Region 12 - DENVER

Legitimate amphetamine diversion has never been a sizeable problem in Region 12. We have from time to time found it necessary to initiate criminal investigations against practitioners in the field of medicine and pharmacy to stop diversions. The prescribing of amphetamine by physicians has dropped greatly in the past few years.

The Colorado Bureau of Investigation Crime Lab for Colorado reports 10% of the amphetamine received by them are diverted legitimate products. Informants have not reported knowledge of diversions in the recent past any where in the Region.

Contact made with Denver Police Department special forged prescription squad reported that 20% of all prescriptions are passed without difficulty in drug stores in Denver area.

Contact with Colorado Bureau of Investigation revealed that approximately 10% of all amphetamines analyzed are from legitimate sources.

With the exception of single dosage units obtained in street arrests police laboratories in Phoenix, Arizona report little experience with legitimately manufactured amphetamines.

A review of order forms retained over a period of years has shown a remarkable decrease in the purchase of amphetamines by physicians known to have previously dispensed amphetamines. Only one physician, in Tucson, Arizona, was found to be dispensing amphetamines to patients for periods of more than 21 days. Some of this physician's patients have been on amphetamine therapy for periods in excess of one year.

Indications are that weight control physicians in Region 12 have switched from amphetamines to such anorectics as phendimetrazine and phentermine.

Region 13 - SEATTLE

The availability of legitimately produced amphetamines through illegal channels throughout Region 13 is sporadic. From all available information, it appears that one of the primary sources of legitimately produced amphetamines obtained through illegal channels is the result of pharmacy burglaries and forged prescriptions. Another source appears to be physicians and weight control clinics dispensing and prescribing amphetamines beyond the short term usage recommendation of the Food and Drug Administration (FDA).

The consensus of opinions from state and local law enforcement agencies within Region 13 is that the source of legitimately manufactured amphetamines through illegal channels is predominantly from burglarized pharmacies and forged prescriptions. A supplemental source appears to be physicians and weight control clinics dispensing and prescribing amphetamines beyond the short term usage recommendation of FDA. State regulatory authorities were not able to furnish any estimates or statistics relative to the availability of legitimately manufactured amphetamines through illegal channels.

After a review of six (6) practitioners' records, it was determined that 549 patients were receiving amphetamines

beyond the 21 day limit recommended by the FDA. It was also noted that 16 patients have been receiving amphetamines for over three (3) years.

Region 14 - LOS ANGELES

Legitimately produced amphetamines are available in Region 14 on an individual basis only. A review of Region 14's sources of information failed to reveal legitimate amphetamines on the streets of Los Angeles. An additional query was made of the Los Angeles Police Department (LAPD) Administrative Narcotics Division (Buy Program), and their response was the same.

Region 14 personnel, LAPD Administrative Narcotics Division, and the State of California Drug Diversion Investigative Unit (DIU), it was learned that in terms of major seizures of legitimately produced amphetamines, there have been no significant cases. The DIU did advise that there are two (2) problem areas they have discovered: The first is prescription forgery rings operating in Region 14, and the second is that of the dispensing and prescribing practitioners. The DIU reports that most licit amphetamine cases are those in which an amphetamine abuser will go to a practitioner and receive prescriptions for amphetamines. It was felt, however, that the amphetamine abuser used these prescriptions for his own use rather than for resale.

In a check with the LAPD Criminalistics Laboratory, it was learned that they receive very few legitimately produced amphetamine tablets to analyze. It is their belief that the few samples they did receive resulted from children stealing the drug from their parent's medicine supply. The DIU estimates that approximately 90% of all Desoxyn (methamphetamine) prescribed by practitioners is for non-medical purposes. The state of Nevada reports that approximately 15% to 20% of the practitioners prescribe 80% to 90% of the amphetamines.

A total of 14 practitioners were interviewed and their records reviewed in Honolulu, San Francisco, Los Angeles, San Diego and Reno, Nevada. The following trends were observed. One, the dispensing and prescribing of amphetamines is on the decline. Two, that in cases where amphetamines are prescribed, the potency is being reduced. Three, the decrease in amphetamine dispensing and prescribing is reportedly due to increased accountability standards and registrant investigations. Practitioners interviewed reportedly write prescriptions for a seven (7) day supply. Some practitioners, however, allowed a 30 day supply. As a group, physicians were either unaware of any short term limitation or they simply ignored it. Long-term use of amphetamines by abusers is not an uncommon occurrence.

In Region 14, California has a triplicate prescription system, but it applies to narcotics only. Nevada does not have a triplicate prescription system. Hawaii has a duplicate system but they have not created an effective retrieval system to secure the information requested.

Trends in Region 14 indicate that amphetamines are available from legitimate sources, in spite of the fact that those sources are aware that the drug is not going to be used for non-medical reasons. Due to accountability standards, dispensing of amphetamines is decreasing while prescribing is increasing.

Conclusion

(1) The abuse of legitimately manufactured amphetamines in the United States appears to be on the increase. This increased abuse can be unquestionably stated as a very serious problem.

(2) It appears that prescribing and dispensing physicians are a prime source of supply for these amphetamine products. Other sources of supply also include pharmacy thefts, in-transit losses, and employee theft from registrants.

BUREAU OF NARCOTICS &
DANGEROUS DRUGS

Attachment A

(Reprinted from Federal Register of February 12, 1973; 38 F.R. 4249)

Title 21—Food and Drugs

CHAPTER I—FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

SUBCHAPTER C—DRUGS

PART 130—NEW DRUGS

Amphetamines for Human Use

On August 8, 1970, there was published in the FEDERAL REGISTER (35 FR 12652) § 130.46 concerning amphetamines and their salts and levamfetamine and its salts. Section 130.46 required the submission of new drug applications for amphetamine or dextroamphetamine and their salts as a condition for continued marketing. The new drug applications were to contain evidence of efficacy, including efficacy in the treatment of obesity.

Pursuant to that requirement 106 new drug applications for amphetamines or amphetamine-containing drugs were received. The analysis of the data submitted concerning the amphetamines and other, nonamphetamine anorectic drugs generally supported the efficacy of anorectic drugs. Use of the drug in obese patients was associated with more weight loss than was diet alone. The degree of extra weight loss was small (a few tenths of a pound a week in many cases), variations were great, and the rate of weight loss decreased after the first weeks of therapy.

On the basis of the currently available evidence, the Commissioner concludes that oral dosage forms of amphetamine and/or dextroamphetamine are effective in the management of exogenous obesity as a short term (a few weeks) adjunct in a regimen of weight reduction based on calorie restriction for patients in whom obesity is refractory to other measures. Appropriate notices concerning such drugs which have been reviewed in the Drug Efficacy Study will be published in the FEDERAL REGISTER.

Use of amphetamines for long periods of time may lead to drug dependence and abuse. Abuse of the amphetamines has been well known. Persistence of abuse under conditions of marketing described herein may lead the Commissioner to take further steps to restrict the use of these drugs.

No data have been received providing substantial evidence of effectiveness of levamfetamine and its salts. Accordingly these preparations continue to be regarded as new drugs requiring approved full new drug applications.

On September 3, 1971, a Drug Efficacy Study Implementation notice was published in the FEDERAL REGISTER (36 FR 17669) stating that methamphetamine hydrochloride injection (intended for other than anorectic indications) was regarded as effective for some indications and less than effective for others. The Commissioner has now fully reviewed the evidence on the safety and effectiveness of this drug, and has concluded that the well-documented history of abuse of parenteral methamphetamine, together with the severe risk of dependence and the availability of safer and equally effective alternative drugs, creates an unfavorable balance of risk to benefit. A proposal to withdraw approval of these new drug applications as lacking evidence of safety is published elsewhere in this issue of the FEDERAL REGISTER. The Commissioner also concludes that, for the same reasons, parenteral preparations containing amphetamine, dextroamphetamine, or levamfetamine or their salts are lacking evidence of safety.

On August 8, 1970, a Drug Efficacy Study Implementation notice was published in the FEDERAL REGISTER (35 FR 12678) stating that various combination drugs containing an anorectic drug were regarded as possibly effective for their claimed anorectic effects and lacking substantial evidence of effectiveness for their other indications. Data were received concerning those drugs and also combination drugs which were subjects of new drug applications submitted as required by § 130.46. The combinations consisted of anorectic agents associated with, for example, sedatives, tranquilizers, rauwolfia derivatives, or vitamins. The data were reviewed and found not to fulfill the criteria set forth in the Statement of General Policy or Interpretation § 3.85 Fixed-combination prescription drugs for humans, published in the FEDERAL REGISTER of October 15, 1971 (36 FR 20037). Further, in view of the lack of substantial evidence of effectiveness of the drugs as fixed combinations, the recognized potential for abuse of the amphetamine, dextroamphetamine, methamphetamine, and phenmetrazine components, and the availability of alternative therapeutic measures which are safer and effective, combinations containing such components also lack proof of safety. Proceedings to withdraw approval of such applications are being initiated, and an appropriate notice is published elsewhere in this issue of the FEDERAL REGISTER.

In a forthcoming issue of the FEDERAL REGISTER, the Commissioner will set forth his policy with respect to anorectic agents in general.

On the basis of all of the data and information submitted pursuant to § 130.46, pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (secs. 502 (f), (j), 505, 701(a), 52 Stat. 1051-53; as amended, 1055; 21 U.S.C. 352(f), (j), 355, 371(a)), and under the authority delegated to him (21 CFR 2.120), the Commissioner of Food and Drugs hereby revises § 130.46 of Part 130, Subpart A to read as follows:

§ 130.46 Amphetamines (amphetamine, dextroamphetamine, and their salts and levamfetamine and its salts) for human use.

(a) Amphetamine and dextroamphetamine and their salts. (1) Pursuant to the drug efficacy requirements of the Federal Food, Drug, and Cosmetic Act, the National Academy of Sciences-National Research Council, Drug Efficacy Study Group, has evaluated certain dosage forms of amphetamines and other sympathomimetic stimulant drugs intended for use in the treatment of obesity and for other uses. The Academy found that such drugs as a class have been shown to have a generally short-term anorectic action. They further commented that clinical opinion on the contribution of the sympathomimetic stimulants in a weight reduction program varies widely, the anorectic effect of these drugs often plateaus or diminishes after a few weeks, most studies of them are for short periods, no available evidence shows that use of anorectic alters the natural history of obesity, some evidence indicates that anorectic effects may be strongly influenced by the suggestibility of the patient, and reservations exist about the adequacy of the controls in some of the clinical studies. Their significant potential for drug abuse was also cited.

(2) In addition to those dosage forms that were reviewed for efficacy by the Academy, other dosage forms of amphetamine drugs are on the market that were not cleared through the new-drug procedures. While certain amphetamines were marketed prior to enactment of the Federal Food, Drug, and Cosmetic Act in 1938, some of the conditions of use subsequently prescribed, recommended, or suggested in their labeling (for example, for the treatment of obesity) differ from uses claimed for the amphetamines before said enactment. Such uses

have not been cleared through the effectiveness provisions of the Drug Amendments of 1962 (Public Law 87-781 which amended the Federal Food, Drug, and Cosmetic Act). These drugs are very extensively used in the treatment of obesity. The extent of use for such purposes as narcolepsy and minimal brain dysfunction in children is believed to be minor as compared with the total usage of these drugs. Because of their stimulant effect on the central nervous system, they have a potential for misuse by those to whom they are available through a physician's prescription, and their abuse by those who obtain them through illicit channels is well documented. Production data indicate that amphetamines have been produced and prescribed in quantities greatly in excess of demonstrated medical needs.

(3) Pursuant to a notice published in the FEDERAL REGISTER of August 8, 1970 (35 FR 12652), which required the submission of new drug applications as a condition for continued marketing of amphetamines, 106 new drug applications for amphetamines or amphetamine-containing drug products were received. The data submitted in those applications, and data obtained from other sources concerning anorectic drugs, generally supported the efficacy of anorectic drugs.

(b) On the basis of currently available evidence derived from short-term studies, the Commissioner concludes that single drug entity oral dosage forms of amphetamine or dextroamphetamine are effective in the management of exogenous obesity as a short-term (a few weeks) adjunct in a regimen of weight reduction, based on caloric restrictions, for patients in whom obesity is refractory to other measures. For purposes of this regulation, a mixture of dextroamphetamine and amphetamine is ordinarily regarded as a single drug entity.

(c) The Food and Drug Administration is not aware of data providing substantial evidence of the effectiveness of levamfetamine and its salts and regards these preparations as new drugs requiring approval full new-drug applications.

(d) In view of the well-documented history of abuse of parenteral amphetamines the severe risk of drug dependence, and the availability of safer alternative parenteral drugs which are equally effective for recognized non-anorectic indications, the Food and Drug Administration regards parenteral amphetamines as lacking evidence of safety.

(e) Any combination drug containing amphetamine or dextroamphetamine is regarded as a new drug requiring an approved full new-drug application as a condition for marketing. Data in new-drug applications are required to fulfill the criteria set forth in § 3.86 governing fixed combination prescription drugs for humans.

(f) New drug applications have been received from persons marketing orally administered single entity amphetamine or dextroamphetamine dosage forms. Any other person who intends to market such drug is required to submit to the Food and Drug Administration an abbreviated new drug application (§ 130.4 (f)) except that in addition, the application shall contain full information required under items 7 and 8 (composition and methods, facilities, and controls) of the new drug application form FD-356H (§130.4(c)).

(g) The labeling conditions for single entity oral dosage forms of amphetamine and dextroamphetamine and their salts are as follows:

(1) The label shall bear the statement "Caution: Federal law prohibits dispensing without prescription".

(2) The drug shall be labeled to comply with all requirements of the act and regulations. The labeling shall bear adequate information for safe and effective use of the drug. The indications for use are:

Narcolepsy.

Minimal brain dysfunction in children (hyperkinetic behavior disorders), as an aid to general management.

Management of exogenous obesity as short-term (a few weeks) adjunct in a regimen of weight reduction based on caloric restriction, for patients in whom obesity is refractory to other measures.

(3) Complete labeling guidelines are available from the Food and Drug Administration.

(h) Regulatory proceedings will be initiated with regard to any such drug within the jurisdiction of the act which is not in accord with this regulaton.

Effective date. This regulation shall be effective on March 14, 1973.

Dated: February 7, 1973.

WILLIAM F. RANDOLPH,
Acting Associate Commissioner for Compliance.

ATTACHMENT B

UNITED STATES GOVERNMENT

Memorandum

TO : Mr. Ernest A. Carabillo, Jr.
Chief, Special Programs Division

DATE: OCT 06 1975

FROM : Chief, Special Studies Section

SUBJECT: Analysis of Amphetamine Abuse Trends

There are indications that the amphetamine abuse problem has changed direction and is now worsening. This paper analyzes the amphetamine abuse trends in terms of the nature of abuse and the sources of the abused drugs.

An examination of DAWN data on a quarterly basis for the three year period ending in June 1976, indicates that a trend of diminishing amphetamine mentions from a peak early in 1974, started to reverse itself during the last six quarters with a 28% increase in DAWN mentions during the past year. The emergency room data and the crisis center data did reflect the reversal of the downward trend (Fig. 1).*

The major reasons given for seeking help in emergency rooms are shown in Figure 2. The number of mentions due to overdoses and chronic effects of amphetamine have been constantly rising since the third quarter of 1973.

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*Medical examiner data accounted for only about one and onethird percent of DAWN amphetamine mentions. They were too sparce and too variable over time to assess trends in amphetamine related deaths.

Unexpected reactions showed a transient rise early in 1974, dropped to a low early in 1975 after which it too began a steady upward climb. When these raw data are converted to percent of each quarter's total, as in Figure 3, it may be seen that while relative changes in overdose and unexpected results portions complement each other, there has been a small but steady increase in the relative frequency of chronic effects as a cause--indications that an increasing portion of amphetamine abuse is accounted for by individuals with access to a continuing supply of the drug.

The major motive for taking amphetamine is its psychic effect as shown in Figure 4, and since the first quarter of 1974, this motive has been increasing in terms of both absolute number of mentions and its share of all other identified motives. Although dependency and self-destruction have continuously increased in number during this period, after the first quarter of 1975, they slowly but steadily diminished in relative importance.

Street buys are consistently the major source of amphetamines leading to emergency room mentions (Figure 5), and a peak in both absolute and relative importance occurred early in 1974, coincident with the peak in unexpected reactions to the drug. This diminished by the beginning of 1975, at which time the number of street buy mentions increased, although its relative importance remained constant. The only other significant source of amphetamine was from legal prescriptions. Its importance, boty absolutely and relatively, bottomed out during the middle of 1974, after which it has been continuously

increasing in terms of absolute numbers (an increase of about 40%), and in its share of all sources.

As street buys as well as legal prescriptions abuse sources can originate from prescribed drugs taken from home medicine chest supplies, an attempt was made to estimate what portion of street available amphetamine is of illicit origin, what portion was stolen or diverted from legal distribution systems, and what portion can be assumed to come from legally dispensed home supplies.

The data available in DEA's STRIDE system can be useful in determining the sources of abused amphetamines. Because the d-isomer of amphetamine is pharmacologically three to four times as potent a stimulant as the l-isomer, commercial manufacturers tend to separate the two isomers and market them separately. On the other hand, the manufacturers of illicit amphetamines do not do so, and their product is usually a 50-50 mixture (dl-amphetamine). Thus, a comparison of the relative amounts of d-amphetamine and of dl-amphetamine exhibits processed by DEA laboratories and entered into the STRIDE system can serve as a crude indicator of changes in the portion of legally manufactured and illicitly manufactured amphetamines made available to street abuse.*

An earlier analysis of such data for the 18-month period from July 1971 to December 1973, determined that 53% of the exhibits were

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*Minichiello, L.P., Lawson, J.B., Gardner, K.A., & Seekamp, L.N. The Supply, Distribution and Usage Patterns of Drugs of Abuse. Drug Enforcement Administration, STS-TR-13, October 1974.

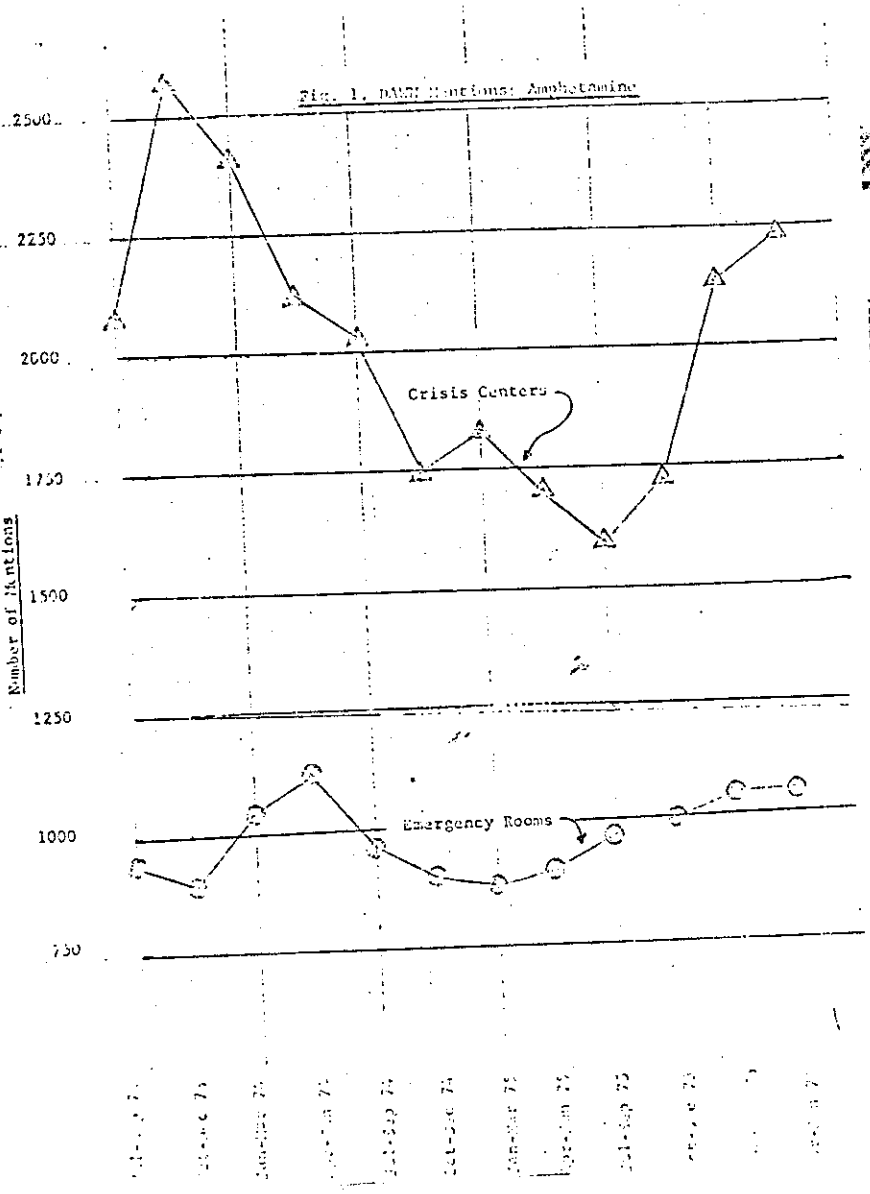
Fig. 1. DAWN Mentions: Amphetamine
2500
2250
2000
1750
1500
1250
1000
750
Number of Mentions
Crisis Centers
Emergency Rooms

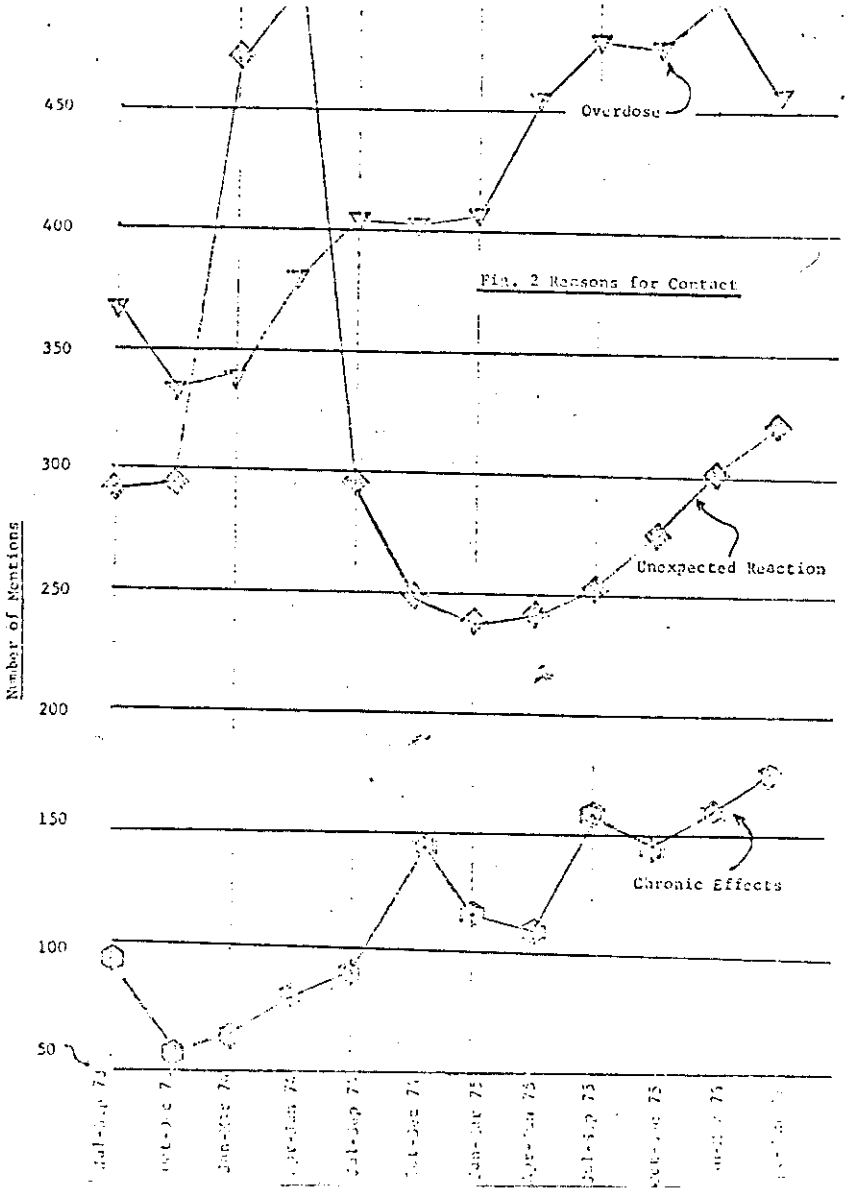

Fig. 2 Reasons for Contact

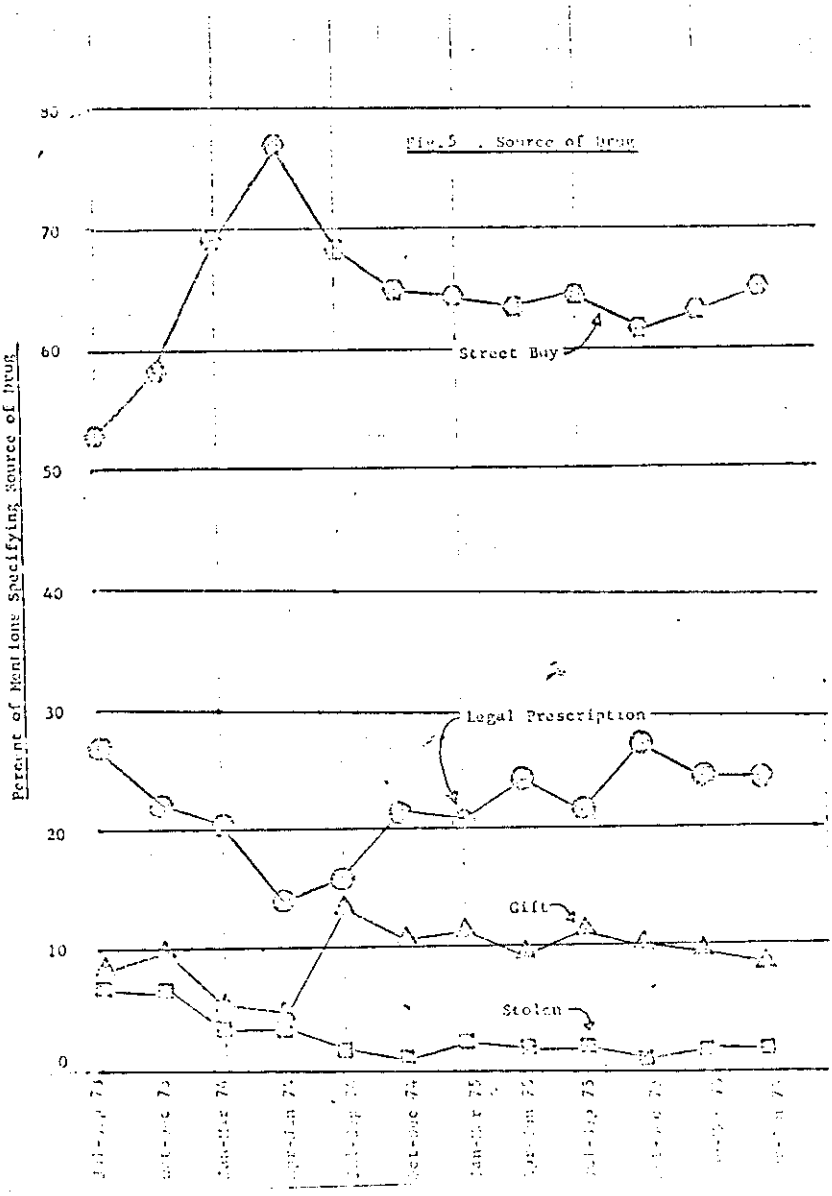
Fig. 5 . Source of Drug
Percent of Mentions Specifying Source of Drug
80
70
60
50
40
30
20
10
0
Street Buy
Legal Prescription
Gift
Stolen

