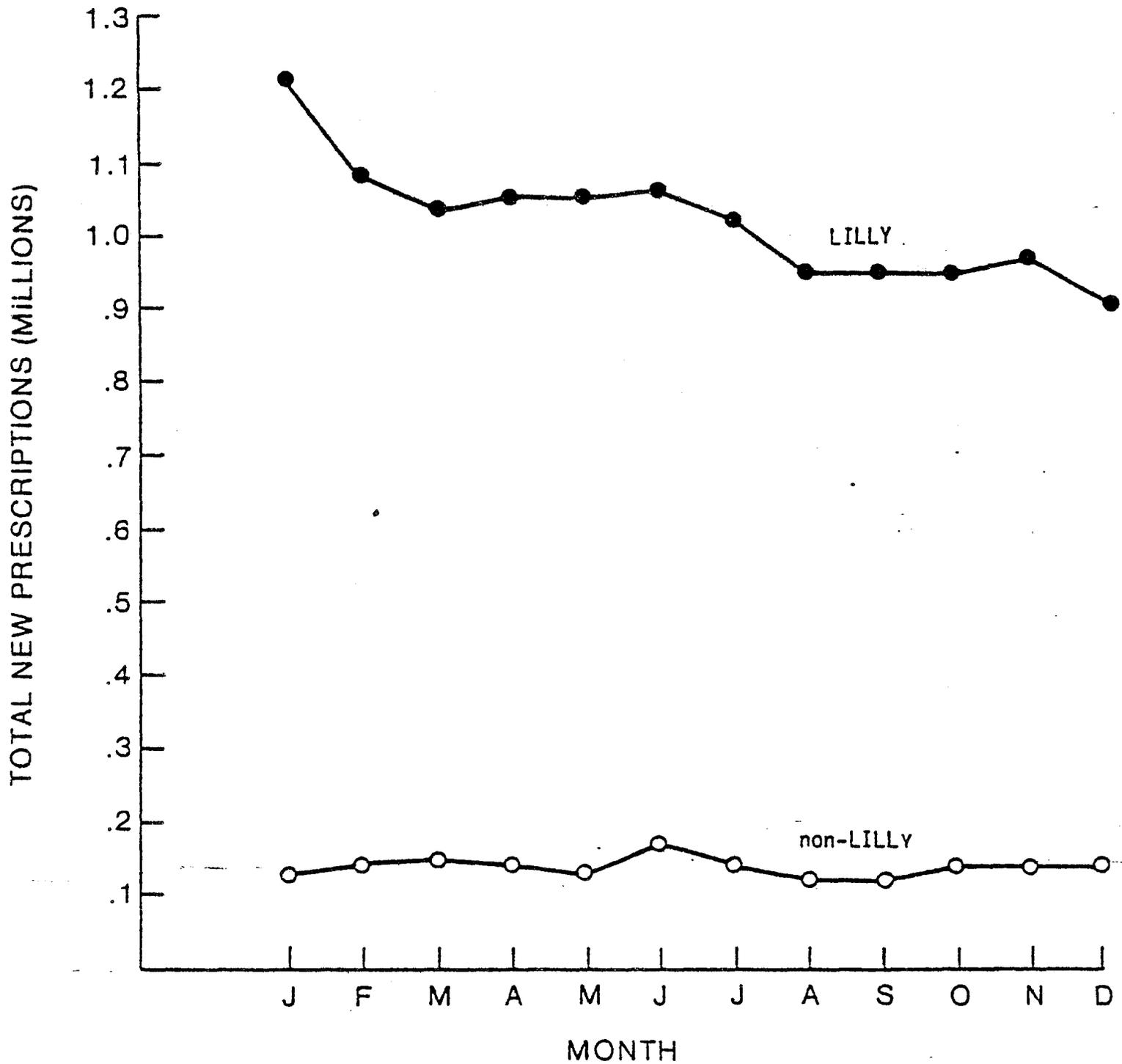
Figure 3 again represents kilograms dispensed, including refills, converted to HCl equivalents to represent total kilograms dispensed monthly for both Lilly and non-Lilly products. This also shows a decrease in Lilly product prescribing with no decrease for other DPX products. Table 8 displays this information in a tabular format.