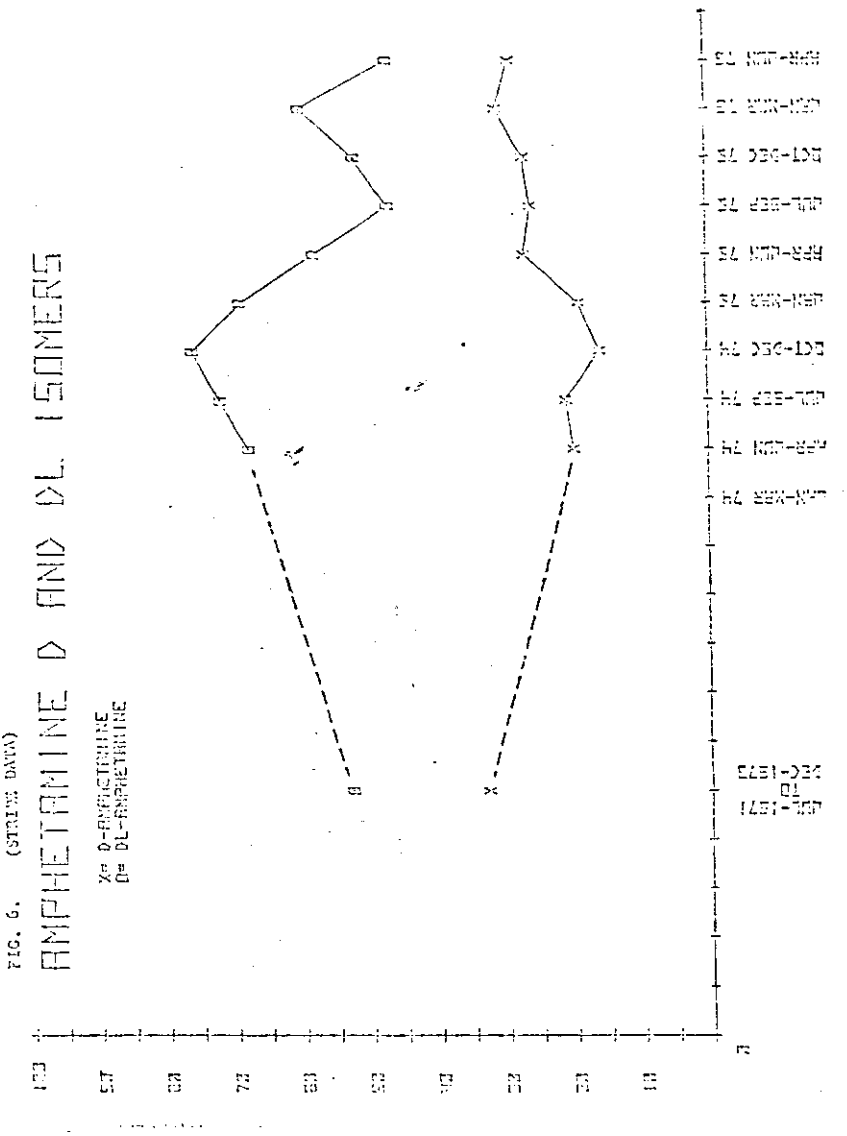

FIG. 6. (STATUS DATA)

TAB:

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AMPHETAMINE EPISODES REPORTED BY ALL DAWN FACILITIES
JULY 1, 1975-OCTOBER 31, 1976

ROWS = FACILITY TYPE COLUMNS = ROUTE OF ADMINISTRATION

		TOTAL	INJ-IV	INJ-SC	INJ-IM	OTH-INJ	INHALED	SMOKED	SNIFFED	MULTI ROUTE	OTHER	UNK NO ANS	KEY
EMERGENCY		6138	668	154	43	306	7	58	60	21	4	535	RAW
ROW %		82.737	6.791	0.153	0.437	3.111	0.071	0.590	0.610	0.020	0.041	5.439	RPR
		32.416	33.806	53.571	74.138	32.868	36.842	33.143	19.295	7.692	30.769	51.541	RPC
MEDICAL EXAMINER		199	26	1		5	1	1	11	11	1	43	RAW
		67.660	11.064			2.128			0.426	0.426		18.298	RPR
		0.933	1.316			0.537			0.322	3.846		4.151	RPC
OTHER		10808	1262	131	151	620	121	1171	2501	231	91	456	RAW
ROW %		85.724	6.538	0.064	0.377	3.162	0.061	0.597	1.275	0.117	0.046	2.336	RPR
COLUMN %		50.951	64.879	46.429	25.362	66.545	63.158	66.857	80.386	88.462	69.231	44.208	RPC
COLUMN TOTAL		251.5	1976	28	58	931	19	175	311	26	13	1036	RAW
		84.591	6.656	9.094	0.195	3.137	0.064	0.590	1.048	0.088	0.044	3.491	RPR
		100.000	100.000	100.000	100.000	100.000	100.000	100.000	100.000	100.000	100.000	100.000	RPC

TABLE

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14 DEC 14

AMPHETAMINE EPISODES REPORTED BY ALL DAWN FACILITIES
JULY 1, 1973-OCTOBER 31, 1976

ROWS = FACILITY TYPE

COLUMNS = ROUTE OF ADMINISTRATION

		ROW SUMS	KEY
	I		
EMERGENCY	I	9636	REA
ROOM	I	100.000	RPR
	I	55.142	RPC
	I		
MEDICAL	I	235	REA
EXAMINER	I	100.000	RPR
	I	0.742	RPC
	I		
CRISIS	I	19607	REA
CENTER	I	100.000	RPR
	I	44.066	RPC
	I		
COLUMN SUMS		29878	REA
		100.000	RPR
		100.000	RPC

TABLE

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14 DEC

AMPHETAMINE EPISODES REPORTED BY ALL DAWN FACILITIES
JULY 1, 1973-OCTOBER 31, 1976

ROWS = FACILITY TYPE COLUMNS = RACE

	WHITE	BLACK	OTHER	UNK NO ANS	ROW SUMS	KEY
EMERGENCY ROOM	7140	1355	329	1012	9836	RAW
	72.596	13.776	3.345	10.284	100.000	RPR
	32.879	44.587	45.638	24.072	33.142	RPC
MEDICAL EXAMINER	187	47	11		235	RAW
	79.574	20.000	4.681		100.000	RPR
	0.861	1.547	0.139		0.792	RPC
CLINIC CENTER	14389	1537	390	3191	19607	RAW
	73.387	6.349	1.989	16.275	100.000	RPR
	66.260	53.866	54.167	75.922	66.066	RPC
COLUMN SUMS	21716	3039	720	4203	29678	RAW
	73.172	10.240	2.426	14.162	100.000	RPR
	100.000	100.000	100.000	100.000	100.000	RPC

TABLE 1

14 DEC 197[illegible]

AMPHETAMINE EPISODES REPORTED BY ALL DAWN FACILITIES
JULY 1, 1973-OCTOBER 31, 1976

[illegible] FACILITY TYPE [illegible] MOTIVATION

	PSYCHIC EFFECTS	DEPEND	PSY-EFF DEPEND ME ONLY	SELF DEST	ROW SUMS	KEY
EMERGENCY ROOM	3452	1327		1872	6651	RAW
	51.902	19.952		28.146	100.000	RPR
	21.514	25.944		82.649	28.370	RPC
MEDICAL EXAMINER	42	27	27	35	131	RAW
	32.061	20.611	20.611	26.718	100.000	RPR
	[illegible]	0.529	100.000	1.545	0.559	RPC
CRISIS CENTER	12551	3753		358	16662	RAW
	75.327	22.524		2.149	100.000	RPR
	78.224	73.427		15.806	71.071	RPC
COLUMN SUMS	16045	5107	27	2265	23444	RAW
	68.440	21.784	0.115	9.661	100.000	RPR
	100.000	100.000	100.000	100.000	100.000	RPC

Motiv
Other
Unknown
No Answer

ER = 3185
ME = 94
CC = 2945
6234

ANTIOBESITY DRUGS—GENERAL

MEMORANDUM

FEBRUARY 5, 1964.

To: Ralph C. Smith, M.D., Acting Medical Director.
From: Robert O. Knox, M.D., Medical Officer.
Subject: Drugs or classes of drugs in which there is a particular question of salary or lack of efficacy.

1. There is serious doubt as to the efficacy of the anorexigenic drugs in general n the treatment of obesity. (Ref: JAIA July 9, 1964, Vol. 175, pp. 1131–1135). According to one report, only 2% accomplish a long-term reduction in weight. Most of the reports claiming efficacy are based on short-term studies, and demonstrate only a few pounds of weight loss.

2. There is also serious doubt as to the efficacy of the peripheral vaso-dilator drugs in the treatment of intermittent claudication. Most workrs feel that they are of little benefit, and there are reports of an actual decrease of blood flow to the muscle, coupled with the danger of hypetension due to cutaneous vaso-dilation.

MEMORANDUM

JULY 28, 1967.

To: Merle L. Gibson, M.D., Acting Director, Division of Neuropharmacological Drugs.
From: Robert O. Knox, M.D., Medical Officer, Division of Neuropharmacological Drugs.
Subject: The need to improve the present package inserts for the "Anorexigenic" drugs.

1. Despite much evidence attesting to the relative ineffectiveness of these, or any other compounds, in the treatment of obesity, numerous preparations are widely distributed and represented to be effective agents.

2. It appears advisable at this time to revise the present package inserts (and thereby the advertising) for these drugs including those already on the market to reflect more accurately the true situation.

3. Attached is a rough draft of a tentative package insert which may serve as a basis for further discussion. It would seem advisable to invite representatives from Drug Surveillance to discuss this matter with us so that we may arrive at a consensus. Several attempts have already been made to accomplish this, but frequent changes in staff have prevented any definitive step being taken.

MEMORANDUM

MAY 19, 1969.

To: Merle L. Gil son, M.D., Director, Division of Neuropharmacological Drugs.
From: Robert O. Knox, M.D., Division of Neuropharamacological Drugs.
Subject: Establishment of an FDA policy regarding anorexigenics.

1. During 1969, the NAS/NRC panels have evaluated various sympathomimetic amines used in the treatment of obesity. For example, phentermine and a phenmetrazine preparation were evaluated as "Effective, but . . ." by the panel on Psychiatric Drugs. A minority of two of the panel members evaluated the sympathomimetic stimulants as "probably effective." The documentation appended to their opinions consist of four references: (a) The first by J. F. Fazekas which discusses various concepts in therapy using anorexigenic agents, but has no actual clinical data. (b) The second is a 1947 article in the AMA by Harris, Ivy, and Searle using Dexedrine. However, there were only seven obese subjects used in two separate four-week periods during which the dose of the drug was progressively increased. The second experiments concerned ten volunteer medical students of normal weight. (c) The third article by Kinard et al. has to do with the use of d-amphetamine in patients on reserpine therapy. (d) The fourth reference is to Harrison's text book of Internal Medicine which of course contains no actual raw data.

2. On November 20, 1968, the Council of the British Medical Association forwarded a report to the Interdepartmental Standing Advisory Committee on drug dependence which contained the following recommendations:

"That amphetamines and amphetamine-like compounds should only be prescribed for those conditions for which no reasonable alternative exists, or as part of the therapy of those patients already dependent on those drugs; more specifically:

(i) These drugs should be avoided so far as possible in the treatment of obesity, but if in individual cases the doctor feels they must be used they should be prescribed for a limited period only . . ."

The report further recommended that ". . . manufacturers, pharmacists, nurses, and doctors should voluntarily take the same precautions, and keep the same records, as they already do for those drugs covered by Part 1 of the Schedule of the Dangerous Drugs Act, 1965." and . . . "that if the voluntary measures of control recommended do not succeed than restrictive legislation seems inevitable. . . ."

3. According to the Report of the 23rd Session of the Commission on Narcotic Drugs of the United Nations Economics and Social Council, dated February 24, 1969, the Government of Sweden asked that amphetamine, dexamphetamine, methamphetamine, methylphenidate, phenmetrazine and pipradol be controlled in terms of Article 3 of the 1961 Convention which has to do with narcotics.

"While there were different opinions in the Commission as to the applicability of the 1961 Convention to the amphetamine-like or any other psychotropic substance, there was conmplete unanimity that the problem of the abuse of the amphetamine-like substances raised by Sweden was indeed a most serious problem."

"The amphetamine-like substances, especially phenmetrazine to which he had referred were taken by some 5,000 to 10,000 persons, especially youths by intravenous injections. . . ."

The Swedish representative "wished to record that this experience of intravenous abuse of certain amphetamine-like substances thus created physical dependence with an abstinence syndrome contrary to the description of other dependence of amphetamine-like substances described by the WHO Committee in their 13th Report."

The unanimously approved resolution of the 24-Nation body declared that abuse of amphetamine-type drugs presents a grave danger both to individuals and to society and that immediate action is necessary to combat this threat to the health of mankind.

According to the Hospital Tribune of March 10, 1969, "Supporting Sweden's appeal for urgent action, D. P. Anand, representing India, said he believed the world was confronting a greater danger through psychotropic drugs than it had with regard to traditional narcotics. He observed that many agricultural countries have accepted controls over such crops as opium, hashish, and coca, making economic sacrifices to do so.

'Is it too much,' he asked, 'to expect that the manufacturing countries will show the same magnanimity as the opium-producing countries, which have risen above their own narrow interests by accepting controls?'

4. As regards the efficacy of the sympathomimetic amines in the treatment of obestiy, it should be noted that contrary to numerous articles appearing in the literature, the efficacy of these compounds is of a very small order. For example, in the case of NDA 16-618, for fenfluramine, the sponsor chooses to indicate the results in terms of average weight loss per week. This is merely a device for observing the fact that the actual pounds of weight loss by patients on fenfluramine averaged in most studies less than five pounds.

It should be noted that most studies submitted to the FDA for anorexigenic compounds run for only a month or two. It is well established that the initial enthusiasm plus the initial impact of a sympathomimetic amine may result in a weight loss during the first few weeks of therapy, but that shortly thereafter tolerance develops, enthusiasm wanes, and weight loss ceases. Indeed, in a large percentage of cases, the weight returns to the previous pre-treatment weight.

In view of the above, it may prove worthwhile: (a) To request the NAS/NRC panels to define their criteria of effectiveness. (b) To consider banning these substances entirely as Sweden has already done. (c) Alternatively, to insist on a package insert and advertising which reveals the actual total pounds of weight lost and the duration of therapy, in tabulated fashion.

ROBERT O. KNOX, M.D.
Division of Neuropharmacological Drugs.

MEMORANDUM

NOVEMBER 18, 1969.

To: John Jennings, M.D., Acting Director, Bureau of Medicine.
From: Robert O. Knox, M.D., DND/OND/MED.
Subject: Pending class labeling for anorexigenics.

I would like to draw your attention to the fact that there is now pending a class labeling for anorexigenics. This class labeling is under consideration for publication in the Federal Register in the near future. This labeling may lead the physician to erroneously conclude that anorexigenics are more effective than they actually are. The labeling of these drugs in the past has been misleading as far as efficacy is concerned. Would it not be desirable to include in the class labeling a factual statement as to the actual amount of weight loss achieved in the studies submitted in support of any given NDA?

The promotion of Pro-Sate is typical in that it gives results in terms of the amount of weight loss *per week* without giving any idea of the total number of pounds lost or the duration of treatment. Most of the studies submitted in behalf of anorexigenics run from one to two months or less. The dissenting minority opinion of the NRC/NAS panel evaluated the sympatho-mimetic stimulants as "probably effective" as anorexiants. Their reasoning for the "probably effective" evaluation was that:

(a) Most studies of the preparations have been for short periods;

(b) There is no available evidence that the use of these anorexiant preparations alters the natural history of obesity;

(c) There is some evidence that anorectic effects may be strongly influenced by the suggestibility of the patient, and

(d) There are reservations about the adequacy of the controls in some of the clinical studies. The minority suggested that controlled studies on the long-term anorectic efficacy of the sympatho-mimetic stimulants be conducted.

Although there may be no precedent for this type of package insert, these drugs fall into a special category as far as efficacy and abuse are concerned.

Enclosed is a copy of my memorandum dated May 19, 1969 concerning the establishment of an FDA policy regarding anorexigenics.

MEMORANDUM

FEBRUARY 17, 1970.

To: John Jennings, M.D., Acting Director, Bureau of Medicine.
From: Robert O. Knox, M.D., DND/OND, MD 120.
Subject: Position paper on FDA policy concerning the labeling of amphetamines and amphetamine-like compounds.

References.—(1) My memo to Dr. Gibson dated May 10, 1969. (2) My memo to Dr. Jennings dated November 18, 1969.

1. I discussed labeling for the amphetamines with representatives of the Office of Marketed Drugs; however, we were unable to agree on the proper wording for the package inserts for these drugs.

2. Therefore, I am summarizing my thoughts on this matter as follows:

A. It is generally agreed that there is a definite danger of abuse connected with the use of these drugs.

B. While there is no unanimity of opinion as to the efficacy of these drugs, the following opinions merit careful consideration:

(a) The British Medical Association has concluded that "These drugs should be avoided so far as possible in the treatment of obesity . . ."

(b) Arthur Grollman has stated that ". . . There is no evidence to indicate that these agents suppress appetite as has been claimed, which is the basis usually for advocating their use. The only rationale for their use is the hope that by counteracting the depression induced by hunger the patient is better able to abstain from overeating. However, the anorexigenic agents have proven of little efficacy in actual practice . . ." (Pharmacology & Therapeutics. Lea and Febiger, 1965.)

(c) Feinstein, A. R., J. Chr. Dis. 11:349–389, No. 4, April 1960. ". . . The results obtained with anorexiant agents therefore (1) are in many instances inferior to those obtained with unsupplemented diets, (2) show the same marked variations present in the tabulated results of diet alone, and (3)

indicate that the newer agents often compared poorly with the older ones whose deficiencies they presumably were intended to correct." ". . . The variety and inconsistency of these results indicate that many nutritional, pharmaceutical, and other theories of weight reduction have not been clinically verified and appear to be the result of fallacious reasoning. In the absence of confirmatory controlled studies and with inadequate techniques for measuring accomplishment, 'successful' performances in weight reduction have been attributed only to features of the diet or dietary adjuncts. Whenever complete results have been given for dietary programs, the data have shown that more patients fail then succeed."

(d) Nutrition Reviews, Vol. 20, No. 2, p. 38, February 1952. "The point which seems to have been almost forgotten in these reviews and reports is that people become and remain obese for a reason. The balance between appetite and requirement is upset by something else, perhaps frustration, boredom or disappointment. This is the reason why diets, drugs, and exercises are relatively ineffective in so many obese persons. Why then should physicians attempt to correct obesity? If not for cosmetic or social reasons, should they do so because obesity shortens life expectancy, hastens the onset of cardiovascular disease, and favors the development of diabetes? Success can be achieved only when the condition for which weight reduction is advised is more serious than the urge which causes the obesity. It seems illogical for physicians to prescribe sympathomimetic drugs which may in themselves cause as much 'stress' in the long run as does the obesity itself . . ."

(e) Edison, George R., M.D., in a letter to Congressman Claude Pepper, dated November 3, 1969. ". . . I stand with a majority of physicians in feeling that these drugs no longer have any place in the practice of medicine, with one or two rare exceptions. I made this proposal in a letter published in the Journal of the American Medical Association over a year ago, a copy of which I am enclosing for your interest.

"I understand that one or two other countries have actually banned the use of these highly dangerous drugs. There is no justification for our continuing their 'legal' use. To continue it would be simply to perpetuate one more massive inconsistency in our standards of morality."

(f) Wolff, Frederick, Research Director at the Washington Hospital Center and Head of George Washington University Clinical Pharmacology Division, testified at a drug price hearing on September 13, 1967. The following statement was quoted in FDC Report of September 18, 1967: "In the only questioning about specific drugs and drug classes, Wolff said that on the whole appetite suppressants which he described as a $100 million a year market, are 'totally unnecessary.' They are grossly over-prescribed, have a very limited use, and on the whole, probably do more harm than good he said."

C. The majority opinion of the National Research Council panel which acted upon the amphetamines declared them to be effective. The NRC has not set forth their criteria for efficacy, but they have given certain bibliographic references. I have previously discussed in paragraph I of my memo of May 19, 1969 the inadequacies of these references. Leo Cass was also cited by them as an authority despite the fact that FDA had previously declared Dr. Cass to be an unacceptable investigator.

3. According to NDA 16-618 (fenfluramine) the weight loss averaged in most studies less than 5 lbs.

4. According to NDA 16-880 (chlortermine), the weight loss ranged from: 0.5 lbs. less than to 4.5 lbs. more than with placebo. The average difference in weight loss in these studies was 2.5 lbs. more with chlortermine than with placebo, for the 4 to 8 weeks for which these studies were run. (These figures represent the total amount of weight loss, not the weekly rate of loss.) In four Phase II studies, the average difference between Pre-Sate and chlortermine was 0.6 lbs., in favor of Pre-Sate.

5. In addition to the fact that the above amounts of weight loss the of dubious clinical significance, there are numerous discrepancies in many of the laboratory values and the case report forms of the NDAs which I have reviewed.

CONCLUSIONS

1. The present labeling fails to give the physician any idea of the degree of efficacy which has been demonstrated in the NDAs for these compounds. It is unlikely that anyone reading the present labeling would suspect that the support-

ing data in the NDAs revealed such a limited degree of efficacy. Although we customarily do not include such information in package inserts, the amphetamines constitute a special case and must be dealt with accordingly.

2. I urge that the labeling of these compounds be revised to include, in each case, a factual tabulation of the actual amounts of weight loss which have been reported by the various investigators, to include the duration of therapy, so that the physician will be in a better position to decide as to whether or not use of a sympthomimetic amine is warranted. The common practice of expressing results in terms of rate of weight loss per week is particularly objectionable and should be discontinued.

3. The duration of therapy to be recommended in the package insert is very important. Various recommendations have been made, e.g.:

a. Use short-term therapy as initial treatment only, with the purpose of re-educating the patient's eating habits, etc.

b. Use long-term therapy in spite of the fact that tolerance is known to develop to the sympathomimetic amines.

c. Use intermittent therapy so as to allow the patient an opportunity to regain sensitivity to the drug.

Only limited results have been demonstrated with the first two methods, and the third method is merely a variation of the second. I suggest that unless long-term therapy can be demonstrated in controlled trials to be significantly effective, only short-term therapy be allowed. The development of tolerance figures prominently in this decision.

4. NDAs which are now under review in the OND pertaining to antiobesity drugs should not be approved unless:

(1) a clinically significant amount of weight loss is shown by controlled trials, and

(2) the package insert conforms to the above suggestions.

MEMORANDUM

APRIL 8, 1970.

To: John J. Jennings, M.D., Acting Director, Bureau of Drugs.
From: Robert O. Knox, M.D.
Subject: A suggested tabulation of therapeutic results to be incorporated into the package insert of a sympathomimetric amine.

1. In accordance with your request of March 24, 1970, for an example of a tabulation that could be incorporated into the package insert of a sympathomimetic amine in order to present the physician with some quantitative results which had been demonstrated by the investigators, the attached model is submitted for preliminary consideration.

2. Some of the points shown by this tabulation are:

(a) the almost total lack of a dose-response relationship.

(b) the fact that most of the studies reveal less than 5 lbs. of total net weight loss.

(c) Dr. Hollingsworth reports greater weight loss following placebo than most of the other investigators reported with fenfluramine—even using the high dose of 120 mg. per day. His results largely depended on whether fenfluramine or placebo was given first.

3. Some relevant excerpts from "Drugs of Choice" by Walter Modell, M.D., The C.V. Mosby Co., 1970, are appended:

"The long-term results of anorexiant therapy are very poor at present. . . . an anorectic agent is likely to have as little effect on the overall problem of obesity as disulfiram (Antabuse) has had on the overall control of alcoholism. . . . none of the anorexiants are effective unless food intake is controlled as well; hence, it is obvious they really are not very effective against this force."

". . . even when the double-blind technique is used to start, after 30 minutes some patients know which is medication and which is placebo, and only the physician remains blind. All the psychic impact of the knowledge that an effective drug is being taken is thus exerted in favor of the drug being tested. From this point of view, therefore, a difference between the effects of the placebo and the drug in these studies may well result from the detection of this difference by the patient as well as from the action of the drug itself."

". . . it is by no means definite that these drugs have any primary effect on appetite at all."

NDA 16-618, PONDEREX, A. H. ROBINS CO., INC.

Investigator	Average total weight loss, pounds: Fenfluramine	Average total weight loss, pounds: Placebo	Net weight loss, pounds	Duration, weeks	Dose, milligram per day	Fenfluramine patients completing the study
Adult:						
1. Hollingsworth [1]	13.8	2.9	15.9	8	120	14
2. Roginsky	14.1	4.4	9.7	12	60	28
3. Roginsky	11.2	4.4	6.8	12	40	27
4. Hollingsworth [2]	7.6	12.8	+3.2	8	120	10
5. Roginsky	7.0	4.0	4.0	12	80	30
6. Fisch	4.8	.3	4.5	4	60	15
7. Rosenberg	4.7	1.7	3.0	1-12	120	29
8. Rosenberg	3.6	1.7	1.9	4-8	60	
9. Stern	3.0	.4	2.6	8	80	20
10. Fisch	2.6	.3	2.3	4	120	14
11. O'Hen	Ineffective			2	40	12
Pediatric:						
12. Andersen	5.7	+.7		3	90	20
13. Bacon [1]	4.8	+.7	3.5	4	20-60	
14. Bacon [2]	2.2	+.7	2.9	4	20-60	20

[1] Crossover, giving fenfluramine first.
[2] Crossover, giving placebo first.

MEMORANDUM

APRIL 9, 1971.

To: Barrett Scoville, M.D., Deputy Director.
From: Robert Knox, M.D.
Subject: Notes on the panel discussion on anorexic drugs held April 6, 1971.

SUMMARY

Dr. Prout, Chairman	Dr Reidenberg
Dr. Goldberg	Dr. Rogers
Dr. Crowell	Dr. Hollingsworth
Dr. Christakis	Dr. Herting, Abbott Labs
Dr. Bray	Dr. Scoville

Dr. Prout reviewed the agenda which had been previously distributed by the FDA, and then called on Dr. Herting to present the industry's view of the matter. Dr. Herting discussed the pharmacology of the amphetamines and their clinical uses. He stated that there does seem to be some definite evidence for the fact that the value of an appetite suppressant is that it gives you about two times the rate of weight loss that diet alone does. That seems to hold up whether you give placebo or not. The duration of these studies was 12 weeks up to 20 weeks; 24 weeks was about the longest but it didn't have placebo. Intermittent and continuous treatment were compared with Tenuate Dospan being used. The actual total weight loss on intermittent was a little greater—but the continuous therapy actually did a little better (sic). Regarding tolerance, he said that there is some evidence that at least it is not a 2–3 week effect. In the literature, a really good program reaches 85 percent of target weight in females in a 12-week period, and 37 percent of the placebo groups arrived at a desired weight loss at the end of the 12 weeks. Males 50–55 percent with drugs; 25 percent with placebo. (When questioned by Dr. Prout as to what constituted "target weight," Dr. Herting replied that in general the target weight was the "Ideal weight as listed in the Metropolitan Tables.) There is little or nothing to prove the long-term efficacy of these drugs. The suspicion is that most of the patients are fat again. The question is whether they would have been fatter without the drugs. Dr. Herting went on to compare the situation to that of the anti-coagulants—does the drug have to be proven to do any real good?

Dr. Prout stated that you obviously can't ask the drug ot do anything in the long range. He asked Dr. Herting to sent a copy of his bibliography to Dr. Scoville (this was in relation to Dr. Herting's claim that 55 percent of ideal weight had been achieved using these drugs for 12 week). Dr. Reidenberg pointed out the importance of realizing the obese patients, are terribly hetrogeneous as to their characteristics, and said we should define the groups in which

it works. He asked how important is the euphoric effect; and went on to say that a certain number are depressed and therefore an anti-depressant drug would be better.

Dr. Hollingsworth seconded Dr. Reidenberg's comment and said that it is vital we know more about CNS effects, nor-epinephrine, growth hormone, insulin . . . we ought to start with animal models. She then said that a large group of obese are never hungry—how then can you evaluate an anorxigenic in these patients? . . . polydipsia is very common on the other hand . . . I have not been able to rationalize placing fat children on drugs.

Dr. Prout then stated that we accept the potential value of these drugs. He next said that it is very important to avoid bias on the part of the person who analyzes the data (this remark seemed to be directed at the statistics). The panel agreed that patients should be at least 20 percent over the Metropolitan ideal weights to be included in a study.

Dr. Goldberg said that we must exclude hypertensives if Phase 1 data suggest that the drug be contraindicated.

Dr. Brey voiced the opinion that of course there are standard reference drugs which are effective. Dr. Reidenberg replied that Dr. Henry Simmons had just indicated that efficacy had not been conclusively demonstrated for any of these drugs.

Dr. Christakis made a plea for caution and responsibility on the part of the profession—the burden is on industry—in view of the great potential for harm from these drugs.

Dr. Prout felt that 12 weeks was the minimum duration of therapy with these drugs that would provide meaningful data. Dr. Bray felt that 6–8 weeks was enough. Dr. Hollingsworth pointed out that obesity was a life-long disease. Dr. Goldberg said that the number of weeks should be put in the package insert.

Dr. Knox then asked Dr. Prout how efficacy could be defined. The reply was that the Federal Register contained the statement that these drugs have short-term efficacy and therefore the Panel could not consider the question as to whether there was a medical significance involved, in other words we must accept any statistically significant difference as acceptable evidence of efficacy. (Dr. Prout followed up by saying that in his opinion none of these drugs were of any value and that he would not use them).

MEMORANDUM

APRIL 12, 1971.

To: Henry E. Simmons, Director, Bureau of Drugs, BD–1.
From: Barrett Scoville, M.D., Deputy Director, DNDP, BD–120.
Subject: Brief abstract of meeting of advisory group on the drug treatment of obesity, April 6, 1971.

A group of consultants with a special interest or experience in the drug treatment of obesity convened on April 6 for a one-day discussion of the questions in the attached agenda.

The conclusions of the group as expressed by the chairman, Dr. Prout appeared to be essentially the following:

1. Anorectic agents are potentially of value.

2. Long-term follow-up in respect to drug efficacy of patients who have lost weight on a regimen involving Anorectic drugs is not the responsibility of drug manufacturing firms. A short term follow-up of a few weeks could reasonably be asked of drug manufactures.

3. Efficacy of anorectic agents should depend on the demonstration of statistical superiority of drug to placebo. The group, through its chairman, explicitly declined to require "biological" superiority, e.g., some minimum loss in terms of percentage of excess weight.

4. A minimum duration for efficacy trials of 12 weeks was proposed. Labeling claims should reflect the duration of trials.

5. A number of changes in details of the PMA version of second-draft guidelines were proposed. The long "philosophical" discussion of various criteria of efficacy on pp. 11–17 was excluded from discussion.

NOTE.—In view of the long-range implications of the group's conclusions for trials of anorectic agents, particularly insofar as they may relax efficacy criteria,

I believe the conclusions should be discussed within FDA before any possible uncritical release of them to the public.

BARRETT SCOVILLE, M.D.,
Deputy Director,
Division of Neuropharmacological Drug Products,
Office of Scientific Evaluation, Bureau of Drugs.

Those present at meeting: George J. Christakis, M.D.; Edward P. Crowell, D.C.; Leon I. Goldberg, Ph. D., M.D.; Dorothy Hollingsworth, M.D.; Daniel M. Rogers, M.D.; Thaddeus E. Prout, M.D.; Marcus Reidenberg, M.D.; George Bray, M.D.; Robert Herting, M.D., Ph. D.; and Barrett Scoville, M.D.

MEMORANDUM

APRIL 19, 1971.

To: Dr. Marion Finkel, Department Director, Bureau of Drugs.
From: Leszek Ochota, M.D., D. Sc., DNPDP.
Subject: IND 420 for Stimsen (thozalinone) Lederle Labs. Dr. Finkel's memo of April 8, 1971.

SUMMARY

Dr. Finkel: Since you may have been possibly misinformed about the discussion of the guidelines for antiobesity agents by the Committee that met at the FDA on April 6, 1971, I would like to call your attention to the following facts:

The Chairman of the Committee, Dr. Thaddeus Prout rather forcefully proposed a minimum of 12 weeks for the study of the anorexigenic agents, with additional 2 weeks for "followup".

While other members of the Committee did not comment on this problem, I did amplify Dr. Bray's position by citing several unpublished, well controlled studies which showed that adequate decision as to the effectiveness may be made after 4 to 8 weeks of study.

N.B: I personally believe that there is no scientific rational for the 12-week studies of the antiobesity agents, and agree with Dr. Bray that 4 to 8 weeks studies are entirely satisfactory.

LESZEK OCHOTA, M.D., D. Sc.,
Supervisor, Medical Office,
Division of Neuropharmacological Drug Products.

MEMORANDUM

SEPTEMBER 22, 1971.

To: The Commissioner.
From: Henry E. Simmons, M.D., M.P.H., Director, Bureau of Drugs.
Subject: Neuropharmacology Advisory Committee Meeting, September 13–14, 1971.

PURPOSE

The following is an abstract of the issues considered and the recommendations made by the Neuropharmacology Advisory Committee at their meeting on September 13–14, 1971.

TEXT OF THE INFORMATION

A. Parafon Forte I and Paraflex

1. The firms can make only these claims for which they have shown sufficient data. It was generally agreed that Parafon showed statistical superiority over placebo with respect to low-back pain; however, there was lack of evidence that the improvement was due to a specific muscle relaxant effect.

2. Other suggestions to be communicated to the firm include:

a. Evaluation of these drugs with standard treatments (sedatives and analgesics).

b. Testing of other specific syndromes (cervical pain, etc.).

c. Optimization of dosage schedules and correlation with blood levels.

d. There should be continued efforts for definition of criteria for improvement.

e. Relationships between statistical significance and clinical significance should be clearly defined.

B. Navane

1. NDA's need to be more adequately organized and the data better documented.
2. It was suggested that Dr. Mitchell Balter (NIMH) be invited to the next considering efficacy based on the material available to the committee members.
3. All medical officer's reviews should be standardized. A sample is to be presented to the Committee prior to the next meeting.

C. Class labeling

1. Committee members were not in total agreement that psychoactive drugs should not be used for stresses of everyday life in non-diagnosis patients. Data at this time, however, is not available. It was the opinion of some of the Committee members that advertising for a psychoactive drug should promote the drug only for symptomatic relief of anxiety in medically or psychiatrically diagnosed disorders. Mr. Jerome Levine (NIMH) is to investigate possibilities for implementing research in the area of psychotronic drugs used for the relief of symptoms produced by everyday stresses.
2. It was suggested that Dr. Mitchell Walter (NIMH) be invited to the next Committee meeting for discussions of his findings concerning the patterns of use of psychoactive drugs.

D. Hydergine

1. The Committee did not vote as to whether or not the submission would be considered acceptable since they had not reviewed the actual data.
2. It was suggested that definite benefits could be derived from appointing a Task Force which would consider the development of geriatric scales (standard) and in establishing criteria for the evaluation of studies in the geriatric population.

E. Anorexigenic agents

1. The length of time for testing such agents should be at least 12 weeks.
2. Criteria have been proposed by a previous committee with expertise in the use of such agents. If data show that such agents are effective in obesity, the Neuropharmacology Advisory Committee will become involved in discussions regarding possible abuse potential.

F. Conflict of interest

1. The Members of the Committee expressed a concern in this area since most, if not all, have been or are involved in consulting with or conducting trials for various drug firms. They wish to the appraised of the legal responsibilities and implications.
2. This topic is to be placed on the next Agenda and specific standards for procedure will be proposed.

G. Review of "possibly effective" drugs

The Committee was generally in favor of Dr. Finkel's discussion of the proposal that Committee members (or Junior Staff) be actively involved in the evaluation of such drugs.

THE FDA REVIEW OF ANORECTIC DRUGS: BACKGROUND, CURRENT STATUS, AND PROBLEM AREAS

(Presented by Barrett Scoville, M.D., Deputy Director and Elmer A. Gardner, M.D., Director, Division of Neuropharmacological Drug Products, Food and Drug Administration, as part of the symposium: "Drugs and the Control of Overweight: Medical Considerations and Public Policy," June 12, 1972, Washington Hilton Hotel, Washington, D.C.)

The Food and Drug Administration is intensely interested in the discussions of this symposium and appreciates both the efforts that have gone into it and the opportunity to exchange ideas with other discussants. This is a time at which policy in respect to the use of anorectic drugs is being formulated, and we are seeking as much input as possible.

The title of the symposium summarizes the issue, which is one not just of a medical decision but one of public policy. It is a particularly difficult area, in which facts and value judgments are often unwittingly confused. Obesity, almost alone among the pathological conditions, remains a moral issue in many people's eyes, as Jean Mayer regretfully noted. It is regarded with the severity

of a sin, rather than with the humility which would be appropriate to a condition the causes of which are poorly known and the treatment of which is difficult. As if that weren't enough, the drugs proposed for treatment almost all involve a set of moral issues of their own, those associated with drug abuse.

In preparing broad policy on the use of anorectic drugs we have been reviewing questions associated with them quite intensively since late last fall, through a project of which I have been the manager and Dr. Gardner the chief adviser, and of which I will tell you more later.

The questions underlying the discussions here are not new, and you may wonder what leads FDA to review the question of anorectics at this time. Broad national concern for drug abuse, including CNS stimulant drug abuse, lies behind many of the questions, but there are four relatively recent elements which have made more acute the need for broad policy.

The first factor was the Drug Efficacy Study. In this study the National Academy of Science/National Research Council and FDA reviewed the status of all drugs—approximately 3000—which were first marketed between 1938 and the passage of the Kefauver-Harris amendments to the Food Drug and Cosmetic Act in 1962. These 3000 drugs included all marketed anorectic agents except one (Pre-Sate or chlorphentermine). The NAS/NRC Panels expressed qualifications as to efficacy of anorectics so that the FDA publications on anorectics to date have indicated them to be less than effective, requiring more evidence in the form of clinical trials. Such evidence has been submitted, and I'll come to that later.

As a corollary of the NAS/NRC review, FDA also reviewed the status of the amphetamines and concluded that they, too, were affected. Amphetamine manufacturers responded in 1971 and 1972 to an FDA announcement to this effect with applications to continue marketing 106 amphetamine drug products.

The need to review the 106 amphetamine applications and other material submitted in the context of the Drug Efficacy Study was the first element leading to our project. A second involved applications for drugs not yet on the market. Within the last year and a half, 3 major manufacturers have requested approval for marketing of anorectic agents which they had been investigating, and of course decisions are required here consistent with any policy relevant to anorectics subject to the Drug Efficacy Study.

The third and fourth elements requiring policy towards anorectics involve drug abuse, with its many medical, social, and legislative implications. The problems of drug abuse led in October, 1970 to the passage of the Comprehensive Drug Abuse Prevention and Control Act. This Act, also known as the Controlled Substances Act, vests a number of responsibilities in the Department of Health, Education and Welfare; two are of particular concern to FDA in respect to anorectics. One is the need to determine the degree of control under the various schedules of the Act appropriate to any drugs with abuse potential or which are abused. More control has been considered necessary for oral methamphetamine, the other amphetamines, and phenmetrazine, for example, and they have now been placed under the restrictions of Schedule II. The remaining anorectics are not controlled under any schedule, and it has been proposed by some that amphetamine congeners like diethylpropion and benzphetamine have abuse potential, too, so that their use should also be restricted. The Secretary of HEW bears fundamental responsibilities in respect to scheduling drugs, and within HEW, FDA plays a leading role in advising the Secretary.

The last major element which has led to the current review of anorectic efficacy is another new responsibility stemming from the Comprehensive Drug Abuse Act. This is the Secretary of HEW's new responsibility to report to the Department of Justice on the legitimate medical and scientific needs in the U.S. for drugs controlled in Schedule II. This means specifically how much amphetamine, methamphetamine, and phenmetrazine is needed each year in the legitimate treatment of obesity. Within the Department of Justice, the Bureau of Narcotics and Dangerous Drugs relies heavily on HEW estimates of medical need in establishing quotas for the amounts of these drugs which may be manufactured each year.

So, to summarize, the efficacy review of older anorectic drugs, the review of applications to market new entities, the responsibility to determine appropriate control schedules for abusable drugs, and the responsibility to estimate medical needs for anorectics have been the four major immediate elements leading to our present work to define more clearly and consistently the place of anti-obesity drugs.

In reviewing the place of anorectic agents in the treatment of obesity, we decided to review the entire therapeutic class. Here are the drugs involved, by generic name (Slide). The list begins with the various amphetamines and Preludin, goes through marketed congeners of the amphetamines of which many practitioners are unaware—Plegine, Didrex, Ionamin, Tenuate, and Pre-Sate—, includes three non-marketed compounds, some of which may be different from the amphetamines,—and ends with a drug at one time marketed over-the-counter for weight control, phenylpropanolamine.

We have looked at the class as a whole for several reasons. One reason might be called intellectual and administrative consistency, that is, that comparable drugs be evaluated in a similar way. But the most important reason involves abuse of these drugs. The abuse potential of the amphetamine and phenmetrazine has been relatively well defined, particularly by events here, in Sweden and Japan. The abuse potential of the lesser known compounds is much more poorly defined. But we believe it should be considered carefully across the board, lest an action decreasing the availability of certain drugs merely lead to the abuse of others, in the way that restrictions on the amphetamines in Sweden appeared to lead to abuse of phenmetrazine and methylphenidate (Slide 2). Here are the prescriptions written for antiobesity agents. The profound drop in amphetamine prescribing represents the impact of the placing of these drugs in Schedule II of the Comprehensive Drug Abuse Act, with its requirements that prescriptions be non-refillable and that separate records be kept. We are watching the prescribing rates for amphetamine cogeners, which are here combined. Will some of them merely replace the amphetamines in the legitimate treatment of the obese—or will their use become characterized by the excesses associated with the abuse of amphetamines?

There appear to us to be a number of options for action in respect to anorectic drugs. They involve removal of drugs, relabeling drugs, rescheduling them, recommending quotas, and requesting further tests. In more detail, the options are as follows:

1. It is conceivable that the amphetamines or other anorectics might be removed totally from the market. The practitioner would then be obligated to use alternative drugs or diet alone in treating the obese. In this respect we see little place for the use of parenteral amphetamines, and at this moment have some doubt about the oral amphetamines when suitable alternatives appear available.

2. The amphetamines and other anorectics might be relabeled in a consistent fashion indicating use only in certain patients, for example those refractory to other regimens or otherwise characterized, or only under certain conditions, for example, only after a brief trial in which the patient is observed to lose weight. The amount of weight loss to be expected and a reasonable duration of therapy might also be indicated.

3. The congeners of amphetamines might be placed in Schedule III or Schedule II of the Drug Abuse Act. Schedule III serves chiefly to alert prescribers to abuse potential; drugs in Schedule II are under fairly severe restrictions referred to previously.

4. Quotas might be imposed on the production of anorectic drugs to decrease their availability for abuse and diversion. At present quotas may only be set for drugs in Schedule II.

5. Further testing, both for clinical efficacy and for potential to induce dependence, might be required for some or all anoretic agents. In respect to abuse potential, drugs might be scheduled in Schedule III or II pending results of studies. A prominent problem here is the uncertain predictive value of even the most promising tests, the self-administration studies in primates.

As you all know, data on which to base a rational choice among these options or against them vary also in quality and quantity for different drugs. For some of the most important questions they may be almost lacking.

In particular, there are unanswered questions as to clinical efficacy and as to abuse potential, and we have concentrated our efforts on these questions. In respect to efficacy, the most important is that of how the pharmacologic effect of anorectic drugs is translated into clinical terms. Weight loss is the chief desideratum. But how much, expressed in what terms, at what rate, for how long? And in what percentage of obese subjects, and what are the characteristics of those who lose? For how long should the drugs be tried before the drug is considered a failure? Given answers to some of those questions, can the different drugs be distinguished one from another, or ranked in terms of efficiency? Are

amphetamines more effective in more people than newer congeners—or could they be replaced by these congeners?

The FDA has in the form of new drug applications and notices of investigations an unparalled respository of data, supplied by manufacturing firms, including in most cases the individual patient data sheets from patients in clinical trials. These exist both for the newest submissions and for those pertaining to most of the older drugs. (Slide).

These are the numbers of applications on file with FDA for anorectics. They constitute over 1100 volumes of material. We believe they contain data which if analyzed will clarify the answers to a number of the questions just referred to. Conventional hand-retrieval and scholarly review of this mass of material is beyond our resources of both staff and time. We thus chose to screen material relevant to efficacy, and submit controlled, double-blind studies to analysis by computer rather than by medical officers. Characteristics of each subject, as well as each study, and follow-up data at each visit were coded and key punched on standard data cards. The cards are then interrogated in different programs, and data tabulated or analyzed in various ways. Here are some of the background facts and findings obtained so far. (Slide) There are now 206 studies available for analysis on anorectic agents. Of these about 143 are parallel studies. The great majority of the studies deal with dextroamphetamine, methamphetamine, diethylpropion, phentermine, phenmetrazine, chlorphentermine, fenfluramine, clortermine, and mazindole. The duration of the studies ranges from 3 weeks to 6 months, although few, if any studies retain a significant number of subjects for longer than 16 weeks.

I had hoped to present a comprehensive overview of all studies. Although those working on the computer end of the project have achieved a great deal, programs are still not fully debugged, so that we are running behind, and I am most regretfully unable to talk on the basis of knowledge of 206 thoroughly analyzed studies. What we do have is satisfying but not startling. In those infrequent studies with relatively low drop-out rates in which obese subjects were treated for eight or twelve weeks with drugs such as dextroamphetamine, phenmetrazine, diethylpropion, fenfluramine and chlorphentermine or with placebo, those treated with active medication do show a weight loss of almost a pound a week more than those on placebo, or about 1 to 2 pounds per week total weight loss. Preliminary analyses in terms of percent of initial weight lost, or percent of excess weight lost appear to confirm the differences. The role of the investigator is important, but even investigators who achieved maximal weight loss on placebo induced even more with active drug. Comparisons between drugs are generally only possible indirectly and so are imperfect at present; but the weight loss induced through the use of different drugs appears to be of the same order of magnitude—no one drug has appeared superior. We now believe that the project will be finally completed by August 1, instead of July 1, as originally projected.

In respect to the question of relative abuse potential of amphetamine cogeners, the data remain meager, as you know. Similar toxicologic and pharmacologic profiles suggest that the drugs differ chiefly in potency. Monkey self-administration data and human "liking" scores are present only for a few drugs and are of uncertain value. Are amphetamine cogeners relatively little abused for intrinsic reasons—or merely because of the easy availability of the cheaper prototype compound? Confronted with incomplete data, do we attempt to predict abuse potential—or do we wait until there is a full-blown epidemic of abuse of a given drug?

This is one of the questions we ask your comments and advice on in discussion today and tomorrow.

Ultimately, we must all weigh the potential benefits of these drugs against the risks of the drugs. Here we hope that in giving your opinion, you will consider risk in its largest sense—not simply the innate clinical toxicity of the anorectics, but the risk to the public health of potential abuse. We do want to hear what these drugs mean in medical practice. But we also must think in the somewhat less familiar terms of drug abuse. Here is a problem from which we cannot divorce our thinking in favor of medical considerations. It is here that the information gaps are greatest, and where we need the broadest, best informed, and most open discussion of the questions on which reasonable and consistent national regulatory policy and medical attitudes towards anorectics must be based.

The questions which must be asked regarding the balance between the benefits to be gained by the use of appetite suppressants in weight reduction and the

risk to society from the abuse of some of these drugs do not present all-or-nothing alternatives; the questions do not simply involve questions such as—is it beneficial for the obese to lose weight and do drugs help in weight reduction for a sizeable proportion of any population group than would diet, exercise, counseling, and so forth without medication. The other questions which must be asked are:

1. Do some of the drugs represent a public health risk and, if so, are there alternative drugs with equal efficiency and less or no public health risk?

2. Are the anorectics being used largely in weight reduction programs for populations with medical disability or increased risk of morbidity and mortality, or is the great bulk of utilization for esthetic purposes—for example in women with mild to moderate obesity.

3. If there is a public health risk due to medical misuse and due to illicit diversion with "street abuse", are we talking about reasonable and legitimate prescription and utilization of these drugs or are we, in fact, dealing with an abundance of drugs which are manufactured in amounts well beyond that needed for any treatment of obesity,—with overprescription and loose or careless utilization? Let me in this respect give you figures on amphetamines and methamphetamine production.

Regardless of whether the anorectics are misused by medical users of these drugs or abused by non-medical users—psychopathic or otherwise—is there a public health risk and, if so, do overprescription, careless prescription, over-production, and the use of drugs with greater abuse potential than others contribute to such a risk, what can be done? Will more intensive medical education campaigns help? Would greater peer review and/or control through medical societies be beneficial? Must some drugs be placed under prescription and record keeping control—as in Schedule II? Must production controls or quotas be maintained for some drugs? When there is a public health risk, these questions can't be ignored and the best information and opinion currently available is needed to make what are obviously complex, multifaceted social as well as scientific judgments and decisions.

FINAL REPORT TO THE DIRECTOR, BUREAU OF DRUGS, BY THADDEUS E. PROUT, M.D., CHAIRMAN, CONSULTANTS ON ANORECTIC DRUGS

On June 27 and July 25, 1972, a group of clinicians and statisticians met under my chairmanship to review data compiled by FDA Staff on the safety and efficacy of anorectic drugs.

After careful review of clinical trials and of pharmacologic data the following conclusions were reached and recomendations made:

CONCLUSIONS

1. Adult obese subjects instructed in dietary management and treated with "anorectic" drugs on the average tend to lose more weight than those treated with placebo and diet in relatively short-term trials.

2. The amount of weight loss associated with the use of an "anorectic" drug varies from trial to trial. The possible origins of the increased weight loss due to the various drug effects are not established. The increased weight loss appears to be related to variables other than the drug prescribed, such as the physician-investigator, the population treated, and the diet prescribed. Studies do not permit conclusions as to the relative importance of the drug and non-drug factors on weight loss.

3. The magnitude of increased weight loss of drug treated patients over placebo treated patients was (only a fraction of a pound a week). The rate of weight loss was greatest in the first weeks of therapy for both drug and placebo subjects and tended to decrease in succeeding weeks.

4. The natural history of obesity is measured in years, whereas the studies cited are restricted to a few weeks duration; thus, the total impact of drug-induced weight loss over that of diet alone must be considered clinically trivial. The limited usefulness of these agents must be measured against any possible risk factors inherent in their use.

5. The amphetamines including methamphetamine have been widly abusd in numerous populations. It is thus in the best interests of the public health

to limit the use of amphetamines as far as is compatible with adequate therapy. This is both to minimize the risk of dependence in susceptible patients being treated and to decrease the amount of drugs being distributed, since widespread prescription of a dependence-producing drug inevitably increases the possibility for diversion to non-medical use and abuse.

6. Evidence presented for newer "anorectic" congeners of the amphetamine family and non-amphetamine drugs do not set them apart as having higher benefit or lower risks than older available drugs. The risk potential of Fenfluramine may be an exception to this general statement.

7. There was no evidence in the data reviewed which showed that combination of an "anorectic" agent with other drugs increase the benefits or reduce the risk of the "anorectic" agent.

8. There are no clinical data which support the parenteral use of these drugs in the treatment of obesity. Obesity is not an indication for the parenteral use of these agents.

RECOMMENDATIONS

1. That all "anorectics" reviewed, (dl-amphetamine, d-amphetamine, methamphetamine, benzphetamine, phentermine, chlorphentermine, clortermine, phenmetrazine, phendimetrazine, fenfluramine, mazindol and diethylpropion) with the exception of fenfluramine, be placed on Schedule II on the basis of abuse potential.

2. That combinations of "anorectics" with other drugs be evaluated in accordance with the policy of the FDA on combination drugs, that each constituent of the drug combination contribute to the total effect claimed for the combined drugs, and that the present available and proposed drug combinations be handled in this manner in view of the lack of demonstrated efficacy for each of the constituents of the drug combinations reviewed.

3. That amphetamines prepared for or in a form suitable for parenteral use not be approved for use in the treatment of obesity.

4. The single-entity oral "anorectic" preparations including the amphetamines be permitted to be labeled for restricted use in obesity provided that they are used in association with a specific weight reduction program and that the clinically trivial contribution of these drugs to the overall weight reduction is properly emphasized. To carry out the latter recommendation of a statement such as that made in the conclusions drawn from this review must be included in all labeling and promotional products. This statement should include the following points: Studies of the effect of "anorectic" drugs in the treatment of obesity when compared with the effects on patients treated in a similar manner without the use of the drugs demonstrate that the magnitude of weight loss of drug treated patients over non-drug treated patients was only a fraction of a pound a week. The rate of weight loss was greatest in the first weeks of study for both the drug and the non-drug treated subjects and tended to decrease in succeeding weeks. The natural history of obesity is measured in years whereas the studies offered for review are restricted to a few weeks duration. Thus, the total impact of "drug induced" weight loss over that of diet alone must be considered clinically trivial. The limited usefulness of these agents must be measured against any possible risk factors such as nervousness, insomnia and drug habituation that might be inherent in their use. Moreover, these agents can only be recommended for use in the treatment of obesity in a carefully monitored and specified weight reduction program under the care of a physician.