G. PRESCRIBING OF OTHER ANALGESICS

Lilly has suggested that there was substantial recent promotion of the analgesics ibuprofen and pentazocine. Ibuprofen has only recently (August 1979) been approved by FDA as an analgesic although it has been widely used as an antiinflammatory drug for several years. A new dosage formulation of ibuprofen was introduced on the market September 1979.

FIGURE 1

PROPOXYPHENE NEW PRESCRIPTIONS DISPENSED LILLY vs. NON-LILLY PRODUCTS 1979-MONTHLY



Data from IMS America's National Prescription Audit

Table 6

PROPOXYPHENE

KILOGRAMS DISPENSED, BASED ON TOTAL RX'S (in HCl equivalents)

YEAR (QUARTER)	<u>Propoxyphene</u>		<u>Propoxyphene Napsylate</u>		<u>All Propoxyphen</u> Total
	<u>Single Entity</u>	<u>Hydrochloride Compound</u>	<u>Single Entity</u>	<u>Compound</u>	
78 (3)	2016	6667	448	8185	17316
78 (4)	2091	6698	354	8808	17951
79 (1)	1792	5834	327	7864	15817
79 (2)	1852	5706	451	7658	15667
79 (3)	1657	4893	311	7431	14292
79 (4)	1733	4862	270	7240	14105

Percent change from 1978 to 1979
 $\left(\frac{4\text{th qtr } 79 - 4\text{th qtr } 78}{4\text{th qtr } 78} \times 100 \right)$ -21%

Data from IMS America, Ltd. (C)

Table 5

PROPOXYPHENE

KILOGRAMS DISPENSED, BASED ON NEW RX'S. (in HCl equivalents)

YEAR (QUARTER)	<u>Propoxyphene</u>	<u>Hydrochloride</u>	<u>Propoxyphene</u>	<u>Napsylate</u>	<u>All Propoxyphene</u> Total
	Single Entity	Compound	Single Entity	Compound	
78 (3)	1058	3537	242	5093	9930
78 (4)	1191	3490	200	5346	10227
79 (1)	997	2927	196	4770	8890
79 (2)	981	2826	287	4498	8592
79 (3)	843	2579	214	4345	7981
79 (4)	915	2432	178	4290	7815

Percent change from 1978 to 1979

$$\left(\frac{4\text{th qtr } 79 - 4\text{th qtr } 78}{4\text{th qtr } 78} \times 100 \right) = -2$$

Also of note, Lilly products have a slightly smaller Rx size than do non-Lilly products (37.4 vs. 41.8).

E. KILOGRAMS OF DPX DISPENSED

Because prescription size can vary, and also because DPX is available in two different strengths, an estimate was made of total kilograms dispensed. This takes into account both changes in Rx size and differences in strength of the product. All the napsylate salt kilograms were converted to equivalent hydrochloride kilograms. In this way a more uniform and comparable value for use can be scrutinized.

Tables 5 and 6 display kilograms dispensed based on new and total Rx's respectively. Both Tables demonstrate a decrease in total amount of DPX dispensed. Further, new kilograms dispensed decreased faster than total kilograms. These changes are comparable to those reflected by prescriptions dispensed.

F. TRENDS OVER TIME: 1979

Figure 1 again demonstrates the trend in new Rx's dispensed for Lilly vs. non-Lilly DPX products, this time monthly for the year 1979. The relative size of the Lilly market compared to all other DPX manufacturers can be seen along with the obvious decrease in Lilly product prescribing over this year.