5. That future approval of all "anorectic" drugs prepared for future use be based on demonstration of efficacy as measured by statistical superiority of the drug over placebo in trial using FDA recommended protocols. These protocols should include provisions, among others, for the testing of a specific target population, specification of a minimum duration trial to assure clinical relevance of the study and give consideration to the handling of patient dropout.

6. Further, that appropriate summary data derived from efficacy studies be presented in labeling and in all promotional material to indicate the degree of weight loss that was found. For this purpose guidelines noted in (4) above should be supplemented by the addition of the specific facts found for the specific drug under consideration.

MEMORANDUM

OCTOBER 6, 1972.

To: The Commissioner.
From: Henry E. Simmons, M.D., M.P.H., Director, Bureau of Drugs.
Subject: Amphetamines and other Anorectics—*Action Memorandum.*

ISSUE

The use of amphetamines and other anorectic drugs in treating obesity has raised questions with respect both to efficacy and to abuse potential of these drugs. FDA must act upon a large number of New Drug Applications for many of these drugs. In addition, FDA must recommend to BNDD whether those anorectic drugs as yet unscheduled under the Controlled Substances Act possess sufficient abuse potential to require rescheduling.

FACTS

By a Statement of Policy and Interpretation (August 8, 1970), FDA required the submission of New Drug Applications for amphetamines. One hundred and six applications were submitted and 55 are awaiting action, 51 having been withdrawn in the interim because marketing ceased.

In addition to the amphetamines, phenmetrazine, phendimetrazine, benzphetamine, phentermine, chlorphentermine, and diethylpropion are also marketed as anorectics. All but chlorphentermine require action under the Drug Efficacy Study, since they were first marketed prior to 1962. The initial publication on these drugs as single entities under the DESI study has not yet occurred.

New Drug Applications for three previously unmarketed drugs (clortermine (Voranil), fenfluramine (Pondimin), mazindole (Sanorex)), have been submitted and also require action.

The amphetamines and phenmetrazine are in Schedule II of the Controlled Substances Act. As such, the Bureau of Narcotics and Dangerous Drugs sets manufacturing quotas for them, based in large part upon estimates of medical need for these substances provided by FDA. Our estimates for 1973 are overdue.

All of the anorectic drugs appear to possess at least some degree of abuse potential, but only the amphetamines and phenmetrazine are currently scheduled under the Controlled Substances Act. The scheduling of all drugs in this class thus appears in need of revision.

DISCUSSION

The attached *action memorandum* from Dr. Crout to me outlines in depth the problems, alternative solutions, and potential impact of various solutions to this complex question. There are numerous drugs involved, the medical condition for which they are used is widespread, and a number of value judgments are involved; none of the solutions is free of controversy.

Staff within the Bureau have studied these problems intensively and compiled all available data over the past seven months, utilizing consultant advice where possible.

I believe that the attached memorandum describes a coherent and reasonable set of actions on these problems. I also believe that action should be taken now on each of the items listed, but we should be explicitly prepared to re-evaluate our position in a year, particularly with respect to the use, or overuse, of the amphetamines and to the possible increased abuse of alternative agents.

RECOMMENDATION

That under the set of *Decisions* below, those alternatives numbered "1" be approved under sections "A" through "D" and all actions except "E5" be approved under "E" and "F".

DECISIONS

A. With respect to the approval of anorectics in general: (These alternatives are mutually exclusive.)

1. Base judgments on the efficacy of anorectic drugs on the currently available substantial evidence derived from short-term studies (up to 3 months). We recommend that this be coupled with a requirement for further testing with respect to abuse potential. (See D–1 below)

Approved ———— Disapproved ————.

2. Require that the efficacy of anorectics be based on substantial evidence that the use of these drugs results in achievement and maintenance of weight loss, with improved morbidity or mortality.

Approved ———— Disapproved ————.

3. Approve anorectics based on short-term trials, but simultaneously require long-term studies.

Approved ———— Disapproved ————.

B. With respect to amphetamines, including oral methamphetamine: (These alternatives are mutually exclusive.)

1. Label amphetamines to exclude use in obesity.

Approved ———— Disapproved ————.

2. Label amphetamines for restricted use in obesity, e.g., for patients refractory to other drug therapy.

Approved ———— Disapproved ————.

3. Continue current labeling for amphetamines, i.e., for narcolepsy, for minimal brain dysfunction, and for short-term adjunctive use in obesity.

Approved ———— Disapproved ————.

C. With respect to abuse potential: (These alternatives are mutually exclusive.)

1. Recommend that all anorectics *except* fenfluramine be placed in Schedule II of the Comprehensive Drug Abuse Act, fenfluramine to be placed in Schedule IV.

Approved ———— Disapproved ————.

2. Recommend that all anorectics including fenfluramine be placed in Schedule II of the Comprehensive Drug Abuse Act.

Approved ———— Disapproved ————.

3. Recommend that some or all the currently unscheduled anorectics be placed in Schedule III and/or IV, (the amphetamines and phenmetrazine remaining in II).

Approved ———— Disapproved ————.

4. Recommend no changes in the current scheduling of these drugs.

Approved ———— Disapproved ————.

D. With respect to possible further testing: (These alternatives are not mutually exclusive; only #1 is recommended.)

1. Require further testing of some or all anorectics with respect to abuse potential.

Approved ———— Disapproved ————.

2. Require further testing of some or all anorectics in long-term prospective trials.

Approved ———— Disapproved ————.

3. Require epidemiologic surveys relevant to how anorectic drugs are used or abused.

Approved ———— Disapproved ————.

E. Other requirements (All but #5 are recommended):

1. Eliminate parenteral amphetamines.

Approved ———— Disapproved ————.

2. Withdraw approval for all currently marketed combination drugs containing amphetamines.

Approved ———— Disapproved ————.

3. Require anorectic drug labeling describing the reservations many experts have with regard to use of anorectic drugs. Draft wording is attached (Tab "C" of attached memo.)

Approved ———— Disapproved ————.

4. Require fenfluramine labeling to include reference to the possibility of unusual adverse effects.

Approved ———— Disapproved ————.

5. Require anorectic drug labeling for the consumer.

Approved ———— Disapproved ————.

F. Certain ancillary or implementing actions (These are all recommended.)

1. Publish an article on anorectics in the *Drug Bulletin* (See draft, Tab "A" of attached memo.)

Approved ———— Disapproved ————.

2. Publish a *Statement of Policy and Interpretation* on anorectics (See draft preamble to SPI, Tab "B" of attached memo.)

Approved ———— Disapproved ————.

3. Publish a *Statement of Policy and Interpretation* on amphetamines.
Approved ———— Disapproved ————.
4. Publish follow-up efficacy notices on DESI drugs for which data have been submitted in response to a previous Notice.
Approved ———— Disapproved ————.

FOOD AND DRUG ADMINISTRATION,
Rockville, Md., March 26, 1973.

DELCO CHEMICAL CO., INC.
7 MacQuesten Parkway North
Mt. Vernon, New York

GENTLEMEN: This letter is being issued under the combined sposorship of the Food and Drug Administration (FDA) and the Bureau of Narcotics and Dangerous Drugs (BNDD) and is in reference to the product(s) you manufacture, distribute, or repack, containing amphetamine, dextroamphetamine or levamfetamine drugs alone or in combination with other drugs.

On February 12, 1973, Regulation 21 CFR 130.46, "Amphetamines (amphetamines, dextroamphetamine and their salts and levamfetamines and its salts) for Human Use", copy enclosed, was published in the Federal Register (38 FR 4249) setting forth the Food and Drug Administration's position regarding:

1. Combination drugs containing amphetamine or dextroamphetamine and their salts in combination with other drugs (for example—sedatives, tranquilizers, rauwolfia derivatives, vitamins, etc.);
2. Parenteral amphetamines;
3. Levamfetamine and its salts; and
4. Specifies certain conditions for marketing of single entity oral dosage forms of amphetamine or dextroamphetamine. (For purposes of the regulation, a mixture of dextroamphetamine and amphetamine is ordinarily regarded as a single drug entity).

The Food and Drug Administration has concluded, in part, that:

1. Combinations of anorectic and other drugs were not found to differ either in efficacy or in the incidence of adverse side effects from the anorectic drugs alone (please see the enclosed Federal Register announcement of October 15, 1971, "Fixed Combination Drugs for Humans");
2. That the benefit-to-risk ratio is unfavorable for parenteral injections of amphetamines, therefore, amphetamines may be marketed in the future only for oral use; and
3. FDA has not received substantial evidence of effectiveness nor is there a general recognition among qualified experts that levamfetamine preparations currently on the market are safe and effective for the treatment of obesity.

If any drug contains an amphetamine or dextroamphetamine or their salts in combination with other drugs such as sedatives, tranquilizers, rauwolfin derivatives, vitamins, etc., or is a parenteral amphetamine preparation, or is or contains levamfetamine, it is subject to the February 12, 1973 announcement, and is therefore a new drug for which an approved new drug application is not in effect and is misbranded under the appropriate provisions of the Federal Food, Drug and Cosmetic Act.

The purpose of this letter is to advise you that Regulation 130.46, which became effective March 14, 1973, makes illegal the continued marketing in interstate commerce of products which fall under the scope of that portion of the announcement which deals with combinations, injectables, or levamfetamine and its salts without an approved new drug application. The continued marketing of such drugs is in violation of the new drug and misbranding provisions of the Act and outstanding stocks of the articles in trade channels are subject to regulatory proceedings under the appropriate provisions of the Act. Consequently, the marketing of such drugs must cease immediately upon receipt of this letter.

The Bureau of Narcotics and Dangerous Drugs will no longer allow procurement quotas for drugs deemed violative under this regulation.

With respect to that portion of the announcement which deals with amphetamines and/or dextroamphetamines and their salts, the announcement also specifies certain conditions for the marketing of single entity oral dosage forms. Any marketing of such drugs must be under an approved new drug application and appropriate labeling as indicated in the regulation. Failure to comply with these provisions will result in regulatory proceedings.

We request your reply within 15 days after receipt of this letter stating your intentions with respect to your products, if any, which are not in compliance with the announcement, and the immediate removal of all outstanding stocks from trade channels down to the retail level.

The FDA district office will contact you shortly to work out the details of the recall. We are enclosing for your convenience, a model recall letter which you may put into immediate use to facilitate your recall efforts, and a representative of BNDD will contact you to inform you of required accounting and disposition procedures for your inventory and returned goods.

In the event you have already discontinued marketing, FDA would appreciate particulars on the following for each product:

(1) the date discontinued;
(2) an estimate of size and frequency of previous shipments for the past year;
(3) to whom shipped; and
(4) an estimate of outstanding stocks on the market and in your possession.

This program is being carried out with the full cooperation of BNDD. Because of the required record keeping under the regulations administered by BNDD (21 CFR 307.21), any destruction of your inventories must be BNDD authorized. Completion of BND–41, (Voluntary Destruction) is required as well as a witness to the destruction. A list of BNDD offices is attached to assist you in notifying BNDD once you are ready to destroy drugs returned to your firm.

For purpose of this recall only, BNDD has waived the need to use order form (BND–222C) until June 30, 1973. In lieu of order forms a complete and accurate record must be retained by *both* your firm and your customer, identifying both parties, date of transaction, and the kind and quantity of each drug that is returned. Any Schedule II controlled substance returned after that date will require the use of order forms.

All responses or inquiries to this letter should be directed to the Food and Drug Administration, Bureau of Drugs, Office of Compliance (BD–317), 5600 Fishers Lane, Rockville, Maryland 20852.

Sincerely yours,

SHERWIN GARDNER,
Acting Commissioner, Food and Drug Administration.
JOHN E. INGERSOLL,
Director, Bureau of Narcotics and Dangerous Drugs.

FOOD AND DRUG ADMINISTRATION,
Rockville, Md., September 28, 1974.

DR. ALEXANDER M. SCHMIDT,
Commissioner of the Food and Drug Administration,
Parklawn Building, Rockville, Md.

DEAR DR. SCHMIDT: We are in receipt of your September 18th letter, and wish to comply with the need of an investigating committee for accurate, complete, and specific information concerning our testimony of August 15, 1974. We cannot fulfill this request immediately, because of the time and care we deem necessary for response and because we feel that final response to you at this time would jeopardize attempts to obtain a reliable account of the agency's work.

We continue to be deeply concerned about your plan to issue a separate report on the issues at hand. We feel that one independent group should do the investigating, and that we should not be subjected to multiple information demands and judgments. Should you issue a report in the near future, the Secretary's committee might find it difficult to override you. If you desire to make an investigation and report, we ask you to do so on the basis of documents and testimony of the Secretary's committee, and issue the report only after that committee has completed and released its work.

We want to publicly present the facts underlying our testimony, so that the American people will be informed.

Any investigation must be open. The potential for serious abuses is inherent in the promise that material will be held confidential. The term "trade secrets" has not be defined. Therefore, we request that any investigating committee refrain from keeping any information confidential, and provide a straightforward, unambiguous definition of "trade secrets."

We are pleased that full access to all agency records has been offered, as we requested in our September 13th letter to you. I have requested through Divisional channels all volumes of NDA 16–618; to date, only six volumes have been delivered.

We appreciate your assurance that we will have an "adequate opportunity to prepare and present . . . views and supporting materials." I shall supply an accurate, complete, and specific report as soon as possible. The following are examples of matters I am reviewing and intend to report upon:

The evaluation and handling of NDA 16–618 and NDA 16–880.

Attached is a condensed summary concerning NDA 16–618.

Sincerely yours,

ROBERT O. KNOX, M.D.

MEMORANDUM

JULY 9, 1976.

To: Ed Melton, OLS.
From: Bill Crabbs, HFD–120.
Subject. Ionamin, Biphetamine, your memo of June 23, 1976.

Steve Kennedy has spoken to Mr. Gordon on the phone and referred him to DEA for drug abuse information on the drugs. I understand that Mr. Gordon is primarily interested in Ionamin, therefore I've concentrated on this drug in gathering the attachments. The attached material about the Task Force review of anorectics applies to both Ionamin and Biphetamine.

The original NDA for Ionamine includes studies by Burton M. Cohen, M.D. and S. Charles Freed, M.D.; the NDA was allowed to become "effective" on May 14, 1959. The Cass study of Ionamin, Biphetamine and Biphetamine-T was included with the firm's annual report on Ionamin submitted on June 24, 1966 and was, as far as I can tell, not requested by FDA. Apparently no medical review of the study was done and the study had no impact on the status of the drug which had previously been allowed to be marketed on the basis of other data.

Ionamin and Biphetamine were originally published as "possibly effective" on August 8, 1970. Two clinical efficacy studies on Ionamin were done as a follow-up to the DESI notice and were reviewed as a part of the Anorectic Task Force. These were done by Eugene Jolly, M.D. and Robin Shearer, M.D. and showed statistically significant efficacy.

Similarly, 3 studies were done on Biphetamine, two by Albert Cohen, M.D. and one by Eugene Jolly, M.D.

As a result of the Task Force review and evaluation, both Ionamin and Biphetamine were upgraded to "effective" (see July 19, 1974 FR statement).

The NDA for Biphetamine-T was withdrawn on March 30, 1973 since the data submitted did not show efficacy of the drug as a fixed combination.

I've attached pertinent reviews, including the Task Force review and a copy of the Cass study.

I don't know if there is any problem with respect to releasing any of the information since some is confidential, but I'll leave that up to you.

MEMORANDUM

To: Director, Bureau of Drugs through the Deputy Director.
From: J. Richard Crout, M.D., Acting Director, Office of Scientific Evaluation.
Subject: Amphetamines and Other Anorectic Drugs—Action Memorandum.

OBJECTIVE

This memorandum is aimed at providing discussion of issues, data, and alternative actions necessary for a comprehensive policy with respect to drugs used as anorectics in the treatment of obesity. Policy and implementing actions will be discussed with respect to both the therapeutic usefulness and the abuse potential of the drugs.

ISSUES

In simplest terms, the major issues are as follows:

1. Some or all drugs used therapeutically as anorectics have marked potential for abuse.

2. The therapeutic usefulness of anorectic drugs has been poorly and variably defined, and the definitions disputed.

3. Regulatory decisions regarding anorectic drugs appear to have been made in the past largely piecemeal; a broad explicit policy with consistent implementation has been lacking.

FACTS

Relevant to the issues above are a number of more concrete facts, old and new, scientific and administrative. The major background facts are listed below. It is suggested, however, that the material attached under Tabs "A" and "B" be read first, as easy and more extensive descriptions of the complex background.

ADMINISTRATIVE ACTIONS WITH RESPECT TO ANORECTIC DRUGS

1. Submissions of NDA's for Currently Marketed Amphetamines required by the Statement of Policy and Interpretation of 8-8-70

Of the anorectics, the most prominent group, the amphetamines, were considered "grandfathered" until August 8, 1970. At that time the FDA published a "Statement of Policy and Interpretation" (see Tab H) which essentially revoked grandfather status and required among other things the submission within a year of New Drug Applications for amphetamines. NDA's were submitted by sponsors, and are the principal documents on which formal action will be taken in implementation of future amphetamine policy. A few NDA's had been submitted a number of years ago for special amphetamine formulations or combinations and will also be acted upon.

The indications for which the amphetamines might be provisionally labeled were set forth in the announcement of August 8, 1970. The indications were: as an adjunct in the treatment of obesity; as a adjunct in the treatment of minimal brain dysfunction in children; narcolepsy. The first indication is the subject of this memorandum, the efficacy of amphetamines in the latter two being somewhat less controversial.

2. Review of currently marketed non-amphetamines by the Drug Efficacy Study (DESI)

All but one of the other, non-amphetamine anorectic drugs currently marketed in the United States are subject to review by the Drug Efficacy Study, so that decisions are pending on these drugs. The only anorectic DESI Notice published to date, (Tab I) on special formulations and combinations, listed the drugs effects as "possibly effective". Efficacy data have been submitted in response to the Notice, and these "E" supplements must be acted upon in implementing this policy on anorectics.

3. Submissions of NDA's for anorectic drugs not previously marketed

New Drug Applications have been submitted for three anorectic drugs not yet marketed: fenfluramine (Pondimin), mazindole (Sanorex), and clortermine (Voranil). These have purposely been held up in their processing with the agreement of the manufacturer, pending development of overall policy. These must be acted upon.

4. Revision of scheduling of anorectic drugs under the Comprehensive Drug Abuse Act

The Comprehensive Drug Abuse Prevention and Control Act (Controlled Substances Act; CSA), passed in October 1970, is designed to impose restrictions on use appropriate to the abuse potential of drugs. Schedule II of the CSA, the most restrictive for marketed drugs, requires non-refillable prescriptions, special records, and manufacturing quotas, among other things; Schedule III and IV have little but psychological impact on the practice of medicine, requiring only a special symbol on the labels and labeling and a practitioner's BNDD number on the prescription. The Schedules of the Act include three anorectics—methamphetamine, the amphetamines themselves, and phenmetrazine. Other anorectics, e.g., diethylpropion, are not included, although they are labeled as having abuse potential, (and almost certainly possess abuse potential).

The Schedules also exhibit other inconsistencies and omissions, and they require revision. Along these lines, the amphetamines and oral methamphetamine were moved from their original place in Schedule III to the more restrictive Schedule II in July 1971, following FDA recommendations. Phenmetrazine was moved from III to II in January 1972, again following FDA recommendations.

No formal move has been made to schedule other anorectics, but their absence from the Schedules appears to be one of the significant omissions of the Act. HEW, and by extension FDA, are obligated both scientifically and by the Act, to advise the Justice Department with respect to drugs with abuse potential. Formal recommendations with respect to the abuse potential of marketed and unmarketed anorectics appear overdue.

5. Deadlines

Deadlines and commitments of various kinds exist with respect to the actions implied above. The NDA's both for amphetamines and new entities have now exceeded the statutory review time limit of 180 days. The DESI Notices implementing 8 NAS/NRC recommendations await publication. Efficacy supplements submitted in response to the "possibly effective" Notice for other anorectics have exceeded the 180-day period. An estimate of medical need for amphetamines and phenmetrazine depends upon our conclusions as to efficacy, and is also overdue: upon it will depend manufacturing quotas and industry plans for 1973. In this regard, we were questioned in February 1972, before the House Subcommittee on Public Health and Environment and the Senate Subcommittee on Juvenile Delinquency as to our conclusions on the use of amphetamines in treating obesity, and we projected an answer for July.

SCIENTIFIC BACKGROUND WITH RESPECT TO ANORECTIC DRUGS

1. Efficacy studies

Repeatedly in discussions with consultants and outside experts the question of the results of anorectic trials in general was raised. FDA staff therefore carried out a unique computer-supported review of all controlled anorectic studies on file in FDA. 206 studies with 11 anorectic drugs were analyzed after screening by physician-medical officers. Individual patient data on 9,800 subjects were recorded on 72,000 IBM cards; and programs for tabulation and analyses of the data were developed and applied. The resulting library of data and analyses provides an unparalleled review of the class of drugs.

The analyses generally supported the efficacy of anorectic drugs. Use of the drugs in obese subjects was associated with more weight loss than was diet alone. The degree of extra weight loss was small—a few tenths of a pound a week in many cases—and variations were great. In trials which continued for 12 or 16 weeks, those subjects who remained in the trials lost a significant amount of weight e.g., 25–40% of excess weight, both in the control groups and when on drugs, but they consistently lost more weight on drugs.

2. Morbidity-mortality data

Larger questions of long standing remain unanswered, such as the long-term effect on morbidity and mortality of the use of anorectics. These questions are of basic importance, since the usefulness of the drugs depends in large part upon the assumption that they somehow help prevent the adverse effects of obesity.

3. Evidence of abuse

Evidence of various sorts of abuse is most abundant for the amphetamines. This is particularly so for use in the "street" and in student populations but also was found in a large sample of people of fixed residence in the conventional occupations.

It is reasonably assumed that abuse is also associated with prescriptions for obesity, but there are only minimal studies of this association. In addition to evidence of abuse of amphetamines, evidence also exists in fair quantity for abuse of phenmetrazine and diethylpropion. For other anorectics evidence of abuse is scanty or lacking. Experience with other abusable drugs has shown, however, that documentation of abuse lags markedly behind abuse, and, when it appears, is only the tip of the iceberg.

4. Animal and other studies on the comparability of CNE effects

Pharmacologic data in animals which would permit detailed comparisons of anorectic agents are imperfect or incomplete. Insofar as they exist, they indicate that the drugs are far more similar than dissimilar. The one exception to this statement is fenfluramine, which appears to possess depressant rather than stimulant qualities.

This pharmacologic contrast is based on observations in both animals and humans.

Animals given fenfluramine in appropriate doses differ from those given amphetamine by exhibiting decreased motor activity, suppressed conditioned avoidance responding, increased total sleep time, and EEG changes of increased slow-wave sleep time, slowed electrocortical activity, and depressed reticular-formation activity.

In humans, sedation is the most prominent side effect of fenfluramine, in contrast to amphetamines. EEG changes correlating with sedation were observed. Amphetamine addicts could not distinguish between fenfluramine and placebo, and rated fenfluramine as less euphoriant than placebo.

These observations generally suggest strongly that fenfluramine should not be considered equivalent to other anoretics with respect to dependence potential of this class of agents.

5. Pulmonary hypertension

A European anorectic drug aminorex (Menocil), pharmacologically related to amphetamines but structurally somewhat different, has been associated with potentially fatal pulmonary hypertension. Congeners have been neither convicted nor exonerated of similar effects, although recent German reviews have publicized the possibility of similar effects. German regulatory authorities have just required warning labeling in this regard, which we are to receive and review.

ASSUMPTIONS

Following this section are the alternative courses of action which we believe may reasonably be considered with respect to anorectic drug policy. Before discussing them, certain assumptions should be made explicit. (As is appropriate to the format of a memo like this, these assumptions are discussed in the DISCUSSION section on page 17, to which the reader may wish to turn before proceeding.) The assumptions are:

1. Actions are best taken with respect to the whole class of anorectics.
2. Actions should not be taken with respect to pharmacologically related agents of different therapeutic classes, but should be restricted to anorectics.
3. Actions should not be deferred.
4. The two indications for amphetamines other than obesity are basically accepted (minimal brain dysfunction in children; narcolepsy).
5. Efficacy demonstrated for some amphetamines can be extended to all amphetamines generically.

ALTERNATIVE COURSES OF ACTION

In implementing policy for an entire class of drugs, indicated in an extremely widespread condition, actions will be numerous, and alternative choices correspondingly numerous. In the interests of clarity, we present here only the major decisions, as we see them, with viable alternative courses of action.

A. With respect to the approval of anorectics in general

The first major area in which alternative courses of action should be distinguished is the area of criteria for demonstration efficacy of anorectic drugs in general. The three alternatives are considered mutually exclusive.

1. Base judgments on the efficacy of anorectic drugs on the currently available substantial evidence derived from short-term studies (up to 3 months). This would be coupled with a requirement for further testing with respect to abuse potential (see D.1 below).

PRO: This is the recommendation of FDA consultants. (See Tab C) Several past attempts to gain support from experts for longer-term trials or for a more "clinical" definition of efficacy (e.g., loss of 50% of excess weight) have failed. Trials of this sort reflect the current state of the art. To increase requirements now would mean that all NDA anorectics are non-approvable for an indefinite period of time. No better alternative drugs exist.

CON: Approval based on short-term trials leaves unanswered questions as to the long-term effect of drug therapy on the natural history of obesity, as well as on morbidity and mortality associated with obesity.

2. Require that the efficacy of anorectics be based on substantial evidence that the use of these drugs results in achievement and maintenance of weight loss and in improved morbidity or mortality.

PRO: Fulfillment of criteria along these lines would provide evidence that these drugs are medically useful in undeniably important ways.

CON: No drugs currently marketed or proposed for marketing have been tested in a fashion adequate to fulfill such criteria. It is not certain that appropriate testing could be practically carried out. Many investigators, as well as drug firms, feel such criteria are unreasonable.

Drugs in other classes are considered useful even if they produce only minor or temporary improvement. Nor is it clear that anorectics are *not* useful as adjunctive therapy for obesity over the long-term; the data are simply not available.

3. Approve anorectics based on short-term trials, but simultaneously require long-term studies.

PRO: More data might be obtained on the course of obesity treated with and without drugs. The FDA would maintain more control over the drugs than if unqualified approval were given.

CON: The type of data to be obtained has not been established. Even if long-term administration of drugs were to be tested, it is debatable whether anorectic drugs should be given chronically. Even if long-term trials revealed no difference between drug-treated and placebo-treated groups, the fact remains that more subjects lose more weight over the short term on active drugs. A collaborative study of the magnitude and thoroughness necessary for meaningful results would represent investment of research effort on the scale of the UGDP study. Neither FDA nor, probably, the research community appears able or willing to design and carry out a definitive, unequivocal trial of the necessary scope. The methodology and results of any single study would be disputed, and it appears somewhat unlikely that a satisfactory study is possible.

B. With respect to amphetamines, including oral methamphetamine

The second major area in which alternative courses of action should be distinguished is with regards to the amphetamines (assuming that other anorectics are considered effective.) These three alternatives are considered mutually exclusive.