Table 4

PROPPOXYPHENE

AVERAGE RX SIZE (Units)

YEAR (QUARTER)	<u>Propoxyphene Single Entity</u>	<u>Hydrochloride Compound</u>	<u>Propoxyphene Single Entity</u>	<u>Napsylate Compound</u>	<u>All Lilly Propoxyphene</u>
78 (3)	40.5	37.4	45.1	34.4	36.0
78 (4)	44.3	38.3	47.6	35.4	37.3
79 (1)	43.3	40.0	41.7	35.2	37.0
79 (2)	45.6	39.4	54.1	35.5	37.8
79 (3)	44.8	39.8	49.1	35.1	37.3
79 (4)	43.3	39.7	45.8	35.8	37.4

Data from IMS America, Ltd. (C)

PROPOXYPHENE

TOTAL PRESCRIPTIONS DISPENSED (000) FROM RETAIL PHARMACIES BY QUARTER

YEAR (QUARTER)	Propoxyphene	Hydrochloride	Propoxyphene	Napsylate	All Propoxyphene		
	Single Entity	Compound	Single Entity	Compound	Lilly	Other	Total
78 (3)	789	2768	183	3805	6762	783	7545
78 (4)	744	2703	137	3949	6651	882	7533
79 (1)	657	2250	153	3538	5838	760	6598
79 (2)	645	2244	172	3436	5736	761	6497
79 (3)	581	1897	116	3339	5250	683	5933
79 (4)	626	1884	111	3196	5033	784	5817

24,845,000

1716

Percent change from 1978 to 1979
 $\left(\frac{4\text{th qtr } 79 - 4\text{th qtr } 78}{4\text{th qtr } 78} \times 100 \right)$ -2

15078
 2
 30156

7533	3533	7533
6598	6497	5933
935	1136	1600

Data from IMS America, Ltd. (C)

Table 2

PROPOXYPHENE

REFILLED PRESCRIPTIONS DISPENSED (000) FROM RETAIL PHARMACIES BY QUARTER

YEAR (QUARTER)	Propoxyphene	Hydrochloride	Propoxyphene	Napsylate	All Propoxyphene	
	Single Entity	Compound	Single Entity	Compound	Lilly	Other
78 (3)	371	1295	86	1448	2876	324
78 (4)	316	1286	60	1558	2834	387
79 (1)	286	1109	62	1392	2513	336
79 (2)	297	1123	64	1416	2575	325
79 (3)	284	888	38	1381	2285	306
79 (4)	291	933	39	1301	2199	365

Percent change from 1978 to 1979

$$\left(\frac{4\text{th qtr } 79 - 4\text{th qtr } 78}{4\text{th qtr } 78} \times 100 \right)$$

(c)
 Data from IMS America, Ltd.

C. TOTAL PRESCRIPTIONS

Table 3 displays the same data for total Rx's dispensed from retail pharmacies quarterly. There was a 23% decrease in total Rx's from fourth quarter 1978 to fourth quarter 1979 for all DPX products. Again, the "other" DPX manufacturers do not show a decrease in sales, whereas, Lilly products account for practically the entire decrease.

D. PRESCRIPTION SIZE

The level of Rx activity does not precisely measure the amount of drug in the retail marketplace, because even if a decrease in Rx's dispensed is seen, the average size of (number of dose units in) the Rx's could increase to cause the amount of drug available for consumption to remain constant. Likewise, if the level of Rx's dispensed remained constant but the average Rx size decreased, there would still be less drug available for patient consumption. A smaller Rx size is often a tactic used by the physician in limiting the risk to abuse/suicide prone patients.

For these reasons, an average Rx size for the same groups of DPX products was calculated, as seen in Table 4. The combination products generally have a smaller Rx size than do the single-entity products. However, the combination products are prescribed to a much greater extent than are the single-entity products.