1. Label amphetamines to exclude use in obesity.

PRO: This would eliminate the major indication for amphetamines, and so would decrease the amount distributed and susceptible to misuse. Manufacturing quotas would be lowered accordingly, thus restricting the amounts produced. The action would eliminate a controversial indication. It would be tacitly approved by many laymen and physicians, probably the majority. Effective alternative drugs are available.

Elimination of the use of amphetamines in obesity would be a dramatic action against abusable drugs which the public would easily understand and approve. Both laymen and some experts have advocated that amphetamines not be prescribed or labeled for obesity. This is because of the abuse of the drugs, and the belief that widespread use increases the opportunity for abuse and, furthermore, may "inoculate" susceptible subjects in weight-reduction programs who might otherwise not have been exposed to the drugs. It is almost certain that pressure to eliminate the use of amphetamines in treating obesity will continue. Alternative agents are available. Abuse of the amphetamines has been far more extensive in the United States than abuse of alternative agents. If amphetamines are labeled only for use in patients refractory to other anorectics this would be an indication for which the drugs in a strict sense have not been tested.

CON: The action would be contrary to the explicit recommendations of FDA consultants and the majority of academic figures who have been heard from. It would restrict *medical* use because of *non*-medical abuse, and data are skimpy with respect to any relationship between the two. Alternative drugs appear to possess abuse potential, too. Decreasing the supply of legally manufactured amphetamines would increase the price of amphetamines on the street, and illicit labs would increase in response to the demand. As noted in the PRO section of recommendation B.1, it would be more appropriate to use the Controlled Substances Act to reduce the drug abuse problem associated with the widespread use of these drugs in the treatment of obesity.

2. Label the amphetamines for restricted use in obesity, e.g., for patients refractory to other drug therapy.

PRO: This is consistent with the recommendations of the consultants. It would take account of the now well-documented action of amphetamines in producing weight loss. The selection of a restricted group of patients would work further to restrict use of the drugs; although not explicitly recommended by consultants, it would be in line with their discussions. The action would

nonetheless leave the oldest and best known anorectics available for the practitioners who believe they possess special efficacy. It would prevent charges of overreacting which have been voiced in advance by well-known academic clinical pharmacologists when the possibility was suggested that amphetamines might no longer be available. This action might be coupled with a commitment to review the situation again at some future period, e.g., in a year. This action, together with further reductions in the quota when indicated, continues to make appropriate use of the Controlled Substances Act as a response to the safety problem of drug abuse.

Eliminating the use of amphetamines for the treatment of obesity as a mechanism for controlling drug abuse would represent utilization of the Food, Drug and Cosmetic Act to control the type of safety problem for which the Controlled Substances Act was promulgated.

CON: Data are anecdotal or lacking that amphetamines do in fact work in patients refractory to other drug therapy. The labeling would imply relative efficacy and/or risk without clear-cut evidence to back up the implications. The labeling would be a somewhat unsatisfactory compromise which would not end controversy on the use of amphetamines in obesity.

3. Continue current labeling for amphetamines, i.e., for narcolepsy for minimal brain dysfunction and for short term, adjunctive use in obesity.

PRO: Amphetamine labeling is already restrictive. Evidence does not exist for efficacy in patients refractory to other drugs. If other drugs are placed in Schedule II, this assumes equal abuse potential, and labeling should not be discriminatory.

CON: The history of amphetamine abuse is so distinctive that amphetamines should receive special labeling. Maintaining the status quo appears completely to underestimate the problem.

C. With respect to abuse potential

The third major in which alternative courses of action should be distinguished concerns abuse potential of anorectic drugs. The four alteratives are considered mutually exclusive.

1. Recommend that all anorectic *except* fenfluramine be placed in Schedule II of the Comprehensive Drug Abuse Act, fenfluramine to be placed in Schedule IV. (see Tabs E, F and G for draft labeling with respect to Drug Dependence.)

PRO: All CNS stimulant anorectics would be treated consistently and restrictively. Physicians, patients, and addicts would not be led to seek out previously unabused drugs simply because they are not on Schedule II.

Pharmacologic and chemical data would be extensively relied on to *predict* abuse before it occurs. Abuse of these drugs would be prevented, so far as is possible under current law.

FDA and the Bureau of Narcotics and Dangerous Drugs have agreed in general that it is desirable to use predictive data.

Since fenfluramine has a different pharmacologic profile and appears to possess less abuse potential in animal tests, it would be distinguished from amphetamines.

CON: Since predictive data are imperfect, some drugs with little or no abuse potential may be scheduled. In the past, scheduling of non-opiate drugs has often depended upon evidence of actual abuse. Placing all anorectics in Schedule II will be viewed by some as overcrowding this Schedule and rendering the less restrictive Schedules almost meaningless. To act only upon the anorectics is to ignore the abuse potential of sympathomimetic amines in other therapeutic classes, e.g., mephentermine. It is not certain that BNDD will formally concur with our recommendations.

2. Recommend that all anorectics including fenfluramine be placed in Schedule II.

PRO: This would eliminate the competitive advantage which might accrue to fenfluramine if all other anorectics are placed in Schedule II. Past claims that other new drugs, e.g., phenmetrazine, meperidine, do not possess the abuse potential of older congeners have been invalidated with the passage of time.

CON: Fenfluramine appears to possess pharmacologic actions qualitatively distinct from other anorectics, which suggests that its abuse potential is at least quantitatively and probably qualitatively, different from other anorectics. Experts consulted have all been of the opinion that fenfluramine should not be lumped with other anorectics.

3. Recommend that some or all the currently unscheduled anorectics be placed in Schedules III and/or IV, (the amphetamines and phenmetrazine remaining in II.)

PRO: This would take account of the lack of documented abuse of unscheduled anorectics relative to amphetamines. It would expose us to less criticism of overreacting. It would not represent the severe competitive differential of alternative #1 between fenfluramine and other anorectics.

CON: Schedule III and IV have little practical effect in preventing overprescription or diversion. Addicts would thus preferentially turn to drugs not previously abused for "administrative" reasons.

4. Recommend no changes in the current scheduling of these drugs.

PRO: This would avoid stigmatizing possibly innocent drugs as possessing abuse potential. I would avoid controversy as to the admittedly imperfect predictive value of pharmacologic data. It would not prematurely advertise the abuse potential of drugs of which addicts may not yet be aware by placing previously unscheduled drugs on display in the Schedules. The Bureau of Narcotics and Dangerous Drugs should monitor the vital information on street abuse of the drugs, and move when abuse becomes important.

CON: This would not deal with the inconsistencies in the Controlled Substances Act and would permit considerable abuse of at least, some of these drugs before any action would be taken.

D. With respect to further testing

A fourth area in which actions may be taken is that of requirements for further testing of various sorts. The three requirements are not mutually exclusive; we recommend only the first at present.

1. Require further testing of some or all anorectics with respect to abuse potential.

PRO: Data would be obtained on the most disputed safety question associated with these drugs, their abuse potential. The Lexington Addiction Research Center of the NIMH is beginning testing of this sort.

CON: Testing methodology has not been standardized. Results of tests done so far are of uncertain predictive value with respect to subsequent abuse under actual marketing conditions.

2. Require further testing of some or all anorectics in long-term prospective trials.

PRO and CON: This is a recapitulation of parts of alternatives A2 and A3, and the arguments presented there apply here.

3. Require egidemiologic surveys relevant to the use and abuse of drugs.

PRO: This requirement should produce drug-use data. Surveys might also reveal abuse earlier than does the present fortuitously received information. This requirement would be an innovative, positive response to long-felt needs for data.

CON: Methodology is imperfect. FDA is not familiar with evaluating data of this sort. Firms would resist a new requirement of this sort.

E. Other requirements

Certain further options can be distinguished with respect to the amphetamines, independent of the two major alternatives above under B. In addition action must be taken on DESI drugs, and labeling changes appear desirable. All but #5 are recommended.

1. Eliminate the marketing of parenteral amphetamines for obesity.

PRO: This is a recommendation of FDA consultants. Amphetamines produce a more intense euphoria and "rush" by parenteral routes; parenteral administration has been associated with the most destructive forms of abuse. No indication for amphetamines exists which cannot be adequately treated by the oral route. (This last argument does not hold for the use parenteral methamphetamine as a pressor agent, but alternative and better pressor agents exist).

CON: Certain practitioners claim that by giving amphetamines by injection they maintain better control over the drug, since the patient does not administer the drug to himself but receives it under supervision.

2. Withdrawn approval for all currently marketed combination drugs containing amphetamines.

PRO: This has been recommend by FDA consultants. Combinations are generally with a sedative or transquilizer, the rationale being to decrease the stimulant action of the amphetamine component.

Data submitted in general fail to demonstrate that the sedative constituents of anorectic combinations contribute to the total effect claimed for the drug (with the possible exception of Eskatrol), so that continued marketing would not be consistent with the FDA combination policy. Elimination of combinations would permit substantial decrease in manufacturing quotas. It would also eliminate certain drugs, (e.g., Dexamyl) which appear to possess qualities attractive to special subpopulations of addicts. The sedative or tranquilizer components produce adverse effects of their own. Phenothiazines, e.g., as in Eskatrol, have never been clearly shown to produce anti-anxiety effects as single entities, let alone in combination. The trials carried out with Eskatrol exhibit technical deficiencies.

CON: Small studies of one combination contrast with other studies in suggesting that prochlorperazine (in Eskatrol) reduces the adverse effects associated with d-amphetamine. (However, prochlorperazine, a phenothiazine, may produce serious adverse effects of its own under certain conditions). The manufacturers of Eskatrol especially have expressed the importance of this product to the firm and may be assumed ready to contest an adverse decision.

3. Require labeling describing the reservations many experts have with regard to use of anorectic drugs. A draft wording is attached (Tab D).

PRO: This is a strong recommendation of FDA consultants. Omitting such labeling appears somewhat inconsistent with principles of full disclosure. Requiring it will prevent unjustified promotional claims from being made. These labeling statement may mollify the critics of anorectic drugs.

CON: The reservation are serious enough to raise questions as to the wisdom of using these drugs at all: for some people they may raise questions as to FDA's wisdom in permitting the drugs to be marketed. Certain practitioners, e.g., bariatricians, will disagree with the statements.

4. Require fenfluramine labeling to include reference to the possibility of unusual adverse effects. (See Tab J for draft wording.)

PRO: It would slightly offset the promotional advantage given fenfluramine by the proposed less restrictive scheduling. This balance is particularly desirable, since with fenfluramine an advantage (Schedule IV) which is basically unimportant for the majority of patients may lead physicians to ignore aspects of fenfluramine's pharamcologic profile which may for many patients be less desirable e.g., potential for producing diarrhea, sedation, or mild post-treatment depression.

CON: This action appears not to have adverse implications.

5. Require anorectic drug labeling for consumer.

PRO: Information would be provided to the patient so that he may participate in a controversial decision. He will be more fully informed on the benefits and risks of anorectic drugs. This would be consistent with the general movement toward more complete informing of the consumer.

CON: Guidelines for determining drugs requiring consumer-oriented labeling have not been established Anorectic drugs do not appear to be more hazardous than many other drug classes which do not have consumer-oriented labeling.

F. Certain ancillary or implementing actions

The fifth area in which alternative courses of action may be distinguished consists of ancillary or implementing actions. (These are all recommended.)

1. Publish an article on anorectics in the *Drug Bulletin* (see draft, Tab A).

PRO: This is desirable no matter what we do, since physicians will learn of our actions sonner or later. The *FDA Drug Bulletin* has been established for such purposes.

CON: Publication may retard our action. We are under pressure to act as soon as possible.

2. Publish a *Statement of Policy and Interpretation* in the *Federal Register* with respect to anorectics. (See draft preamble to SPI, Tab B).

PRO: This will establish explicitly and officially our policy towards these drugs. Even as a proposal it would establish many points for the record.

CON: This would commit us to a firm policy, whereas we may wish to revise policy after assessing the impact of our initial actions.

3. Publish a *Statement of Policy and Interpretation* for amphetamines.

PRO: This would be an appropriate follow-up to the August 8, 1970, SPI on amphetamine, which led to the current amphetamine submissions. It would enables us to make desirable distinctions between amphetamines and other anorectics.

CON: This should not be allowed to prevent speedy action on individual amphetamine NDA's.

4. Publish follow-up efficacy notices on DESI drugs for which data have been submitted in response to a previous notice.

PRO: This appears inescapably logical from an administrative point of view.

CON: Nothing.

DISCUSSION

1. Assumptions

The assumptions noted on p. 6 of this memo appear largely self-explanatory, but can be debated. We believe, first, that a "class action" is fairer in an administrative sense, and more valid scientifically. The last is particularly true with respect to drugs with abuse potential, for unless action is taken on a broad front, addicts may abandon the restricted drug merely to begin to abuse similar drugs not yet scheduled.] Piecemeal action might appear "conservative" but we believe it fails to take account of such considerations as the great lag between abuse and documentation of abuse.

The second assumption may appear partially inconsistent with the first, in that we suggest limiting action to anorectics rather than extending them, for example, to all sympathomimetic amines.

While this may neglect for the moment such abusable drugs as mephentermine, it is a valid assumption with respect to efficacy and to the way in which the drugs are used, i.e., orally and subacutely. Moreover it limits our actions to a manageable size and to drugs sharing a common indication. In addition, decisions on efficacy in treating obesity involve a number of policy decisions, independent of the scheduling questions.

The third assumption, that actions should not be deferred, appears far preferable to any compromise or delaying action. New Drug Applications have been submitted and will continue to be submitted, and they should be acted on. Early decisions are also required with respect to determinations of "medical need" for anorectics and manufacturing quotas of scheduled substances.

The fourth assumption, to leave aside discussions of minimal brain dysfunction (MBD) and narcolepsy, is a logical determination in terms of the scope of the memo. If we wish, we will have the opportunity to revise our position on MBD later since there is ongoing discussion of the place of CNS stimulant drugs in treating MBD; a current consultant task force should help us here if necessary.

The fifth and last assumption is that a decision can be made generically for all amphetamine drug products. This appears a sound approach, because clinical experience and clinical trials have used various drug products without results suggesting differences.

2. Recommended actions and arguments in support of them

Briefly we recommend the following actions, discussed at greater length above, together with their alternatives: (The letters and numbers in paranthesis refer to alternatives discussed above—in the ALTERNATIVE COURSES OF ACTION SECTION.)

(A.1.) Base approval of anorectics for which NDA's are currently under review on demonstrated superiority to placebo in relatively short-term (e.g., 4–12 weeks), trials of weight reduction. Further testing of some sort, e.g., for abuse potential, would be a desirable corollary.

(B.1.) Label amphetamines to exclude use in obesity.

(C.1.) Place all anorectics except fenfluramine in Schedule II, and fenfluramine in Schedule IV.

(D.1.) Require further testing of anorectics with respect to abuse potential.

(E.1.) Prohibit marketing of parenteral formulations of anorectic drugs for obesity.

(E.2.) Reject NDA's recently submitted for amphetamine-sedative combinations and withdraw approval from older DESI's combination NDA's for which efficacy supplements were submitted.

(E.3.) Require anorectic drug labeling to detail more explicitly the limitations and hazards of use.

(E.4.) Require fenfluramine labeling which balances decreased abuse potential against other possible increased adverse effects.

(F.1–4.) Make the actions public through the *FDA Drug Bulletin* and two SPI's as well as through appropriate DESI notices and follow-up notices.

In summary, arguments in support of these recommended actions are as follows: The actions are consistent with the best available data. They establish and implement a comprehensive policy for a difficult class of drugs. They pro-

vide a reasonable basis for approving drugs, the approvability of which in the past has depended upon rather arbitrary value judgments. The most controversial use of the most controversial drugs, the amphetamines, is eliminated. The actions restrict the use of other drugs with respect to abuse so far as current statutes permit, but maintain the availability of drugs for those practitioners who depend upon them. They inform the practitioner of the limitations of use and of the risks associated with these drugs. Most practically, they are consistent with the closest approximation to a consensus of experts and practitioner which we can strike, with the exception of the ampetamines, and even there we may still expect much professional and lay support. In short, the actions represent the policy which best balances the limited but demonstrated efficacy of anorectic drugs against their potential for abuse.

3. Problems with recommended actions

In acting on an entire class of drugs used in a condition as prevalent as obesity, and with a special hazard of abuse potential, we should expect multiple problems in implementing any policy; it should be clear that no action or set of actions will satisfy all sectors. We can anticipate problems that will almost certainly result from the recommended actions and no doubt others, as yet unforeseen, will arise. But we believe that a clear stand on the major problems we can expect which are discussed below will put us in an optimal position. (Minor problems are discussed only above, in the section entitled ALTERNATIVE COURSES OF ACTION.)

a. The central problem appears to be that of according formal recognition of efficacy to a disputed class of drugs. Some authorities object to calling drugs effective if they do not alter the long-term course of obesity. We believe, however, that this is an unreasonable requirement in view of a demonstrated effect on weight loss over the short term, and in the absence of more effective alternative therapy.

b. A second problem will result from eliminating the indication of obesity from amphetamines labeling. Academic medical figures and many practitioners will criticize us for over-reacting or for depriving physicians of a useful drug with which they are familiar. We will be going against the advice of our small consultant group.

c. A third major problem will be the recommendation to schedule in Schedule II. We wish to make it quite clear that a *basic issue in drug scheduling is involved*, that is, whether we await evidence that a drug is being abused before scheduling it or attempt to predict abuse potential. Data here are imperfect and spotty, as they so often are, and we can be challenged on individual drugs. But the overall picture is one of drugs that are more alike than dissimilar. They all possess CNS stimulant activity and appear very likely to be attractive to addicts, particularly if previously preferred drugs were in Schedule II. In addition there are scattered reports of actual abuse for almost all the non-scheduled drugs. Of all the currently non-scheduled drugs diethylpropion is the one for which evidence of *abuse*, as well as of abuse *potential*, is best documented.

d. A fourth problem is that of quotas. Quotas must be established for almost all anorectics in the near future, if they are put in Schedule II, and we are uncertain how to establish them. This however, appears only one more manifestation of a problem which should remain secondary to the primary consideration of restricting abuse. We are developing techniques for projecting medical needs and quotas.

e. The fifth major problem is that of fenfluramine. Fenfluramine will receive a marked competitive advantage if, as proposed, it is the only anorectic drug not placed in Schedule II. It seems unreasonable however to fly in the face of pharmacologic data for reasons of marketing. The proposed labeling will help slightly to place the probable decreased abuse potential in perspective.

4. Political implications

Congressman Pepper, Senator Bayh, and Congressman Rogers have all been interested as Congressional Sub-committee chairmen in the use of CNS stimulant drugs to treat obesity. The stand of Congressman Pepper has been formally to oppose such use; the latter two tend towards such a stand but until now have been content to await FDA policy.

These Sub-committee chairmen quite certainly represent the opinion of a substantial portion of the electorate, which vaguely disapproves of "diet pills", considered obesity to stem from lack of will power, and of course is extremely

concerned about drugs with abuse potential. A vocal consumer group, *The Huntington* (Long Island) *Narcotics Council*, has publicly decried using CNS stimulant drugs to treat obesity, and on this basis has twice petitioned BNDD to reduce manufacturing quotas, once for amphetamine and once for phenmetrazine.

RECOMMENDATION

That the attached memorandum summarizing recommended actions be signed and forwarded to the Commissioner for concurrence.

DISPOSITION

After concurrence or revisions have been indicated by the Commissioner, the package should be returned to this office for preparation of implementing documents. DESI should be informed of the recommendations which they should implement.

TAB A—DRAFT ARTICLE FOR DRUG BULLETIN

AMPHETAMINES

This paper will serve as technical background for possible discussion on the control and distribution of amphetamines and other central nervous system stimulant drugs with abuse potential. It refers briefly to the history of amphetamine use and abuse, describes in some detail the recent control actions taken by HEW and the Department of Justice in the context of the Controlled Substances Act and refers to recent educational actions of FDA.

Racemic amphetamine and dextroamphetamine were introduced into clinical medicine in the early 1930's; their capacity for being abused was recognized within the same decade. The drugs were quite widely used for their stimulant effects by both sides during World War II; perhaps as a consequence more widespread abuse began to occur in the post-war years, with a particularly extensive and well documented epidemic of amphetamine abuse occurring in Japan. In the post-war years, clinical use of amphetamines also grew extensively, as the drugs became widely used in the treatment of obesity, and other conditions.

The abuse potential of amphetamines was not initially fully acknowledged by the general medical community. As it became so, the availability and distribution of amphetamines was progressively restricted. Benzedrine inhalers and other amphetamine products were placed on prescription; controls were applied under the Drug Abuse Control Amendments of the Food, Drug and Cosmetic Act in 1965. More recently, further controls were applied under the Controlled Substances Act.

The Controlled Substances Act, passed in October of 1970, as Title II of the Comprehensive Drug Abuse Prevention and Control Act, includes five "schedules" into which drugs with abuse potential are to be placed, each schedule differing somewhat in the degree of abuse potential of the drugs which it contains and in the degree of control which is applied to the drugs within it. The most stringent is Schedule I, restricted to investigational drugs. For marketed drugs, Schedule II applies the most severe controls and presumably contains drugs with the most severe abuse potential, while Schedule V applies minimal controls and penalties.

The Act when first passed included injectable methamphetamine in Schedule II. Oral methamphetamine as well as oral and injectable amphetamines were included in Schedule III, together with methylphenidate (Ritalin) and phenmetrazine (Preludin) two related stimulant drugs. Other anorectic drugs used in the treatment of obesity were not controlled at all, although possessing central nervous system stimulant activity.

Many people interested in the control of abusable substances both inside and outside government felt that the controls of Schedule III were inadequate for the abuse potential which the amphetamines had demonstrated in the past. Thus, relatively early in 1971, the Food and Drug Administration together with other units within the Department of Health, Education, and Welfare recommended that the oral amphetamines and methamphetamines be moved from Schedule III into the more stringent Schedule II. This was accomplished with the accord of the Department of Justice through its agency, the Bureau of Narcotics and Dangerous Drugs (now the Drug Enforcement Administration). Later in the same year, methylphenidate and phenmetrazine were also moved up into Schedule II.

In 1972 the Food and Drug Administration carried out an overall review of all drugs used in the treatment of obesity. The FDA concluded that all drugs used in treating obesity or proposed for treating obesity did indeed possess some abuse potential; the control of the remaining drugs was finally achieved in 1973. (The drugs placed under control were as follows: phendimetrazine (Plegine), benzphetamine (Didrex), chlorphentermine (Pre-Sate), mazindole (Sanorex), clortermine (Voranil), all in Schedule III and fenfluramine (Pondimin), diethylpropion (Tenuate), and phentermine (Ionamin), into Schedule IV, the latter two in IV only because the manufacturer petitioned for a hearing—they had been recommended for Schedule III).

The changes in scheduling have had an interesting, differential effect. Schedule II prohibits refilling of prescriptions, and allows the Justice Department to impose production quotas that are based in large part on HEW estimates of medical and scientific needs. Schedules III and IV allow five refills of prescriptions in six months time, and do not impose production quotas. The impact of imposing Schedule II controls resulted in a drastic decrease in the distribution of amphetamines following the transfer of these drugs from Schedule III into Schedule II. Monthly pharmacy prescriptions dropped from between one and a half million to two million per month to approximately six hundred and fifty thousand prescriptions per month. There has been an additional continuing downward trend; on the basis of the downward trend together with the elimination of certain combination and injectable amphetamine products, the Bureau of Narcotics and Dangerous Drugs, utilizing FDA recommendations, has now imposed quotas permitting only approximately 8% of the amphetamines production which existed prior to rescheduling. The rescheduling of drugs into Schedules III and IV has not so far produced a decrease in prescriptions for these drugs.

TAB B—DRAFT PREAMBLE TO PROPOSE ANORECTIC SPI

The Food and Drug Administration has reviewed extensive data on "anorectic" drugs used in obesity and concludes that the drugs have a limited place in obesity treatment regimens. The Agency concluded that all of the drugs investigated possess some potential for abuse and so should be used with particular care. The most controversial members of the therapeutic class, the amphetamines, produce weight loss, too, and so will continue to be labeled for use in obesity. The Agency will continue to check all evidence of non-therapeutic use and diversion through prescription abuse; if present control measures prove inadequate during the next year, further restrictions will be necessary.

These decisions were made following a review of seven months time of the over 200 controlled, double-blind studies submitted to the Agency in the last 12 years by manufacturers of anorectic drugs. These include a number of amphetamine preparations such as Dexedrine, Biphetamine, and Obotan, and closely related congeners, such as phenmetrazine (Preludin), methamphetamine (Syndrox, Desoxyn), benzphetamine (Didrex), phendimetrazine (Plegine), diethylpropion (Tenuate, Tepanil), phentermine (Ionamin, Wilpo), and chlorphentermine (Pre-Sate). In addition, studies carried out with three as yet unmarketed drugs were also reviewed and indicated that these drugs are basically comparable with older agents. They will thus probably be approved for marketing after technical details are ironed out.

The FDA relied in part on the advice of a task force of outside consultants, chaired by Dr. Thaddeus E. Prout of Johns Hopkins. Consultants and FDA agreed that the risks of parenteral injections of amphetamines outweighed any possible advantages associated with these routes of administration, so that "anorectic" drugs will be marketed only for use by the oral route.

Data were also reviewed on the efficacy of combination drugs, chiefly on the possible role of barbiturates or tranquilizers in counteracting the adverse effects of the principal active agents. The combinations generally were found not to differ in a statistically significant way either in efficacy or in the incidence of adverse side effects.

The review project made unique use of the massive files of data in FDA to obtain a computerized overview of the whole therapeutic class. After initial screening and review by six physician-medical officers, records of 206 drug trials were found adequate for in-depth analysis. Individual patient records including patient characteristics, treatments, serial weights, dates of all visits, and any

adverse effects were abstracted and key punched onto IBM cards. The resulting 73,000 cards contained over 4,000,000 pieces of information on 9,900 patients tested with various drugs or placebo for periods ranging from 3 weeks to 1 year. After tabulating data and analyzing them for significance, it could be seen that adult obese subjects instructed in dietary management and treated with "anorectic" drugs on the average tend to lose more weight than those treated with placebo and diet in relatively short-term trials. Further conclusions were:

The amount of weight loss associated with the use of an "anorectic" drug varies from trial to trial. The possible origins of the increased weight loss due to the various drug effects are not established. The increased weight loss appears to be related in part to variables other than the drug prescribed, such as the physician-investigatior, the population treated, and the diet prescribed. Studies do not permit conclusions as to the relative importance of the drug and non-drug factors on weight loss.

The magnitude of increased weight loss of drug-treated patients over placebo-treated patients was only a fraction of a pound a week. The rate of weight loss was greatest in the first weeks of therapy for both drug and placebo subjects and tended to decrease in succeeding weeks.

The natural history of obesity is measured in years, whereas the studies cited are restricted to a few weeks or months duration; thus, the total impact of drug-induced weight loss over that of diet alone must be considered clinically small. The limited usefulness of these agents must be measured against any possible risk factors inherent in their use.

Evidence presented for newer congeners of the amphetamine family and non-amphetamine drugs do not set them apart as having higher benefit or lower risks than older available drugs. The addiction risk potential of fenfluramine may be an exception to this general statement, but it may have some depression inducing capability.

Consultants also noted that the amphetamines, including methamphetamine, have been widely abused in numerous populations. It is thus in the best interests of the public health to limit the use of amphetamines as far as is compatable with adequate therapy. This is both to minimize the risks of dependence in susceptible patients being treated and to decrease the amount of drugs being distributed, since widespread prescription of a dependence-producing drug inevitably increases the possibility for diversion to non-medical use and abuse.

The FDA will thus recommend that "anorectic" drugs be placed under the recordkeeping and other requirements of the Controlled Substances Act. Statements will be required in the labeling of all anorectic drugs advising the practitioner of the limited nature of benefits he may expect with use of drugs and diet rather than diet alone. Labeling will also include statements alerting him to the potential of these drugs for inducing drug dependence and for being abused. The amphetamines will carry a special warning in view of their past history and they will be recommended only for trials in obese patients who have not responded to alternative drugs.

The total effect of the FDA actions will thus be to leave anorectic drugs available for practitioners while informing them more fully of the limitations and risks associated with use of the drugs. The individual physician prescribing or dispensing "anorectic" drugs will thus decide whether in his judgment individual patients require a given drug in addition to the basic essentials of a calorically restricted diet, supportive therapy, and clinical follow-up.

TAB C—CONSULTANT STATEMENTS

CONSULTANTS ON ANORECTIC DRUGS

MEETINGS, CONCLUSIONS, AND RECOMMENDATIONS

FDA has consulted with a number of experts on anorectic drugs in the past including a large consultant group under the Chairmanship of Dr. T. E. Prout in early 1971. Dr. Prout is Associate Professor of Medicine at Johns Hopkins and (until July 1, 1972) member of the FDA Advisory Committee on Metabolic and Endocrine Drugs. For the present review, a small working group was invited, again under the Chairmanship of Dr. Thaddeus Prout. The other clinicians in the group were the Chairman of the Metabolic-Endocrine Committee, Dr. T. S.

Danowski, Professor of Medicine at the University of Pittsburg, Dr. Jay Tepperman, Professor of Medicine at the State University of New York at Syracuse, also a member of the Metabolic-Endocrine Committee, and Dr. H. J. Levin, a general practitioner, valued for his common-sense comments and careful opinions from the point of view of the day-to-day practice of medicine.

In addition to the clinicians, one or both of two statistical consultants were present at each meeting: Dr. Samuel Greenhouse and Mr. Jerome Cornfield, of the FDA Biometry Advisory Committee, Dr. Greenhouse being the Chairman of that Committee. The statisticians advised an interpretation of data, but did not make clinical recommendations.

The Consultants met twice, on June 27 and July 25. At the first meeting they studied the first results of the FDA review, acquainted themselves with background, format, and major decisions to be made and commented in preparation for the second meeting. In the latter meeting, consultants pored over data, drug by drug, and then drafted conclusions. Recommendations were drafted by the Chairman and Dr. Scoville in line with the conclusions and discussion of the meeting. These draft conclusions and recommendations were then mailed to the consultants for revision and concurrence. We have received letters from all four clinicians indicating concurrence (except for minimal editorial changes).

TAB D—DRAFT ANORECTIC DRUG LABELING: ACTIONS AND INDICATIONS

CLASS "ACTIONS" AND "INDICATIONS"

LABELING SECTIONS FOR ANORECTIC DRUGS

Actions.—Is a sympathomimetic amine with phamacologic activity similar to the prototype drugs of this class, the amphetamines. Actions include central nervous system stimulation and elevation of blood pressure. Tachyphylaxis and tolerance have been demonstrated with all drugs of this class in which these phenomena have been looked for.

Drugs of this class are commonly known as "anorectics" or "anorexigenus". It has not been established, however, that the action of such drugs in treating obesity is primarily one of appetite suppression. Other central nervous system actions, or metabolic effects may be involved, for example.

Adult obese subjects instructed in dietary management and treated with "anoretetic" drugs lose more weight on the average than those treated with placebo and diet, as determined in relatively shor-term clinical trials.

The magnitude of increased weight loss of drug-treated patients over placebo-treated patients is only a fraction of a pound a week. The rate of weight loss is greatest in the first weeks of therapy for both drug and placebo subjects and tends to decrease in succeeding weeks. The possible origins of the increased weight loss due to the various drug effects are not established. The amount of weight loss associated with the use of an "anorectic" drug varies from trial to trial, and the increased weight loss appears to be related [in part] to variables other than the drug prescribed, such as the physician-investigator, the population treated, and the diet prescribed. Studies do not permit conclusions as to the relative importance of the drug and non-drug factors on weight loss.

The natural history of obesity is measured in years, whereas the studies cited are restricted to a few weeks duration; thus, the total impact of drug-induced weight loss over that of diet alone must be considered clinically trivial.

Indication.—Is indicated in the management of exogenous obesity as a short term (a few weeks) adjunct in a regimen of weight reduction based on caloric restriction. The limited usefulness of agents of this class (see ACTIONS) should be measured against possible risk factors inherent in their use such as those described below.

TAB E—DRUG DEPENDENCE WARNING FOR ALL NON-AMPHETAMINE ANORECTICS EXCEPT FENFLURAMINE

Is related chemically and pharmacologically to the amphetamines. Amphetamines and related stimulant drugs have been extensively abused, and the possibility of abuse should be kept in mind when evaluating the desirability of including a drug as part of a weight reduction program. Abuse of amphetamines

and related drugs may be associated with intense psychological dependence and severe social dysfunction. These are reports of patients who have increased the dosage to many times that recommended. Abrupt cessation following prolonged high dosage administration results in extreme fatigue and mental depression; changes are also noted on the sleep EEG. Manifestations of chronic intoxication with anorectic drugs include severe dermatoses, marked insomnia, irritability, hyperactivity, and personality changes. The most severe manifestation of chronic intoxications is psychosis, often clinically indistinguishable from schizophrenia.

TAB F—DRUG DEPENDENCE BOX WARNING FOR AMPHETAMINES

(Proposed wording if amphetamines are labeled for restricted use in obesity.)

Amphetamines have a high potential for abuse. They should thus be tried only in weight reduction programs for patients in whom alternative agents have been ineffective. Administration of amphetamines for prolonged periods of time in obesity may lead to drug dependence and must be avoided. Particular attention should be paid to the possibility of subjects obtaining amphetamines for non-therapeutic use or distribution to others, and the drugs should be prescribed or dispensed sparingly.

(In addition, the current Drug Dependence WARNING for amphetamines would be retained in the body of the package insert. See Tab "H" for current labeling.)

TAB G—DRUG DEPENDENCE WARNING FOR FENFLURAMINE

Pondimin (fenfluramine) is related chemically to the amphetamines, although it differs somewhat pharmacologically. The amphetamines and related drugs have been extensively abused and can produce tolerance and severe psychologic dependence, as well as other adverse organic and mental changes. In this regard, after cessation of prolonged administration of fenfluramine in humans, depressive mood changes and "rebound" sleep EEG changes have occurred. Fenfluramine did not produce signs of psychologic dependence in monkeys, however, in contrast to amphetamines, and appears to produce more sedation than CNS stimulation, suggesting that it's abuse potential may be less than that of the amphetamines. Since negative pharmacologic data are of uncertain predictive value with respect to the abuse potential of amphetamine-related drugs, the possibility that fenfluramine may induce dependence should be kept in mind in evaluating the desirability of including it in a weight reduction program. (Tab H—Amphetamine SPI of 8-8-70 unavailable.)

TAB I—DESI NOTICE OF CERTAIN ANORECTIC DRUGS OF AUG. 8, 1970

OD, BD-1

DESI Announcement—Certain Oral Anorectic Preparations (DESI 5378). Charles C. Edwards, M.D. Commissioner of Food and Drugs. OC-1.

1. We recommend publication in the FEDERAL REGISTER of the enclosed draft implementing 23 reports of the National Academy of Sciences-National Research Council on the subject drugs. Twenty-nine preparations (23 NDA's) are covered by the announcement. The drugs are:

Amphetamine with dextroamphetamine as sufonated polystyrene complexes (prolonged release).

Amphetamine with dextroamphetamine and methaqualone as sulfonated polystyrene complexes (prolonged release).

Dextroamphetamine Sulfate with Meprobamate.

Dextroamphetamine Sulfate with Prochlorperazine Maleate (sustained release).

Dextroamphetamine Sulfate with Reserpine.

Diethylpropion Hydrochloride (continuous release).

Methamphetamine Hydrochloride.

Methamphetamine Hydrochloride with Reserpine (long acting).

dl-Methamphetamine Hydrochloride.

dl-Methamphetamine Hydrochloride with Amobarbital (sustained release).

Methamphetamine Saccharate and Hydrochloride with Amphetamine Sulfate and Dextroamphetamine Sulfate.

Phenmetrazine Hydrochloride with Vitamins and Minerals.

Phentermine as the sulfonated polystyrene complex (prolonged release).

2. All of the preparations were evaluated by the Panel on Psychiatric drugs. Other panels also participated in the evaluations. The Academy's evaluations for the anorectic claims for these drugs ranged from "effective, but" through ineffective. We conclude that although some of the anorectic agents are effective in other products, the highest classification for these particular products should be possibly effective. The enclosed evaluation sheets set forth the indications for which the reviewed drugs are regarded as possibly effective and ineffective by the FDA and explanations of differences in the FDA evaluations from those of the Academy.

3. A majority of the members of the Panel on Psychiatric Drugs concluded that sympathomimetic stimulants as a class have been shown to have a generally short-term anorectic action. They are not a treatment of obesity in themselves and should be used as an adjunct to a total program of weight reduction. Further, the anorectic effect often plateaus or diminishes after a few weeks. Clinical opinion as to the contribution of the sympathomimetic stimulants in a weight-reduction program varies widely. Most studies of these preparations are for short periods. The panel suggested that controlled studies of the long-term effects of sympathomimetic stimulants in a weight-reduction program be conducted.

4. The Panels' reasoning for their possibly effective classifications for the anorectic indications of these drugs falls into four broad categories:

a. Sustained- or prolonged-release preparations. Documentation stated to be available to the Panel regarding blood levels of these drugs following the use of the sustained-release form was inadequate to show any superiority of such form. (Acc. Nos. 1290, 1295, 1296, 1302, 1303, 1306, 1308, 1318, 1321)

b. Combinations containing reserpine. The Panel questioned the effect of reserpine in the combination and the amount of reserpine in a usual dose. (Acc. Nos. 1291, 1311)

c. Methamphetamine as an ingredient. On the basis of a presumed pharmacologic similarity to amphetamine, methamphetamine may have a similar anorectic effect. However, supporting evidence is inadequate. (Acc. Nos. 1292, 1298, 1299, 1309, 1310, 1312, 1313, 1318, 1321, 1324, 1325)

d. Combination preparations. The utility of the combination in the treatment of the conditions claimed for each ingredient has not been determined; there is a total absence of positive controlled studies. (Acc. No. 1291, 1295, 1300, 1303, 1304, 1306, 1308, 1311, 1321)

5. The proposed announcement provides for deletion of ineffective indications within 60 days and 6 months to submit effective data, and for sustained-release forms, data showing that the drug is available at a safe and effective rate.

6. Other phenmetrazine products (Geigy's Preludin Tablets and Preludin Endurets) are being covered in another announcement (DESI 11752).

7. Other diethylpropion products (Merrell's Tenuate Tablets and National Drug's Tepanil Tablets) and another phentermine product (Dorsey's Wilpo Tablets) are being covered in DESI 11673, as are other effective anorectics, benzphetamine and phendimetrazine.

8. Parenteral methamphetamine reports will be announced later.

9. Numerous other anorectic preparations, not subjects of NDA's, are on the market.

10. Marketing of two of the products listed in the announcement (NDA 6390 Amphedroxyn Hydrochloride Tablets, Lilly, and NDA 12-371 Prelu-Vite Capsules, Geigy) has been discontinued.

11. The holders of NDA's for products reviewed by NAS will be sent a copy of the NAS-NRC report prior to publication of this announcement. Subsequent to publication the holders of NDA's for similar drugs not reviewed by NAS (see enclosed list) will be advised that their products will also be affected.

HENRY E. SIMMONS, M.D.,
Director, Bureau of Drugs.

TAB J—SPECIAL LABELING FOR FENFLURAMINE

Under ACTIONS:

Most of the statements from the class ACTIONS section for anorectics (Tab D) are applicable. In addition, a statement along the following lines should be included.

Fenfluramine does not appear to possess the degree of abuse potential of such abused anorectics as the amphetamines, when tested in animals and humans (see below under *Drug Dependence*).

Under PRECAUTIONS:

Fenfluramine differs in its pharmacologic profile from other "anorectic" drugs with which the prescribing practitioner may be familiar. Correspondingly, there are possible risks not associated with other "anorectics"; such risks include those of diarrhea, sedation, and posttherapeutic depression. The possibility of these hazards should be weighed against the possible advantage of decreased central nervous system stimulation and/or abuse potential.

In addition the consultants reviewed and approved the draft preamble to a policy statement which forms the attachment under Tab B.

The conclusions and recommendations were as follows:

CONCLUSIONS

1. Adult obese subjects instructed in dietary management and treated with "anorectic" drugs on the average tend to lose more weight than those treated with placebo and diet in relatively short-term trials.

2. The amount of weight loss associated with the use of an "anorectic" drug varies from trial to trial. The possible origins of the increased weight loss due to the various drug effects are not established. The increased weight loss appears to be related to variables other than the drug prescribed, such as the physician-investigator, the population treated, and the diet prescribed. Studies do not permit conclusions as to the relative importance of the drug and non-drug factors on weight loss.

3. The magnitude of increased weight loss of drug treated patients over placebo treated patients, was only a fraction of a pound a week. The rate of weight loss, was greatest in the first weeks of therapy for both drug and placebo subjects and tended to decrease in succeeding weeks.

4. The natural history of obesity is measured in years, whereas the studies cited are restricted to a few weeks duration; thus, the total impact of drug-induced weight loss over that of diet alone must be considered clinically trivial. The limited usefulness of these agents must be measured against any possible risk factors inherent in their use.

5. The amphetamines including methamphetamine have been widely abused in numerous populations. It is thus in the best interests of the public health to limit the use of amphetamines as far as is compatible with adequate therapy. This is both to minimize the risk of dependence in susceptible patients being treated and to decrease the amount of drugs being distributed, since widespread prescription of a dependence-producing drug inevitably increases the possibility for diversion to non-medical use and abuse.

6. Evidence presented for newer 'anorectic" congeners of the amphetamine family and non-amphetamine drugs do not set them apart as having higher benefit or lower risks than older available drugs. The risk potential of Fenfluramine may be an exception to this general statement.

7. There was no evidence in the data reviewed which showed that combination of an "anorectic" agent with other drugs increase the benefits or reduce the risk of the "anorectic" agent.

8. There are no clinical data which support the parenteral use of these drugs in the treatment of obesity. Obesity is not an indication for the parenteral use of these agents.

RECOMMENDATIONS

On the basis of the data reviewed and from all evidence at hand the following actions are therefore recommended:

1. That all "anorectics" reviewed, (dl-amphetamine, d-amphetamine, methamphetamine, benzphetamine, phentermine, chlorphentermine, chlortermine, phenmetrazine, phendimetrazine, fenfluramine, mazindol and diethylpropion) with the exception of fenfluramine, be placed on Schedule II on the basis of abuse potential.

2. That combinations of "anorectics" with other drugs be evaluated in accordance with the policy of the FDA on combination drugs, that each constituent of the drug combination contribute to the total effect claimed for the combined drugs, and that the present available and proposed drug combinations be handled in this manner in view of the lack of demonstrated efficacy for each of the constituents of the drug combinations reviewed.

3. That amphetamines prepared for or in a form suitable for parenteral use not be approved for use in the treatment of obesity.

4. That single-entity oral "anorectic" preparations including the amphetamines be permitted to be labeled for restricted use in obesity provided that they are used in association with a specific weight reduction program and that the clinically trivial contribution of these drugs to the overall weight reduction is properly emphasized. To carry out the latter recommendation a statement such as that made in the conclusions drawn from this review must be included in all labeling and promotional products. This statement should include the following points:

Studies of the effect of "anorectic" drugs in the treatment of obesity when compared with the effects on patients treated in a similar manner without the use of the drugs demonstrate that the magnitude of weight loss of drug treated patients over non-drug treated patients was only a fraction of a pound a week. The rate of weight loss was greatest in the first weeks of study for both the drug and the non-drug treated subjects and tended to decrease in succeeding weeks. The natural history of obesity is measured in years whereas the studies offered for review are restricted to a few weeks duration. Thus, the total impact of "drug induced" weight loss over that of diet alone must be considered clinically trivial. The limited usefulness of these agents must be measured against any possible risk factors such as nervousness, insomnia and drug habituation that might be inherent in their use. Moreover, these agents can only be recommended for use in the treatment of obesity in a carefully monitored and specified weight reduction program under the care of a physician.

5. That future approval of all "anorectic" drugs prepared for future use be based on demonstration of efficacy as measured by statistical superiority of the drug over placebo in trial using FDA recommended protocols. These protocols should include provisions, among others, for the testing of a specific target population, specification of a minimum duration trial to assure clinical relevance of the study and give consideration to the handling of patient drop-out.

6. Further, that appropriate summary data derived from efficacy studies be presented in labeling and in all promotional material to indicate the degree of weight loss that was found. For this purpose the guidelines noted in (4) above should be supplemented by the addition of the specific facts found for the specific drug under consideration.

MAY 6, 1976.

Since the Panel discussions on January 18, 1976 and March 16, 1976 reveal that the Panel members were not fully conversant with the manner in which the computer analysis of the 206 anorectic studies was carried out, and since the remarks of the Executive Secretary and the Chairman (see transcripts of January 18, 1976, pages 138–153, and March 16, 1976, pages 13–15) may have given the Panel members a very erroneous impression of the nature of this computer analysis and of how it was subsequently used by the outside consultants, I would like to draw the Panel's attention to the following:

1. An undated Action Memorandum,[1] concerning the FDA's posture on the anorectics, from Dr. Crout to Dr. Simmons, contains, as Attachment A, an FDA Drug Bulletin draft which states on page 2:

"* * * After initial screening and review by six physician-medical officers records of 206 drug trials were found adequate for in-depth analysis."

These six physicians were asked to give their opinions as to whether each of the studies they reviewed was adequate to permit valid conclusions. (One of the Study Description sheets is attached.) Of the 206 studies reviewed, 122 were contained in just three NDAs. As can be seen from the following tabulation derived from data accumulated by FDA statisticians, the reviewing physicians deemed less than half of the 122 to be adequate to permit valid conclusions:

NDA No.: Name of drug	Reviewing physician	Does study permit valid conclusions? Yes	No	Uncertain	Total
16-618: Pondimin	Dr. Freeman	0	21	0	21
	Dr. Wright	0	16	0	16
16-880: Voranil	Dr. Trilling	33	18	3	54
17-247: Mazindol	Dr. Woo	16	6	9	31
Total		49	61	12	122

[1] Which was followed by an Action Memorandum, dated October 6, 1972, from Dr. Simmons to then Commissioner Edwards.

In spite of the above, the statisticians were instructed to include all 122 in their computer analysis!

2. The above judgments of inadequacy were based primarily on the inadequacies of, and deviations from, the clinical protocols; the objections raised in my Medical Officer Reviews (copies of which were submitted to Commissioner Schmidt on March 7, 1975) included serious doubts as to the validity of some of the lab data and hence are additive, rather than merely corroborative of the above tabulation.

3. On June 27 and July 25, 1972, four outside clinicians headed by Dr. Prout and aided by two outside biostatisticians considered the computer-generated data prepared by the FDA staff and concluded that:

Perhaps even more surprising is that if the sample size were increased to 30, and all 30 were "good," you might still have 98 "bad" ones undetected!

In other words, such an approach would be a waste of time and effort and could be quite misleading.

ROBERT O. KNOX,
19323 Dunbridge Way,
Gaithersburg, Md.

[From National Institute on Amphetamine Abuse, Edwardsville, Ill., 1966]

Chapter II

USE, MISUSE AND ABUSE OF AMPHETAMINE-TYPE DRUGS FROM THE MEDICAL VIEWPOINT

Maurice Seevers, Ph.D., M.D., *Department of Pharmacology, University of Michigan Medical School, Ann Arbor, Michigan.*

CENTRALANT DRUGS of the amphetamine type are subject to extensive and increasing misuse and abuse in the United States. Estimates based upon incomplete figures suggest that seventy tablets of amphetamine and amphetamine-type drugs are prescribed legally in the United States for every man, woman and child. This is almost three times the estimated yearly production of barbiturates. Although illicit manufacture of amphetamines exists and is apparently on the increase, no estimates of production are available. It is safe to state that the total production is greatly in excess of proper medical need, some estimates using a factor of 10 or more. Since there is no satisfactory yardstick for measuring the need of this class of drugs in proper medical practice, guessing is the basis of most estimates.

The amphetamines have been used in medical practice about thirty-five years. The principal derivatives of these phenethylamines, are amphetamine itself, the racemic form, the isomer dextroamphetamine and methamphetamine (desoxyephedrine). These are prescribed singly or in combination usually with central nervous system (CNS) or autonomic drugs. Other compounds with amphetamine-like activity, phenmetrazine (Preludin®) and diethylpropion (Tenuate®) have been developed in the hope of reducing the CNS stimulant properties but retaining other pharmacological actions, such as the antiappetite properties. This, however, has not been accomplished and all such compounds are misused or abused. At least seventy-one preparations containing amphetamine-type drugs are available on the American market for prescription use. These are listed in Appendix A.

All of these drugs have a certain value in proper medical prac-

tice and are available legally only on prescription. Unfortunately, the indication for their use is not very precise and is subject to considerable controversy in the medical profession. A clear distinction should be made between actual medical use (total of all "amphetamines" currently prescribed by physicians) and proper medical need (total actually required to fulfill the need in ideal medical practice). This distinction is important since misuse by physicians represents a recognizable part of the problem. Modern day medical practice, where personal contacts are limited, is partly responsible since the proper use of stimulants is a difficult therapeutic area — so much depends on the good judgment of the physician and proper rapport and continued regular contact with his patient.

Although the terms *misuse* and *abuse* are technically synonyms, we have found it useful to utilize the term *misuse* to describe improper or unethical prescribing by physicians, reserving the term *abuse* for improper or illicit use by the patient or user.

Amphetamines and amphetamine-type drugs have been used largely for the following purposes:

1. To prevent or reduce the effects of narcolepsy.
2. To relieve or prevent real fatigue in individuals with deteriorated psychomotor performance.
3. To treat mild depression in chronic neurasthenia.
4. To antagonize the pharmacological actions of depressant drugs (barbiturates, alcohol, etc.).
5. To reduce appetite in antiobesity treatment.
6. To induce insomnia and counteract fatigue in persons required to perform mental or physical tasks of long duration.
7. To increase athletic performance of normal individuals.
8. To induce "kicks," hallucinations and other abnormal psychotic responses.

It should be pointed out that with few exceptions the principal medical indications, items 1 to 5, call for prolonged, continuous medication. This establishes the basis for psychological dependence in susceptible persons with this class of drugs.

The first three indications listed are more clearly in the cate-

gory of proper medical practice and less controversial, although available, controlled studies of the use of *d*-amphetamine in mild depression and fatigue states, as seen in general practice, have shown this drug to be less effective than placebo.

The use of stimulants to antagonize drug depression in acute poisoning is a clear-cut proper indication, but the use of these stimulants chronically by alcohol and barbiturate dependent persons in an effort to increase mental or physical performance is a most dangerous practice since it permits the subject to take larger and larger quantities of depressant drugs leading to mental and physical deterioration. In the same hazardous category is the regular use of amphetamines in the morning to antagonize hangover effects from the "spree" use of excessive alcohol and barbiturates. This often leads directly to dependency.

Amphetamine-type drugs are prescribed to reduce appetite in weight control and reduction programs. Although it is clearly demonstrated that these drugs are capable of appetite suppression, neither weight control nor reduction is likely to be successful with stimulant drugs alone. The best medical clinics rely solely on dietetic control and diuretic drugs for weight reduction. This is undoubtedly the largest area for physician misuse. Prescribing amphetamines on a continuing basis to patients who have shown no substantial weight reduction will, in many cases, lead to the establishment of strong psychological dependence. Once established strongly, the patient begins to abuse the drug compulsively and often seeks other sources of supply to fulfill his increased need as tolerance develops. Careful epidemiological studies made in Great Britain indicate that a majority of amphetamine abuse was in women in the thirty-five to fifty age range.

Since these drugs show comparatively little acute toxicity with ordinary clinical doses, ethical physicians are often careless about prescribing large quantities without a "no refill" order. Obesity clinics have, from time to time, been established by unethical physicians; patients receiving their supply of drug from a nurse, often without medical examination of any kind. These are now fairly well controlled by medical boards of licensure. Drug manufacturers are attempting to find antiappetite drugs without stimu-

10 *Amphetamine Abuse*

lant properties. This problem has yet to be solved since the substitute drugs presently available are stimulants and have been misused and abused.

Amphetamines in moderate dosage (5-10 mg) are capable of rendering most individuals more alert, more wakeful (often to the point of insomnia), and less aware of fatigue. These properties have legitimate medical usage in situations where the individual must continue to perform adequately both mentally and physically under great stress for comparatively long periods of time. All of the important combatant nations in World War II used these drugs judiciously in aviation, especially during prolonged and hazardous bombing missions. In fact, dumping large amounts of surplus amphetamines on the postwar Japanese market where it was, at that time, available without prescription, established a serious drug-abuse problem, especially among juveniles. This reached a peak of 55,000 convictions under a newly created anti-amphetamine law in 1954 and conditioned a social pattern of drug abuse which has plagued Japan ever since. Strict laws and rigid enforcement control of amphetamine distribution has currently reduced the problem but many types of other stimulants (SPA, ephedrine, and the like) and many depressants (barbiturates, Hyminal, a sedative hypnotic, etc.) are currently abused. Furthermore, there has been a concurrent sharp increase in heroin dependency.

Probably, the greater use for alerting and insomniac purposes in the United States is by truck drivers and students. From a medical point of view, reasonable use of the drugs for this purpose would appear to be proper. In fact, within the limits of reasonable fatigue, amphetamines could be life-saving in night-driving situations involving a few extra hours. Abuse comes into the picture when attempts are made to drive the human organism beyond the maximum mental and physical capabilities of the individual. The same logic applies to the use of drugs by students to study for examinations. There is no carefully controlled study of comparable performance of amphetamine users versus nonusers. The few studies available fail to reveal any significant difference and leave the question unanswered of whether it is possible to increase mental performance over the normal maximum.

A principal hazard of general use of these drugs by self-administration lies in the fact that the user is rarely capable of making satisfactory evaluation of his performance and is most likely to overmedicate, thus frequently leading to chronic abuse in neurotic and poorly balanced individuals.