Table 1

PROPOXYPHENE

NEW PRESCRIPTIONS DISPENSED (000) FROM RETAIL PHARMACIES BY QUARTER

YEAR (QUARTER)	Propoxyphene		Propoxyphene Napsylate		All Propoxyphene		T
	Single Entity	Hydrochloride Compound	Single Entity	Compound	Lilly	Other	
78 (3)	418	1473	97	2357	3886	459	43
78 (4)	428	1417	77	2391	3817	496	43
79 (1)	371	1141	91	2146	3325	424	37
79 (2)	348	1121	108	2020	3161	436	39
79 (3)	297	1009	78	1958	2965	377	30
79 (4)	335	951	72	1895	2834	419	32

Percent change from 1978 to 1979

$$\left(\frac{4\text{th qtr } 79 - 4\text{th qtr } 78}{4\text{th qtr } 78} \times 100 \right)$$

Data from IMS America, Ltd. (C)

II. LEGITIMATE MEDICAL USE

A. NEW PRESCRIPTIONS

Using NPA data, an analysis was made of propoxyphene (DPX) products by salt, by dosage formulation, and by Lilly products vs. products from other manufacturers. Table 1 describes the above DPX categories in terms of new prescriptions (Rx's) dispensed from retail pharmacies by quarter beginning with the third quarter of 1978. Each category decreased substantially in dispensed Rx's over the six quarter period. Lilly products, however, decreased to a greater extent than products manufactured by other firms. The extent of new Rx's for all DPX products decreased by 25% between the fourth quarter of 1978 and the fourth quarter of 1979.

B. REFILL PRESCRIPTIONS

The same information is described for refill Rx's in Table 2. Both HCl and napsylate salts and single-entity and combination formulations, likewise, showed decreased use, although not to the extent that new prescribing decreased. However, even though Lilly's DPX products decreased substantially, other DPX products refills were relatively unchanged. This may indicate Lilly was associated with the events surrounding DPX in 1979 to a greater degree than other manufacturers. For all DPX products, the decrease in refilled Rx's was 20%.

programs as well as their surveys of physician and patient attitudes and surveys of outcomes including abuse and death. A copy of this report is attached (Tab C).

Several members of the FDA staff representing several disciplines reviewed the Eli Lilly report in detail. Previous discussions in October 1979 established the date of January 20, 1980 as the date for receipt from Lilly of a number of descriptions of their efforts including their educational campaign. It was the consensus of the FDA reviewers' of this report that Lilly had failed to meet its proposed program in several respects. Some of these problem areas include the following:

1. Studies of Prescription Data, DAWN Data and Prescription Data Services and Drug Utilization Data. The Drug Use Analysis Branch in the Division of Drug Experience reviewed the data carefully. In general, there were several discrepancies between information provided in the Lilly Report and information summarized in the early part of this Quarterly Report (Appendix III).
2. Eli Lilly had promised in early conversations a general summary of deaths reported in 18 coroner's offices throughout the country. This survey as indicated was not completed by the time of the report.
3. The remaining materials provided including reports from the Wisconsin Crime Laboratory Reports, the proposed study by Dr. Dorsey and the proposed material from Dr. Lietman were of interest but did not allow for adequate evaluation of the overall magnitude of the problem. It is possible that in future reports these data may be helpful.
4. Although Lilly indicated that the audiovisual film prepared was available in 57 Lilly offices, no information was provided as to how these films were being used so the meaning of this particular item in the report was unknown.

The substance of these comments are also being communicated to Eli Lilly.

B. Deaths Recorded by DAWN Medical Examiners

Deaths reported to consistently reporting medical examiners were tabulated from January 1976 through June 1979 the last month for which complete data are available. Deaths which were specifically reported as suicide were separated from other deaths although the diagnosis of suicide is often moot in many jurisdictions. Deaths associated with propoxyphene (both suicidal and nonsuicidal) have decreased since 1977 and are approximately equally distributed between suicidal and nonsuicidal events. Overall ~~there was a 50% decrease in propoxyphene related deaths as reported to DAWN between the second quarter of 1977 and the second quarter of 1979 with 30% of this decrease between the second quarters of 1978 and 1979.~~ However, a continued trend line through 1979 would be necessary before a final conclusion can be reached as to the effect of the 1979 proceedings and this will be included in forthcoming reports.