It should be inferred from the statements that the writer condones the widespread use of amphetamines for these purposes. Amphetamines offer no magic source of mental or physical energy; but serve only to drive the individual to a greater expenditure of his own native resources, often to the point of fatigue of the structures from which greater output is expected. Automobile drivers who continue beyond their mental and physical capabilities risk their lives and those of others, with or without amphetamines.

The use of amphetamines in athletics is more widespread than is generally admitted. In contrast to the situation with mental performance, carefully controlled studies have demonstrated that amphetamines are capable of driving trained athletes to increased performance in individual athletic events involving strength and endurance. In the past, they have been used extensively for "doping" race horses but there is no substantial proof of efficacy in this "doped" situation.

Since the use of amphetamines — and other drugs for that matter — to increase performance involves ethical and moral as well as pharmacological and medical considerations, and is not likely to lead to individual harm or antisocial behavior, a very thin line exists between whether it should be termed use, misuse, or abuse. Regardless of how it is designated, such use could not logically be considered to be in the same category as chronic abuse or spree abuse of illicit drugs.

Amphetamines as a generic class of drugs all have certain pharmacological properties in common with other sympathomimetric or adrenergic drugs like epinephrine and other catecholomines on the autonomic nervous and cardiovascular systems and smooth muscle. They differ in possessing, in addition, a much greater capacity to stimulate the CNS. In small doses, this is limited to elevation of mood and the induction of a state of "well-being." As the dosage is increased, apprehension, volubility, tremor and excitement occur, and with larger doses hallucinations, and

even convulsions — the latter being more prominent after large doses given intravenously, the common technique used by "street addicts." Abuse of this class of substances arises from and is perpetuated solely by the psychic drives to attain maximum euphoria. Physical dependence does not develop. Qualitatively, these psychologic effects are similar to those produced by cocaine. However, cocaine is a much more dangerous agent, and quantitative comparison would not be valid. In contrast to the amphetamines, cocaine is capable of inducing severe cytotoxic effects in nearly all tissues, including the brain.

A characteristic feature of the amphetamines is their capacity to produce tolerance. This property is possessed by only a few CNS stimulants. Although tolerance develops slowly, progressive increments in dosage permit ingestion of amounts hundreds of times greater than the original therapeutic dose. The daily ingestion of 1700 mg of amphetamine has been reported. For instance, progressive increase in dosage over many weeks permits the monkey to tolerate ten to twenty times the average lethal convulsive dose. It would appear that all the components of the brain do not become tolerant at the same rate. Thus, a user will experience increased nervousness and insomnia as the dose is increased. Ingestion of very large quantities may induce profound behavioral changes, often of a psychotoxic nature, including hallucinations and delusions. The latter effects are much more likely to occur following intravenous injection. Indeed, "addicts" take amphetamine by this route for the purpose of obtaining bizarre mental effects often associated with sexual fantasies, even orgasm.

Another characteristic feature of the amphetamines is that the cardiovascular system becomes tolerant to large doses rather rapidly so that the heart rate and blood pressure are not significantly increased in those who abuse amphetamines chronically.

Although amphetamines do not induce physical dependence as measured by the criterion of a characteristic and reproducible abstinence syndrome, it would be inaccurate to say that withdrawal of large doses is symptomless. The sudden removal of a stimulant drug which has masked chronic fatigue and the need for sleep permits these to appear in an exaggerated fashion. The

withdrawal period is characteristically a time of depression, both psychic and physical, and this depression probably reinforces the drive to continue the drug. However, the withdrawal of amphetamine is not comparable to the withdrawal of morphine, barbiturates, alcohol and other substances which create physical dependence. It is never life-threatening and requires psychologic rather than supportive medical therapy.

Discussion of the last use on the list — the abuse of the drugs obtained most often through illicit channels to induce hallucinatory experiences — being the major subject of this book will be brief since it will be covered extensively in other chapters. From a social viewpoint it falls into an entirely different category than other situations which we have described. Although chronic amphetamine poisoning may be associated with harm to the individual, rarely does the amphetamine dependent individual represent a social menace. Even more rarely could the spree abuse of amphetamines by the street addicts be traced to prior medical use or misuse by the physician. Such abuse could conceivably, however, find its origin in any situation which involves the illicit supply of these drugs whether this be middle age women who learned to abuse the drug in a phony obesity clinic, a truck driver, or even a student.

In closing, it should be pointed out that the amphetamine problem is only one facet of a much larger drug abuse problem which probably involves at least 5 per cent of the adult population of the United States. The same factors, emotional immaturity becoming manifest more commonly in unfavorable environmental circumstances and precipitated by stressful situations, are common to all types of drug abuse and require the same type of treatment.

RECOMMENDATIONS

1. Educate and reeducate those who have legal access to these drugs, i.e., physicians, dentists, veterinarians, nurses and the pharmacists who fill prescriptions, to the hazards of loose and illegal prescribing, dispensing and handling of these drugs.

2. Educate the public to the medical hazards of drug abuse and the characteristics of each type of drug abuse through the news

media, printed, auditory and visual; the schools, first the teachers and then to the students; and in public forum in large municipalities where this problem is usually concentrated. Funds should be sought at municipal, state and federal levels for this purpose.

3. Support the newly established law (P. L. 89-74) activated February 1, 1966 which requires manufacturers, distributors and retail pharmacists to keep open records of all supplies of stimulants, depressants and hallucinogens which have been shown to have been abused or possess a potential for abuse. Although this drug law was aimed primarily at the amphetamines and barbiturates, it is also of such scope as to include all drugs which are capable of abuse.

4. Keep the amphetamine abuse problem in proper perspective with other drug abuse, recognizing it as a part of a larger whole with many problems in common.

5. Encourage all those who deal with drug abuse situations to recognize them as medical and psychological as well as enforcement problems, and that drug dependent individuals who are also criminals may be both for the same psychological reasons.

6. Encourage current efforts at addict rehabilitation at all levels — medical, legal and social.

7. Encourage any well-designed program which would elevate the environmental conditions in our great municipalities.

PERSPECTIVE

Amphetamines: A Dangerous Illusion

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Amphetamines are among the most dangerous of currently abused psychoactive drugs. They cause dependence, behavioral toxicity, and physical damage. Despite their extensive medical use, the evidence suggests they are ineffective or minimally effective in most of the conditions for which they are prescribed. Their widespread use in medical practice is more likely the result of the euphoria and the dependence they induce than of any significant clinical results. This paradox, presented by the legality of amphetamine use, compounds the difficulty of treating youthful drug abusers and educating potential abusers. The following recommendations are urged: prescription of these drugs should, with few exceptions, cease; and production should be sharply curtailed and probably be limited to one or two pharmaceutical companies.

THE RAPIDLY increasing abuse of amphetamines among the young makes it important to revaluate the status of this group of agents in medical practice. Are they valuable drugs, and in what conditions? What results can be expected from their use? What is their mode of action? To what extent are they indispensable? What are their hazards? How often do these hazards occur? Does their medical use have any influence on their illegal use? This article briefly reviews evidence suggesting that the amphetamines are both ineffective and unsafe, offers speculations about why we continue to use them, and recommends changes in the way we use them.

History

Amphetamine, a close relative of epinephrine, ephedrine, and other sympathomimetic amines, was synthesized in 1927. Shortly thereafter, descriptions of its effects on blood pressure and nasal congestion began to appear. Within 5 years it was found to act as a bronchodilator and a respiratory stimulant and also to have remarkable effects on the central nervous system, specifically cerebral stimulation and reduction in appetite. Because of these central effects, several authors warned of the possibility of dependence and tolerance as early as 1937. These warnings are well reviewed by Connell (1).

Despite the warnings, the amphetamines and their uses have proliferated to an amazing degree. The list of "accepted" medical indications for their use now includes obesity, mild depressive reactions, epilepsy, parkinsonism, central nervous system depression caused by barbiturates and other sedative-hypnotics, narcolepsy, and hyperkinetic reactions of children. They have also been used widely to maintain alertness and to increase physical performance.

The 1970 edition of the *Physicians' Desk Reference* (2) lists 65 amphetamine and amphetamine-like preparations produced by 40 companies. These are available either as single-drug preparations or in combination with salicylates, barbiturates, tranquilizers, and other substances. One can obtain a choice of vitamins or hormones along with an amphetamine in 15 preparations from 14 companies. This listing does not, of course, exhaust the preparations available from pharmaceutical companies.

In four cases companies describe in the *Physicians' Desk Reference* the amphetamine they produce and only one other product. In four other cases the amphetamine is the company's sole listed product.

What amount of amphetamines is legally manufactured? No one knows exactly. Estimates range from 5 billion to 8 billion doses a year. The Food and

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Drug Administration estimated, for example, that over 100,000 lb were available in the United States in 1962—enough to supply each man, woman and child with 250 mg (3). About one half of this supply is thought to be diverted into illegal channels (4).

Effectiveness of Amphetamines

While production has flourished, the list of indications has gradually withered, for three reasons: [1] For such conditions as parkinsonism, epilepsy, and depressive reactions newer kinds of treatment have simply proved more effective; [2] for severe central nervous system depression from drug intoxication it is now accepted that no drug is as effective as other treatment such as artificial ventilation, support of the circulation, and hemodialysis (5); [3] for obesity control, now the commonest reason for use, it has slowly become obvious that although appetite-suppressants may have some temporary utility, they are ineffective in long-term treatment.

Narcolepsy and hyperkinetic reactions of children remain the two conditions for which amphetamines are still said to have effect. For narcolepsy, however, methylphenidate is "the present drug of first choice," according to the *Cecil-Loeb Textbook of Medicine* (6); for hyperkinetic reactions preliminary evidence suggests that if any drug is indicated, imipramine may be more effective than amphetamines (7), so that even here good alternatives may be available.

The two commonest reasons for prescribing amphetamines are depression and obesity, and it is for these conditions that we must examine most carefully the evidence for amphetamine effectiveness.

NONEFFECTIVENESS IN MILD DEPRESSIVE REACTIONS

Depressive reactions include a variety of syndromes with a wide range of severity and a strong natural tendency toward spontaneous remission. Their very diversity makes evaluation of any treatment extraordinarily difficult. Yet, common to many depressed persons are conflicts around oral-dependent needs, which suggests that drugs such as alcohol, barbiturates, and amphetamines be used with caution because of their ability to produce dependence. Indeed, depression is the underlying mood in many, if not most, high-dose amphetamine abusers or "speed freaks" (8).

But many doctors ask if amphetamines, although theoretically dangerous, are nonetheless a useful and practical measure for treating mild depressions. Tradition grants them a position of sorts in the treatment of mild cases, although recommendations for their use are becoming increasingly rare (for example, the 1968 edition of Noyes' *Modern Clinical Psychiatry* ignores them). Occasionally one finds a favorable mention, as in Mendelson's article (9) in Freedman and Kaplan's textbook of psychiatry:

> The amphetamines are often useful and sometimes gratifyingly efficacious in lifting the spirits in a mild depression. When antidepressive medication is resorted to, the amphetamines should probably be tried before prescribing the newer antidepressive drugs.

Virtually no authority, however, supports their use for more than an immediate euphoriant lift, and most believe that they have no place at all in the treatment of depression. According to Jarvik, in Goodman and Gilman's text, (10), no well-controlled long-term study has been able to demonstrate their effectiveness.

> The sympathomimetic amines, such as amphetamine and phenmetrazine, and similarly acting central nervous system stimulants, such as methylphenidate and pipradrol, were tried in the treatment of depression and found wanting except in certain mild cases in which a drug-induced acute euphoric state would suffice. . . .

The report of an AMA committee states (3):

> Published studies have indicated that, in general, dextroamphetamine is only slightly more effective than a placebo in ameliorating depressive symptoms.

Cole and Davis (11), also writing in Freedman and Kaplan's textbook, review the evidence thus:

> Amphetamine was found to be less effective than placebo in the treatment of depressed outpatients by British general practitioners. . . . In still another British study, amphetamine also proved less effective than phenelzine, and no better than placebo, in the treatment of depression. In a Veterans Administration study, dextroamphetamine was no more effective than placebo in treating hospitalized depressed patients.

In a recent review of the pharmacologic treatment of depressions Schildkraut (12) states:

> The psychomotor stimulants (for example, amphetamine, methamphetamine and methylphenidate) cause mood elevation, increased alertness and enhanced performance in normal subjects. These drugs may alleviate some of the symptoms of depression in certain depressed patients, but such beneficial effects are often transient and may be accompanied by a number of unwanted side-effects. . . . It is fairly generally agreed that the psychomotor stimulants have relatively little to offer in the treatment of major depressive disorders.

NONEFFECTIVENESS IN CONTROLLING OBESITY

Obesity is usually regarded as a complex, long-

term problem with major social and psychological determinants. Frequently recognized psychological factors are chronic tension and depression, unusually strong oral dependent needs, inability to tolerate frustration, and substitution of food for other forms of gratification. These psychological characteristics may lead to dependence on many kinds of drugs as well as on food. As in the case of depressive reactions, it may be illogical to include in the treatment of such a condition drugs that have a strong potential for causing dependence. "In fact, the use of amphetamine-type drugs is contraindicated for alcoholic persons and other dependence-prone persons" (3).

Short-Term Effect: It is granted by most that amphetamines can induce a period of appetite suppression and increased weight loss for a few weeks. Whether this is of lasting value is questionable, however, since in most cases obesity continues to be a problem over a period of years. Very few short-term gains in treatment of obesity have been translated into long-term successes. More importantly, it is likely that short-term effectiveness is caused more by a stimulant effect than by any direct effect on the appetite control center of the brain. Thorn and Bondy (13), in their textbook article, state:

> As a result of stimulation, or a "lift," the patient's drive toward overeating may be significantly modified and as far as he is concerned, the over-all effect of the drug is "appetite-depressing." Obviously, drugs which create such a state of euphoria may lead to habituation in certain individuals.

Modell (14) pointed out in his 1960 report:

> Central stimulation, not a specific central depressant effect on appetite, is then the common mechanism through which these drugs act; it is clear, therefore, why undesirable central stimulant effects, which have constituted their chief clinical limitation, have thus far appeared to be indivisible from anorexigenic action.

In other words, obese patients may use the drugs in the same way the "speed freak" does—to obtain a "high."

There is also some doubt whether amphetamines are effective in the short term. Again from Modell's report (14):

> The amphetamines present special problems in the evaluation of their effectiveness. Patients often promptly recognize the drug by one or another of the central stimulant effects (usually the "lift"). Thus, they can distinguish between drug and placebo when these are used in what theoretically appears to be a well-designed clinical evaluation with a double-blind control. In patients with emotional disturbances particularly, who include most compulsive overeaters, the ability to distinguish medication from placebo by any effect other than the one under examination (in this case weight loss) makes it exceedingly difficult to prevent bias and psychological factors from shaping the apparent effects of the drug.

Long-Term Effect: Thorn and Bondy (13) evaluate pharmacological treatment of obesity as follows:

> Depression of appetite by a pharmacologic agent can facilitate weight loss, although it is apparent that as soon as the pharmacologic effect wears off, or the medication is discontinued, appetite will return and weight gain will recur unless the patient's inherent capacity to control his food intake has been altered fundamentally. *That the pharmacologic agent used for these purposes be devoid of serious toxic side effects is axiomatic* [emphasis added].
>
> Unfortunately there is no pharmacologic agent available at this time which acts primarily by depressing the "appetite center."

In her textbook article Albrink (15) devotes 3,600 words to the treatment of obesity. This is her discussion of amphetamines:

> Drugs. Appetite-suppressant drugs of the amphetamine group are effective for only a few weeks. Dependence on their stimulatory effect occasionally makes withdrawal a problem. Such drugs have no demonstrated role in the long-term management of obesity.

Reinforcing this opinion is the report of the AMA Committee on Alcoholism and Addiction and Council on Mental Health (3):

> In long-term (more than a few weeks) programs of weight reduction, the superiority of these substances to placebo has not been demonstrated.

In 1959 Stunkard and McLaren-Hume (16) reviewed the literature on the treatment of obesity. Their summary states:

> A review of the literature on outpatient treatment for obesity reveals that the ambiguity of reported results has obscured the relative ineffectiveness of such treatment. When the per cent of patients losing 20 and 40 pounds is used as a criterion of success, the reports of the last thirty years show remarkably similar results. Although the subjects of these reports are grossly overweight persons, only 25% were able to lose as much as 20 pounds and only 5% lost 40 pounds.

In 1966 Glennon (17) reported a follow-up:

> Review of the literature since 1958 did not reveal a successful long-term study using a diet regimen by itself or in combination with drugs, psychologic treatment, or an exercise program.

Astwood (18) is even more negative in his evaluation of all methods of treatment, including the pharmacologic.

> All of us know that we can't get fat people to become slim by suggesting a diet, so we conclude, for the time being at least, that obesity is incurable.

Modell (14) reemphasizes the point in the summary of his report:

> New and logical pharmacotherapy for persons who overeat will more likely come with understanding of the processes involved than through the current practice of developing more variations on old themes which have already been well exploited and have not satisfied the need. There is really nothing new on the scene. There are no "anorexiants" to fit specific disturbances in eating patterns, and there are no useful depressants of the appetite center, wherever it may be. . . . Current pharmacotherapy for persons who overeat has limited use. Insofar as drugs are concerned, at the very best, their potential is secondary to the elimination of the cause of the hyperphagia. Drugs which give assistance along the lines now available provide short-lived symptomatic relief only.

Despite 20 years of extensive use, then, the place of amphetamines in clinical practice is far from established. They represent the treatment of choice for only a small number of those patients for whom they are prescribed. Their effectiveness in treating obesity and depressive reactions is minimal and controversial.

Interestingly, the pharmaceutical industry tells us indirectly that the amphetamines and related drugs offer only a low order of effectiveness by constantly introducing new congeners and combinations. For example, in the 1970 *Physicians' Desk Reference* eight companies have listed nine "new" amphetamine products not listed in the 1968 edition. The industry sends the same message in another more encouraging way; within the last 2 years four companies have voluntarily discontinued their production of amphetamines (Methedrine®, Burroughs Wellcome; Phetobese®, Cole; T.V.D. Formula®, Lambda; Ad-Nil®, Medics).

Hazards of Amphetamines

The irony of the amphetamine situation is that whereas we have been slow to admit the negligible utility of these agents, we have also been slow to recognize their dangers. Their illegal and casual use as stimulants of the central nervous system has grown tremendously. They have become perhaps the most serious drug of abuse in the United States (as in several other countries), except in the large cities, where heroin addiction is widespread. Most physicians are not yet sufficiently familiar with these hazards, which are well documented elsewhere (1, 3, 8, 19-22). Briefly, they fall into all three major areas of concern in psychoactive drugs.

1. Amphetamines are associated with *tolerance* and with an intense *psychological dependence*, which makes it difficult to withdraw from the drug without help. High-dose use may begin in a pattern of illegal experimentation, but it may also begin with a physician's well-intended prescription. The nature of the drug's effects leads easily to progressively increasing dosage in susceptible persons. Prediction of "susceptibles" cannot be made with confidence, but patients for whom amphetamines are prescribed are probably, by the very nature of their illnesses, among those most likely to increase the dose and become dependent. Then begins a prolonged struggle to discontinue drug use, an effort usually attended by intense lethargy and depressive symptoms. The period of depression during the withdrawal (or "crash") is frequently associated with suicidal feelings and actions. The absence of physical dependence in amphetamine abuse may give the impression that it is easier to withdraw from than heroin. This has not generally been the case; in fact, the reverse may be true, although data on this point are lacking.

2. The *behavioral toxicity* of high doses is usually such that the user cannot maintain work, school, or family relationships. With high doses a typical psychosis often develops, characterized by hyperactivity, distortions of reality, impaired judgment, paranoid ideation, and hallucinations. Despite this disturbance, the sensorium is clear, and the individual may appear superficially normal (19).

3. The *physical toxic effects* on the autonomic nervous system and cardiovascular system include sympathetic gastrointestinal and urinary symptoms, occasional systolic and diastolic hypertension, sometimes cardiac arrhythmias (8, 21), and possible necrotizing angiitis (22). In addition, malnutrition, hepatitis, and other serious infections are associated with the intravenous use of these drugs.

These are the major toxic manifestations of illegal, high-dose amphetamine use. But damage also results from the less spectacular adverse reactions to small, legally prescribed amounts and may cause disability for greater numbers of people. These case examples are familiar to most practicing physicians:

Case 1: A 23-year-old male first-year medical student asked his physician for stimulants to help him overcome classroom drowsiness, difficulty in studying, and mild depression. He did not have narcolepsy. Dextroamphetamine, 5 mg daily, was prescribed. He was asked to return but did not. When next seen, he had flunked out of school. Although not the sole factor in this patient's failure, the amphetamine obviously did not help his studying and may have been a critical determinant in his avoiding early, appropriate counseling.

Case 2: To control her appetite a 47-year-old woman had used various amphetamines almost daily for 10

years. Despite this, she was grossly obese. She realized that she had continued to take the medication largely to avoid lethargy and to get through each day. She was now attempting to withdraw but was finding herself depressed, gaining weight, unable to mobilize enough energy to keep her house clean, fighting with her husband, and blaming herself for all her children's personal problems because she had worked while they were growing up. Her use of amphetamines had allowed her to manage her personal and family problems in ways she no longer considered appropriate and had provided a comfortable alternative to counseling (which she had tried unsuccessfully). With the children grown, menopause reached, and husband alienated, she was now decompensating without the drug.

Case 3: A 20-year-old female student was well-adjusted but occasionally depressed in the face of religious conflicts between strict parents and a more relaxed fiancé. With marriage and a job 6 months away, she felt the need to lose some weight even though she was not obese. She approached her physician for diet pills. He reluctantly prescribed 30 Desbutal Gradumet® tablets, each containing 10 mg of methamphetamine hydrochloride and 60 mg sodium pentobarbital. She lost 7 lb in the next 30 days. She also engaged in her first coitus during this period, experiencing deep guilt. After finishing the prescribed amount she felt lethargic and depressed. Four days after taking the last tablet she had fights with her fiancé and her sister, became very upset and depressed, and impulsively ingested 30 tablets of a sedative-analgesic (Fiorinal®), each containing 50 mg of an intermediate-acting barbiturate (butalbital). She was hospitalized moderately intoxicated, and recovered. For this girl the combination of major emotional conflicts and the depression caused by amphetamine withdrawal led to a suicide attempt.

It is important to recognize that these patients were giving their physicians a common message: they needed help with an emotional problem. The physician's response to the overt request for a pill prevented him from providing help for the real problem.

Why Are Amphetamines Still Being Prescribed?

Why are drugs of such dangerous potential and so little objective advantage still in wide use? Amphetamines are, after all, not life-saving agents. Several explanations are possible:

1. Most physicians have not had an opportunity to observe a seriously affected high-dose amphetamine abuser or "speed freak."

2. Most physicians feel a need to offer something to the patient trying to lose weight, both physician and patient often sensing, but not verbalizing, that they are dealing with a problem nearly untreatable in traditional terms.

3. The economic value of amphetamine sales is substantial, judging from the industry's enthusiastic promotion of these agents despite the serious questions about their utility.

4. Tens of thousands of respectable adults are to some extent dependent on them and exert suasion on their physicians to continue prescribing them.

5. Physicians themselves use and abuse psychoactive drugs more often than the general population (23). This suggests that sometimes they may also have difficulty objectively evaluating the use of these drugs for their patients.

6. It is possible that amphetamine popularity reflects American culture. As Fiddle (24) has observed, the amphetamine user is a caricature of many widely admired American traits: intense activity, efficiency, persistence and drive, and the desire to excel, to break records, and to move with ever greater speed. These are admirable behavior patterns that are not easily relinquished, even when a drug may be required to achieve them.

The result is the perpetuation of the legal use of dangerous agents of little therapeutic advantage. This is not the first description of the hazards or of the minimal effectiveness of these drugs, nor is it the first effort to suggest that their medical use be curtailed (25-27). But the problem grows.

To some extent the current drug-abuse epidemic may relate to the way we as physicians have handled the amphetamine problem. Our use of the drug may be providing a poor model for children and adolescents to emulate. By treating with drugs a condition such as obesity, which probably most often has its roots in social custom and psychological conflict, are we giving license by example to youngsters who would treat their own social and psychological discomforts pharmacologically?

The time to face the unpleasant facts is long overdue. Amphetamines are fascinating substances with a wide range of effects—some good, some bad. Their use represents a sincere effort to treat major causes of human suffering. At present, however, we are not in a position to handle them safely. The situation raises uncomfortable questions: If amphetamine use of all types—legal and illegal—were to cease completely tomorrow, would we be better or worse off with regard to health than we are today? Do we really need these drugs?

We must begin taking steps now to end the epidemic overuse and misuse of amphetamines. Few of us would welcome more restrictive legislation in the drug field or more extensive activity by the Food and Drug Administration. Yet this is the prospect if we avoid taking immediate remedial action.

This action should begin with the physician's voluntary cessation or sharp reduction of prescriptions for amphetamines and their congeners. Exception might be granted in individual cases for the treatment

of narcolepsy and hyperkinetic reactions of children but rarely in other conditions. It is difficult, if not impossible, to justify their continued use in obesity and depression. Physicians may need a buffer against pressures for continued prescriptions from some patients. If so, a medical committee or board could be established to authorize these exceptions, as in Sweden (28). To circumvent the weariness most of us feel toward more committee work and the suspicion that an endless list of drugs may later come under such scrutiny, let me suggest that it is no more than we would do if heroin were made legal. Amphetamines are no less a menace.

Severe curtailment of production is essential. Less than 1% of the current volume would probably be an adequate supply for the exceptional case. No more than two pharmaceutical houses are needed to provide this amount. The industry's voluntary action toward this goal would provide refreshing evidence that it puts the public welfare first and that legislation is not required on every urgent health matter. Finally, advertising of these products in medical journals is inappropriate.

We need not delude ourselves that these measures will end amphetamine abuse: they will not. It is not certain they will even reduce it measurably for several years. Black-market production will doubtlessly expand. The diagnosis of narcolepsy may suddenly become more popular. These measures are, however, a step in the direction of removing one major inconsistency in our approach to drugs and of establishing a climate that does not so vigorously promote drug abuse.

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[From the Medical Letter, 14:94-6, Dec. 8, 1972]

DRUGS IN PREGNANCY

Since the thalidomide tragedy, there has been increased concern about the effects of drugs on the unborn child; testing of new drugs in pregnant experimental animals has been required in the United States since 1962. In one study, more than 90 per cent of 3,072 pregnant women took at least one drug and four per cent took 10 or more; the average number of different drugs taken during pregnancy was four (C. H. Peckham and R. W. King, Am. J. Obstet. Gynecol., 87:609, 1963). A more recent survey of 1,369 women found that 97 per cent took at least one drug during pregnancy (M. M. Nelson and J. O. Forfar, Br. Med. J., 1:523, 1971).

CYTOTOXIC DRUGS - Most cytotoxic agents used in cancer chemotherapy and immunosuppression have teratogenic potential. Aminopterin given during the first trimester in 52 pregnancies was associated with 34 abortions; malformations were noted in 10 of 12 fetuses that were examined (H. O. Nicholson, J. Obstet. Gynaecol. Br. Commonw., 75:307, 1968). Methotrexate administered during the first trimester has been reported to have caused malformations of the skull, face and extremities (A. Milunsky et al., J. Pediatr., 72:790, 1968; H. R. Powell and H. Ekert, Med. J. Aust., 2:1076, 1971). Mercaptopurine (Purinethol), azathioprine (Imuran), and cyclophosphamide (Cytoxan) taken in the first trimester have been associated with a high incidence of abortion, but not with an increase in major malformations in the small number of pregnancies that ended in live births.