C. DAWN Deaths as a Proportion of Use

A comparison was made of propoxyphene with other drugs that are frequently associated with death as reported by DAWN coroners when the number of deaths associated with drugs are divided by the extent of use in the population as noted in previous reports (see Federal Register Report - March 2, 1979). ~~Propoxyphene continues to rank third while barbiturates and sedative hypnotics are first and second respectively.~~

Part B - Eli Lilly Reports and FDA Comments

I. Summary

As agreed in previous conversations with Eli Lilly, the firm provided a report of their progress on their educational

internists although a substantial amount of use is also seen in general surgery, obstetrics and orthopedics. This is essentially unchanged.

III. Acute or Non-Fatal Medical Problems and Abuse

Reliable information on the extent of the abuse is difficult to obtain and the only sources of information for this report were the cases of addiction or dependence reported to the FDA and the reports from the DAWN emergency room panel. Twenty-seven cases of addiction or dependence were reported to FDA in 1979, 21 of which involved propoxyphene only. DAWN Emergency Room Panel data from consistently reporting emergency rooms shows a substantial decrease in emergency room mentions of propoxyphene beginning in 1978 and continuing through the end of 1979 with a peak in January 1979, the month of initial publicity and Senate hearings. Overall, there was a 35% decrease in DAWN Emergency Room mentions between the fourth quarter of 1977 and the fourth quarter of 1979 with 25% of this decrease occurring since the fourth quarter of 1978. Since DAWN emergency room data lags six to nine months after the occurrence of the event, it is too early to estimate or ascertain whether or not the events in 1979 have in fact affected this trend. This should be more evident in forthcoming reports.

IV. Fatal Medical Problems

A. Deaths reported to FDA

There were 19 cases of fatal overdoses reported to the FDA in 1979, five of which indicated a suicide attempt but several of which were poorly documented. Eight of the 22 cases involved propoxyphene alone; the remainder were associated with other drugs or alcohol. This proportion is consistent with a review of previous reports. Because of the voluntary nature of the system, the number of reports cannot be used quantitatively as a reliable measure of propoxyphene death.

decreased, the same is true for all prescriptions. Accordingly, the decrease in propoxyphene was compared with that for all drugs. It was found that whereas overall prescribing decreased by less than 2%, prescribing for Lilly's propoxyphene fell by nearly 25%, non-Lilly propoxyphene prescribing actually increased by 7%, however, the non-Lilly products represent only about 12% of the propoxyphene market.

G. Prescribing of Other Analgesics

It was suggested by Lilly that there was substantial recent promotion of the analgesics ibuprofen and pentazocine during 1979. Ibuprofen was approved as an analgesic in August 1979 (although it has been widely used as an anti-inflammatory drug for several years). It is of note that ibuprofen has increased over 50% in sales in 1979 while pentazocine has remained fairly constant in new prescription use.

H. Demographics of Propoxyphene Users

There has been a slight increase in the 60 year or older age group with a concomitant decrease in the under 20 age group in 1979 as compared with 1978. This may be a favorable indicator that those with greatest abuse and suicide potential are receiving less drug.

I. Indications for Use

In 1979, compared with 1978, there are only slight changes in indications for use with an increase for bone and movement disorders and postpartem disorders. The age group in which there is a high proportion of use was in women ages 15-24 and 25-34 where 18% and 13% of use respectively was postpartem.

J. Prescriber Specialty

Over half of propoxyphene use is by general practitioners, family practitioners and

products decreased substantially (~25%) since the third quarter of 1978 with a greater decrease in Lilly products than in other manufacturers products.

B. Refill Prescriptions

Although there is a slight decrease in refills, particularly in Lilly products, the number of other propoxyphene products refills was relatively unchanged. For all propoxyphene products the decrease in refilled prescriptions was 20%, from the fourth quarter of 1978 to the fourth quarter of 1979.

C. Total Prescriptions

There was a 23% decrease in total prescriptions from fourth quarter 1978 to fourth quarter 1979 for all products. Lilly products accounted for practically the entire decrease in total prescriptions.

D. Prescription Size

Since decreasing the prescription size is often a tactic used by prescribers in limiting the risk of suicide-prone patients, average prescription size was evaluated. In general, there was an overall slight increase in prescription size rather than a decrease from the latter part of 1978 to the fourth quarter of 1979.

E. Kilograms of Propoxyphene Dispensed

Since prescription size can vary and because propoxyphene is available in two different strengths, an estimate was made of total kilograms. This verifies the information on new and refill prescriptions showing a decrease of approximately 24% and 21% for new and total prescriptions, respectively, in 1979.

F. Trends Over Time: 1979

Although the prescribing of propoxyphene has

3. The NIDA National Survey on Drug Abuse (these data are not yet available for this report but should be present in the following report).
4. The NIMH National Household Survey (these data are likewise not available for this report but should be for forthcoming reports).

C. Measures of Deaths Associated with Propoxyphene

1. Drug Abuse Warning Network (DAWN) which collects drug death data from approximately 90 medical examiners primarily on drugs of abuse.
2. Mortality Statistics from the National Center for Health Statistics which analyzes all U.S. death certificates. These data are only available annually. (These data will be included on the forthcoming report.)
3. The National Clearinghouse for Poison Control Centers which collects data on visits to selected emergency rooms including data on fatal outcomes.
4. FDA's Adverse Reaction Reporting Program which also collects data on deaths and provides qualitative data.

RESULTS

II. Legitimate Medical Use

Utilizing the data bases provided, changes in legitimate medical use were tabulated. Findings of note include the following:

A. New Prescriptions

Dispensed prescriptions for all propoxyphene

2. Between the beginning of 1977 and the end of 1979, apparent abuse of propoxyphene decreased by 35 percent as estimated by emergency room mentions in the DAWN system. Between the beginning of 1977 and June 1979, propoxyphene-associated deaths reported to DAWN decreased by 50 percent. Because reports of deaths in the DAWN system lag 6 to 9 months behind the actual events, it is not yet possible to estimate whether the number of deaths has been affected by FDA's new warnings on propoxyphene and by Lilly's informational campaign; these events occurred in the fall of 1979. Such an appraisal may be possible by July 1980 and certainly by October 1980.
3. Lilly has not conducted its campaign to prescribers as FDA had expected. Detail persons visiting physicians failed to emphasize the user warnings in the majority of visits, left samples of Darvon in 50-75 percent of visits, and on the average spent less than half of the time on Darvon during the visits.

Because propoxyphene-associated deaths and the prescribing of propoxyphene are continuing to decrease, FDA is not planning a major new review of the drug's scheduling or labeling in the near future. FDA will continue to highlight the dangers of propoxyphene to the medical profession and the public, however, and will continue to press the drug industry to promote this drug responsibly. Current actions include the following:

- o FDA has already asked Lilly to repeat its informational campaign to prescribers, this time under guidelines to ensure its integrity (Tab E).
- o FDA has obtained commitments from some generic manufacturers (but not all) to include patient package inserts (PPIs) with their products. We will contact lagging manufacturers again to seek their cooperation.
- o FDA is conducting a survey of the extent to which PPIs are being distributed by pharmacists.

Our next report to you, covering January through March 1980, is scheduled for May 15, 1980.

Attachments

- Tab A - June 15, 1979 Memorandum from Mr. Califano
- Tab B - Executive Summary
- Tab C - Quarterly Report
- Tab D - Eli Lilly Report
- Tab E - FDA Comments on Eli Lilly Report
- Tab F - Letter to Lilly

GROUT LETTER:

PURPOSE:

This is the second quarterly report on propoxyphene as originally requested by Secretary Califano (Tab A). It presents an assessment of the use, abuse, morbidity, and mortality associated with propoxyphene and covers the period from the third quarter of 1978 through the fourth quarter of 1979. The first report, submitted on November 1, 1979, covered the nine months preceding the third quarter of 1978.

FACTS:

The report consists of two major parts preceded by an executive summary (Tab B). The first part (Tab C) is a review--by the Division of Drug Experience, Bureau of Drugs, FDA--of use, abuse, morbidity, and mortality associated with propoxyphene as tabulated from a variety of data bases described in Appendix I to Tab C. The second part is the report provided by Eli Lilly (Tab D), followed by comments on it from FDA Staff (Tab E). As a separate but related matter, FDA has conducted its own analysis of Lilly's informational campaign. A letter to the President of Lilly on this subject is included (Tab F).

Briefly, the review to date reveals the following:

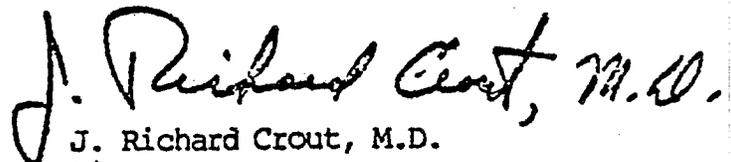
1. Prescribing and use of the Lilly propoxyphene products decreased by 20-25 percent during 1979, depending upon the measure used. The dispensing of non-Lilly products, representing approximately 12 percent of the market, has either remained stable or increased slightly.

NDA-10-997

Richard D. Wood
Eli Lilly and Company
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I look forward to your early decision on whether Lilly intends to conduct a meaningful informational campaign in accordance with the above guidelines. My staff and I would be pleased to meet with Lilly representatives on this matter at your discretion. While this educational campaign is voluntary on Lilly's part, the commitment of Lilly to conduct such a campaign was accepted by FDA and the Department as an important element in our national effort to reduce propoxyphene-associated deaths and in our scheduling decision. Lilly's performance to date, and in the future, in fulfilling its public commitment with integrity will be considered by the FDA, its Drug Abuse Advisory Committee, and the Department in our continuing assessment of the safety of propoxyphene-containing products.

Sincerely yours,



J. Richard Crout, M.D.
Director
Bureau of Drugs

cc:
Mr. Eugene L. Step, President
Pharmaceutical Division
Eli Lilly and Company

Richard D. Wood
Eli Lilly and Company
Page 3

In view of these findings, I wish to inform you that the FDA does not consider Lilly to have met agency expectations for the promised informational campaign to prescribers of Darvon products. In addition, I doubt seriously that the campaign to date would meet the expectations of our Drug Abuse Advisory Committee.

For Lilly's informational campaign to prescribers to be meaningful and credible, we believe the following conditions should be met:

1. The intent of every visit related to propoxyphene products should be to emphasize the precautions necessary for the judicious prescribing and safe use of these products. This message should be conveyed, unencumbered by any diluting or qualifying information, in 100% of the visits made.
2. Detail persons should not provide any samples of propoxyphene products. In fact, we are surprised that Lilly commonly provides free samples of Darvon products under any circumstances. The official position of the Pharmaceutical Manufacturers Association, as expressed by former PMA president Joseph Stetler in his testimony before Senator Kennedy's Subcommittee on Health and Scientific Research on May 18, 1979, supports the sampling provision of S. 1075, the Senate-passed Drug Regulation Reform Act of 1979. This provision prohibits free sampling except on written request from the practitioner. The accompanying bill report from the full Committee on Labor and Human Resources makes quite clear that the intent is to limit the common current practice of indiscriminate sampling.
3. Any visit to a practitioner that is part of this informational campaign should consider a discussion of Darvon products to be the primary purpose of the visit. Presentation of information on these products should occur first and should occupy the majority of the time of the visit.
4. Finally, we believe that Lilly management should consider relieving Lilly detail persons visiting practitioners of any conflict of interest in conducting such a campaign. That is, Lilly should consider deleting sales of Darvon products as a factor in computing commissions or other compensation of detail persons during this campaign.