CENTRAL-NERVOUS-SYSTEM DEPRESSANTS - Barbiturates, opioids and other central-nervous-system depressants may cause neonatal respiratory depression when administered in high dosage during labor. Reserpine administered at term produces nasal congestion that can lead to serious respiratory obstruction in the newborn.

Narcotic abuse by a pregnant woman often produces withdrawal symptoms in the newborn infant; these can be lethal if they are not recognized and treated. Withdrawal symptoms appear to be especially prolonged in infants born to women taking methadone, as compared with heroin (B. K. Rajegowda et al., J. Pediatr., 81: 532, September 1972). There is some evidence that LSD taken in early pregnancy may produce malformations in the fetus (S. R. Assemany et al., Lancet, 1:1290, 1970; J. L. Eller and J. M. Morton, N. Engl. J. Med., 283:395, 1970).

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ANTICONVULSANTS - Drugs used for the treatment of convulsive disorders include a number with pharmacologic properties that pose a potential threat to the fetus. Diphenylhydantoin (Dilantin; and other brands) for example, can interfere with folic acid metabolism. A recent survey of the outcome of 427 pregnancies in 186 women being treated for seizure disorders found twice the usual frequency of major congenital malformations. The most common deformities were cleft lip with or without cleft palate and microcephaly (B. D. Speidel and S. R. Meadow, Lancet, 2:839, October 21, 1972).

ANTICOAGULANTS - Oral anticoagulants can produce hemorrhage during labor, leading to fetal death. If coumarin-type drugs are used in pregnancy, they should be stopped about one week before labor is expected to begin. If anticoagulation is required in a pregnant woman at term, heparin is the drug of choice.

ANTIBIOTICS AND ANTIMALARIALS - Sulfonamides taken near term can increase the risk of kernicterus in the infant. Streptomycin administered at any time in pregnancy and quinine near term have caused deafness of the newborn. Tetracyclines chelate with calcium and are deposited in bones and teeth; these drugs cross the placenta, collect in fetal calcified tissue and remain as stains in deciduous teeth. The penicillins are generally considered safe for administration during pregnancy.

One of the earliest reported drug-induced human malformations was masculinization of female fetuses by maternal progestational therapy. Many synthetic progestins, as well as methyltestosterone, have been implicated.

Recent studies report that vaginal adenocarcinomas occurred in adolescent girls whose mothers took diethylstilbestrol (DES) during pregnancy. The number of cases reported recently in young women exceeds the total number found before the drug was used in pregnancy (A. L. Herbst et al., N. Engl. J. Med., 284:878, 1971; P. Greenwald et al., N. Engl. J. Med., 285:390, 1971). Whether other drugs can produce such long-delayed effects is not known.

ANTIHISTAMINES - Some piperazine antihistamines were once frequently used as antiemetics in early pregnancy. Animal studies have shown that three commonly used drugs — meclizine (Bonine), cyclizine (Marezine), and chlorcyclizine — are teratogenic in the rat (C. T. G. King et al., J. Pharmacol. Exp. Ther., 147:391, 1965). The severity of these deformities and their frequency, approximating 100 per cent, led to concern about their use in man. Although retrospective studies, including thousands of infants whose mothers had taken these drugs, found no increased incidence of abnormalities, most Medical Letter consultants consider it prudent to avoid them during the first three months of pregnancy. Nausea of pregnancy is more safely managed with small, frequent feedings.

VITAMINS - Excessive quantities of vitamins may harm the fetus. Very large amounts of ascorbic acid are now widely used to prevent and treat colds and other acute respiratory infections. Such high doses taken during pregnancy may cause scurvy in infants when birth abruptly removes them from the high ascorbic acid environment (W. A. Cochrane, Can. Med. Assoc. J., 93:893, 1965). Synthetic vitamin K given in large doses near term can raise serum bilirubin concentration and increase the possibility of kernicterus. High maternal doses of pyridoxine have been implicated in withdrawal seizures in infants (W. A. Cochrane, cited above).

CONCLUSION - Many drugs taken during the first three months of pregnancy are teratogenic. An even greater number produce fetal injury when taken after the first three months or at term. The 1962 Amendment to the Food, Drug and Cosmetic Act requires testing of new drugs in pregnant animals before testing in man, but there is often a difference between teratogenic effects in animals and humans. Drugs that do not produce these effects in several species of animals might still be teratogenic in humans; careful clinical observation over many years is essential to exclude injurious effects. Unless a drug is urgently needed, it should not be administered during pregnancy, especially during the first trimester or close to the time of delivery.

[From Science, vol. 194, pp. 1027-28, Dec. 3, 1976]

AMPHETAMINES: TIGHTER CONTROLS ON THE HORIZON

(By Constance Holden)

The abuse of the central nervous system stimulants known as amphetamines has dropped since "speed" had its hey-day in the 1960's. But amphetamine abuse is still a major problem in terms of physical damage and emotional dependency. And despite the fact that manufacture and distribution of the most dangerous varieties of the drug have been under strict federal controls since 1971, it still seems to be available to anyone who wants it.

Thats what Senator Gaylord Nelson (D-Wis.), chairman of the monopoly subcommittee of the Senate Small Business Committee, heard in 5 days of hearings he conducted last month on the safety and efficacy of antiobesity drugs.

The major condition for which amphetamines and ampetamine-like drugs (amphetamine congeners) are legally prescribed is obesity. But the evidence is strong that for most of the 2.25 million Americans estimated regularly to take prescribed amphetamines—not to mention uncounted users who buy them on the street—the drugs are not primarily being used for legitimate medical purposes.

It has been 6 years since Congress passed the Controlled Substances Act, which enabled the government to put restrictions on the production and distribution of licit drugs that are subject to abuse. Amphetamines and their congeners are controlled under the law, which has sharply reduced prescriptions of the formulations thought to be most dangerous. But the act seems to have reached the limits of its effectiveness, because the level of amphetamine consumption, according to Food and Drug Administration (FDA) statistics, has remained constant over the past 3 years. Furthermore, consumption of amphetamine-like drugs has gone up and there are many experts who believe their potential for abuse is almost as great as it is for amphetamines.

This phenomenon, combined with accumulating evidence to the effect that diet pills are of marginal use in combating fat, has led Nelson to conclude that, according to an aide, "the time is ripe" for amphetamines to be wiped off the market altogether, and for stricter controls to be put on other sympathomimetic diet drugs. There remain two respectable applications for at least one amphetamine congener—Ritalin (methylphenidate)—which are narcolepsy and childhood hyperkinesis. Ritalin is not used as a diet drug but it and Preludin (whose only indication is for obesity) are said to be the most heavily abused drugs in the amphetamine family.

It has been 4 years since an FDA advisory panel concluded that amphetamine-type diet drugs were "clinically trivial." The preponderance of testimony from nongovernment witnesses at the hearings was to the effect that the drugs are neither safe nor efficacious. They curb appetite for a short time, but tolerance is quickly built, and if the pills are withdrawn the appetite returns in full force. Tentative evidence was also presented that these pills taken in the early weeks of pregnancy may cause fetal heart defects and other malformations.

Now, judging from what government witnesses said at the hearings, it appears that the FDA and the Drug Enforcement Administration (DEA) are getting ready to agree that the abuse potential of many of these drugs outweighs whatever short-term benefits they have in helping obese people change their eating habits.

As J. Richard Crout, director of the FDA's Bureau of Drugs, testified, in view of the failure of the Controlled Substances Act to minimize abuse, "the only meaningful next step which can be taken is to remove the indication for obesity from the labeling for amphetamines or to remove them from the market." Since obesity is the only indication for some, changing the label would be tantamount to outlawing them altogether.

It has been more than a dozen years since various groups, including members of Congress, have been attempting to curb or even ban entirely the marketing of anorectic (appetite-suppressing) drugs. But the success has been limited in the face of dedicated resistance on the part of pharmaceutical manufacturers—amphetamines and their relatives are the backbone of the diet pill business—and undiscriminating prescription practices on the part of some physicians—all catering to voracious public demand for fast-acting means to thinness and happiness.

The 1970 act sharply reduced production of diet pills—which reached an all-

time high of 12 billion in 1971—by putting the most dangerous substances, amphetamine, methamphetamine, and phenmetrazine (otherwise known as Preludin) on Schedule II of the Controlled Substances Act. This is the most restrictive category for licit drugs. It lays down production quotas, requires detailed monitoring and record-keeping, and forbids renewals of a prescription without a physician's approval. Other amphetamine-like drugs were put on Schedules III and IV, a move that recognizes their abuse potential but doesn't restrict distribution other than through prescription requirements.

The regulatory problem has become increasingly complex in recent years as companies have come out with new drugs that are amphetamine-like in varying degrees. Some of these have been put on Schedule III or IV even though their abuse potential would seem to warrant tighter restrictions. For example, Pennwalt Corporation, the country's biggest manufacturer of diet pills, rechanneled its energies to marketing a drug called Ionamin after its big seller, Biphetamine, was put on Schedule II. Pennwalt claims that Ionamin is not an amphetamine and does not have the associated side effects. Lester Grinspoon, psychiatrist at Massachusetts Mental Health Center and the lead-off witness at the Nelson hearings, says, however, that the chemical structure is similar to amphetamine, and any minor chemical change is unlikely to change the drug's action much. [There is a class of amphetamine-like compounds that exert effects that are more sedative than stimulant, and sometimes hallucinogenic. Fenfluramine (marketed as Pondimin) is an example. These are not subject to much abuse, but neither is their anorectic value clearly established.] The fact is, say Grinspoon and others, the search for a drug that reduces appetite without producing the side effects characteristic of amphetamine has met with failure. (He says the situation is analogous to what happened when researchers tried to synthesize a nonaddicting opiate analgesic. The "hero" drug they came up with in 1898 was named heroin.)

There is a distinct division of opinion on this matter. Government officials believe some congeners are reasonably safe and Crout said, "I suspect a strong safety case against the nonamphetamines can't be made at this time." The best supporting data for their addiction potential are government statistics showing that, indeed, Schedule II drugs are much more widely and heavily abused than those subjected to more lenient controls.

The popularity of amphetamines and their sympathomimetic relatives has been phenomenal since they first became available in pill form in the 1950's. And, says Grinspoon, "there's been nothing like this in the way it's been embraced by the medical profession and pushed by industry."

According to testimony of Frederick A. Rody, Jr., of the DEA, some pharmaceutical companies have raised strenuous resistance to having their drugs more tightly controlled, even in the face of massive abuse of their product. Some have asked for an expansion of their production quotas to meet expected demand, said Rody, even though the demand projections were considerably higher than DEA estimates of legitimate medical need.

Rody related how one company, Pennwalt Corporation, responded to forthcoming restrictions on its amphetamine drug Biphetamine. Just before it was put into Schedule II, the company exported large quantities of the raw materials to its subsidiary in Mexico City. There the stuff was encapsulated, under the name Bifetamina, presumably for sale in Mexico. So much of the substance was smuggled back into the United States and sold on the black market that DEA had to mount a special operation, "Operation Blackjack," to clamp down on the traffic. Subsequently, under pressure from DEA, Pennwalt agreed to get out of the amphetamine export business. But then, in what a DEA agent called a "deadly parallel" to the Biphetamine episode, Pennwalt has exported over the past 2 years 600 kilograms of the bulk powder from which Ionamin (a Schedule IV drug) is manufactured—enough for 20 to 40 million pills. There has recently been found to be heavy trafficking and abuse of "Ionamina" in states adjacent to the Mexican border. "Discussions" with DEA have recently been held, and Pennwalt has now agreed to stop shipments of Ionamin powder to Mexico.

The president of Pennwalt's pharmaceutical division, Isaac R. McGraw, defended his company, saying it had always scrupulously obeyed the law and eagerly cooperated with the government. "We do not believe there is any probative evidence that our anti-obesity products show meaningful statistical or other factual evidence of abuse," testified McGraw. And, "Pennwalt is not aware of any significant illegal use of its anti-obesity products."

Other witnesses, including those dealing with street level addicts, in fact agreed that most "uppers" are obtained through legal channels. Rody said illicit

manufacture and diversion of the drugs is on the decrease, so the increasing availability of supplies are created "largely by prescriptions and direct dispensing by physicians," who are apparently "prescribing and dispensing well over the patients' actual medical needs." Such practitioners include the small but notorious handful of "fat doctors" in Long Island who, witnesses said, minister to the needs of 800 to 1200 people a week, very few of whom are fat.

The American Medical Association has not tried very hard to curb such practices, according to Grinspoon. AMA spokesman Frank Chapple says its manual, *AMA Drug Evaluations*, recommends against prescribing amphetamines and like substances for weight control, but that otherwise the organization is not preoccupied with the problem. The AMA disbanded its Council on Drugs in 1971 after that body issued a strong warning about amphetamines, and Grinspoon notes that it has generally tried to avoid offending the drug industry, which, he estimates, is supplying over half the AMA budget with $15 million worth of drug advertising a year.

Grinspoon believes a total ban on amphetamine-like substances—such as has been enacted in Sweden and Japan—is unfeasible. The stuff is too easy to manufacture illicitly and, as with Prohibition, it just wouldn't work. Frank Reynolds, director of Teen Challenge Youth Centers and another witness at the Nelson hearings, deals with drug problems at the street level. From his vantage point neither prohibition nor tighter restrictions on drugs are going to make much of a dent on the problem so long as the belief prevails from Park Aveune to the ghetto that if you have a problem you solve it with a pill. The technological approach to solving human problems was implicitly confirmed by other witnesses who persisted in referring to obesity as a "disease." Obesity is a condition, and for most people it is no more a "disease" than is loneliness or any of the other emotional factors that cause people to overeat.

[From the Federal Register, vol. 35, No. 154, Aug. 8, 1970, pp. 12678–79]

NOTICES

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

[DESI 5378]

CERTAIN ANORECTIC DRUGS

Drugs for Human Use; Drug Efficacy Study Implementation

The Food and Drug Administration has evaluated reports received from the National Academy of Sciences-National Research Council, Drug Efficacy Study Group, on the following anorectic drugs:

1. Biphetamine "7½" Capsules, Biphetamine "12½" Capsules, and Biphetamine "20" Capsules, respectively, containing 3.75 milligrams, 6.25 milligrams, and 10 milligrams each of dextroamphetamine and amphetamine per capsule, all as cation exchange resin complexes of sulfonated polystyrene; Strasenburgh Laboratories Division of Wallace and Tiernan Inc., Post Office Box 1710, Rochester, N.Y. 14603 (NDA 10–093).

2. Biphetamine-T "12½" Capsules and Biphetamine-T "20" Capsules, respectively, containing 6.25 milligrams each of dextroamphetamine and amphetamine, and 40 milligrams methaqualone per capsule, and 10 milligrams each of dextroamphetamine and amphetamine and 40 milligrams methaqualone per capsule, all as cation exchange resin complexes of sulfonated polystyrene; Strasenburgh Laboratories Division of Wallace and Tiernan Inc. (NDA 11–538).

3. Ionamin "15" Capsules and Ionamin "30" Capsules, respectively, containing 15 milligrams phentermine and 30 milligrams phentermine per capsule, both as cation exchange resin complexes of sulfonated polystyrene; Strasenburgh Laboratories Division of Wallace and Tiernan Inc. (NDA 11–613).

4. Du-Oria Tablets containing 10 milligrams methamphetamine hydrochloride, and 0.25 milligram reserpine per sustained release tablet; B. F. Ascher and Co., Inc., 5160 East 59th Street, Kansas City, Mo. 64130. (NDA 9–946).

5. Obetrol-10 and Obetrol-20 Tablets, respectively, containing 2.5 milligrams each or 5 milligrams each of methamphetamine saccharate, methamphetamine hydrochloride, amphetamine sulfate, dextroamphetamine sulfate per tablet; Obetrol Pharmaceuticals, Division of Rexar Pharmacal Corp., 382 Schenck Avenue, Brooklyn, N.Y. 11207. (NDA 11-522).

6. Prelu-Vite Capsules containing 25 milligrams phenmetrazine hydrochloride, 2,000 USP units vitamin A, 200 USP units vitamin D, 2 milligrams thiamine mononitrate, 2 milligrams riboflavin, 20 milligrams niacinamide, 3 milligrams calcium pantothenate, 1 milligram pyridoxine hydrochloride, 0.5 microgram cobalamin concentrate, 37.5 milligrams ascorbic acid, 5 milligrams iron, 140 milligrams calcium, 103 milligrams phosphorus, 0.1 milligram iodine and 1 milligram copper per capsule; Geigy Chemical Corp., Ardsley, N.Y. 10502 (NDA 12-371).

7. Methedrine Tablets containing 5 milligrams methamphetamine hydrochloride per tablet; Burroughs Wellcome & Co. (U.S.A.), Inc., 1 Scarsdale Road, Tuckahoe, N.Y. 10707 (NDA 5504).

8. Amphedroxyn Hydrochloride Tablets containing 5 milligrams methamphetamine hydrochloride per tablet; Eli Lilly and Co., Post Office Box 618, Indianapolis, Ind. 46206 (NDA 6390).

9. Delfeta-sed Stedytabs containing 30 milligrams dl-methamphetamine hydrochloride and 120 milligrams amobarbital per sustained-release tablet; Eastern Research Laboratories Inc., 302 South Central Avenue, Baltimore, Md. 21202 (NDA 12-415).

10. Delfetamine Stedytabs containing 30 milligrams dl-methamphetamine hydrochloride per sustained-release tablet; Eastern Research Laboratories Inc. (NDA 12-416).

11. Desoxyn Tablets containing 2.5 milligrams or 5 milligrams methamphetamine hydrochloride per tablet, Desoxyn Gradumet Tablets containing 5, 10, or 15 milligrams methamphetamine hydrochloride per tablet, and Desoxyn Elixir containing 20 milligrams methamphetamine hydrochloride per 30 milliliters; Abbott Laboratories, 14th and Sheridan Road, North Chicago, Ill. 60064 (NDA 5378).

12. Drinalfa Tablets containing 5 milligrams methamphetamine hydrochloride per tablet; E. R. Squibb and Sons, Inc., Georges Road, New Brunswick, N.J. 08903 (NDA 5756).

13. Bamadex Tablets containing 5 milligrams dextroamphetamine sulfate and 400 milligrams meprobamate per tablet; Lederle Laboratories Division, American Cyanamid Co., Post Office Box 500, Pearl River, N.Y. 10965 (NDA 11-280).

14. Bamadex Sequels containing 15 milligrams dextroamphetamine sulfate and 300 milligrams meprobamate per sustained release capsule; Lederle Laboratories Division, American Cyanamid Co. (NDA 12-570).

15. Tenuate Dospan Tablets containing 75 milligrams diethylpropion hydrochloride per continuous release tablet; The William S. Merrell Co., Division of Richardson-Merrell Inc., 110 East Amity Road, Cincinnati, Ohio 45215 (NDA 12-546).

16. Appetrol Tablets containing 5 milligrams dextroamphetamine sulfate and 400 milligrams meprobamate per tablet; Wallace Pharmaceuticals, Division of Carter-Wallace, Inc., Half Acre Road, Cranbury, N.J. 08512 (NDA 12-127).

17. Appetrol-S.R. Capsules containing 15 milligrams dextroamphetamine sulfate and 300 milligrams meprobamate per sustained release capsules; Wallace Pharmaceuticals (NDA 12-624).

18. Eskatrol Spansule containing 15 milligrams dextroamphetamine sulfate and 7.5 milligrams prochlorperazine (as the maleate) per sustained release capsule; Smith Kline and French Laboratories, 1500 Spring Garden Street, Philadelphia, Pa. 19101 (NDA 12-042).

19. Racemic Desoxyephedrine Hydrochloride Tablets containing 5 milligrams dl-methamphetamine hydrochloride per tablet; High Chemical Co., 1760 North Howard Street, Philadelphia, Pa. 19122 (NDA 5-969).

20. Miller-Drine Tablets containing 10 milligrams dl-methamphetamine hydrochloride per tablet; Smith, Miller and Patch, Inc., 401 Joyce Kilmer Avenue, New Brunswick, N.J. 08902 (NDA 6-003).

21. Dexserpine "5" Tablets containing 5 milligrams dextroamphetamine sulfate and 0.1 milligram reserpine per tablet; Nysco Laboratories, Inc., 34-24 Vernon Boulevard, Long Island City, N.Y. 11106 (NDA 10-207).

22. Norodin Tablets containing 5 milligrams methamphetamine hydrochloride per tablet; Endo Laboratories, 1000 Steward Avenue, Garden City, Long Island, N.Y. 11533 (NDA 5-632).

23. D-O-E- Tablets containing 5 milligrams methamphetamine hydrochloride per tablet; Tilden-Yates Laboratories, Inc., 295 Lafayette Street, New York, N.Y. 10012 (NDA 5-603).

A. *Effectiveness classification.* 1. The Food and Drug Administration has considered the reports of the Academy, as well as other evidence, and concludes that there is a lack of substantial evidence of effectiveness of the methamphetamine-containing preparations for: use as an adjunct in some cases in which nervousness, tension, and irritability are combined with feelings of depression, anxiety, and lassitude; use in the management of alcoholism (acute and chronic); enuresis; nausea and vomiting of pregnancy; use as a mild analeptic in barbiturate overdosage; restoration of optimism and mental alertness in the case of depressive state of mind; and temporary or emergency use as a cerebral stimulant to decrease fatigue and increase the urge to work.

2. All the above-listed drugs are regarded as possibly effective for their claimed anorectic effects; for their claims for prolonged, continuous, or sustained release; and for all other labeled indications not listed in paragraph A1.

B. *Marketing status.* 1.a. Within 60 days from the date of publication of this announcement in the Federal Register, the labeling of methamphetamine-containing drugs should be revised as needed to delete those indications described in paragraph A1 for which substantial evidence of effectiveness is lacking.

b. The holder of any previously approved new-drug application for such drug is requested to submit a supplement within 60 days after publication hereof to provide for such revised labeling. The supplement should be submitted under the provisions of § 130.9 (d) and (e) of the new-drug regulations (21 CFR 130.9 (d) and (e)), which permit certain changes to be put into effect at the earliest possible time. Failure to put such labeling into use may result in a proposal to withdraw approval of the new-drug application.

2.a. Holders of previously approved new-drug applications for the drugs listed above and persons marketing any of these drugs without approval will be allowed 6 months from the date of publication of this announcement in the Federal Register to obtain and to submit in a supplemental or original new-drug application data to provide substantial evidence of effectiveness for those indications for which these drugs have been classified as possibly effective.

b. For preparations claiming sustained-action, timed-release, or other delayed or prolonged effect, such data should be adequate to assure the biologic availability of the drug in the formulation which is marketed and should show that the drug is available at a rate of release which will be safe and effective and that it has the prolonged effect claimed.

3. At the end of the 6-month period, any such data will be evaluated to determine whether there is substantial evidence of the effectiveness for such uses. After the evaluation, the conclusions concerning the drug will be published in the Federal Register. If no studies have been undertaken or if the studies do not provide substantial evidence of effectiveness, procedures will be initiated to withdraw approval of the new-drug applications for these drugs, pursuant to the provisions of section 505(e) of the Federal Food, Drug, and Cosmetic Act. Withdrawal of approval of the applications will cause any such drugs on the market to be new drugs for which an approval is not in effect.

The above-named holders of the new-drug applications for these drugs have been mailed a copy of the NAS-NRC reports. Any interested person may obtain a copy of a report by writing to the office named below.

Communications forwarded in response to this announcement should refer to DESI 5378 which identifies this announcement and should be directed to the attention of the following appropriate office and addressed, unless otherwise specified, to the Food and Drug Administration, 5600 Fishers Lane, Rockville, Md. 20852:

Supplements (identify with new-drug application number): Office of Marketed Drugs (BD-200), Bureau of Drugs.

Original new-drug applications: Office of New Drugs (BD-100), Bureau of Drugs.

Comments on this announcement: Special Assistant for Drug Efficacy Study Implementation (BD-201), Bureau of Drugs.

Requests for NAS-NRC reports: Press Relations Staff (CE-200), Food and Drug Administration, 200 C Street SW., Washington, D.C. 20204.

This notice is issued pursuant to provisions of the Federal Food, Drug and Cosmetic Act (secs. 502, 505, 52 Stat. 1050–53, as amended; 21 U.S.C. 352, 355) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 2.120).

Dated: July 30, 1970.

CHARLES C. EDWARDS,
Commissioner of Food and Drugs.

[F.R. Doc. 70–10354; Filed, Aug. 7, 1970; 8:47 a.m.]

[From the Federal Register, vol. 35, No. 154, Aug. 8, 1970, pp. 12652–53]

RULES AND REGULATIONS

TITLE 21—FOOD AND DRUGS

Chapter I—Food and Drug Administration, Department of Health, Education, and Welfare

SUBCHAPTER C—DRUGS

PART 130—NEW DRUGS

Subpart A—Procedural and Interpretative Regulations

AMPHETAMINES (AMPHETAMINE, DEXTROAMPHETAMINE, AND THEIR SALTS, AND LEVAMFETAMINE AND ITS SALTS) FOR HUMAN USE; STATEMENT OF POLICY

Pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (secs. 502(f), (j), 505, 701(a), 52 Stat. 1051–53, as amended, 1055; 21 U.S.C. 352(f), (j), 355, 371(a)) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 2.120), Part 130 is amended by adding to Subpart A the following new section:

§ 130.46 Amphetamines (amphetamine, dextroamphetamine, and their salts and levamfetamine and its salts) for human use; statement of policy.

(a) *Amphetamine and dextroamphetamine and their salts.* (1) Pursuant to the tional Academy of Sciences-National Research Council, Drug Efficacy Study Group, has evaluated certain dosage forms of amphetamines and other sympathomimetic stimulant drugs intended for use in the treatment of obesity and for other uses. The Academy found that such drugs as a class have been shown to have a generally short-term anorectic action. They further commented that clinical opinion on the contribution of the sympathomimetic stimulants in a weight reduction program varies widely, the anorectic effect of these drugs often pleateaus or diminishes after a few weeks, most studies of them are for short periods, no available evidence shows that use of anorectics alters the natural history of obesity, some evidence indicates that anorectic effects may be strongly influenced by the suggestibility of the patient, and reservations exist about the adequacy of the controls in some of the clinical studies. Their significant potential for drug abuse was also cited.

* * * * * * *

PRECAUTIONS

Caution is to be exercised in prescribing amphetamines for patients with even mild hypertension.

Insulin requirements in diabetes mellitus may be altered in association with the use of amphetamines and the concomitant dietary regimen.

Amphetamines may decrease the hypotensive effect of guanethidine.

The least amount feasible should be prescribed or dispensed at one time in order to minimize the possibility of overdosage.

ADVERSE REACTIONS

Cardiovascular: Palpitation, tachycardia, elevation of blood pressure.
Central nervous system: Overstimulation, restlessness, dizziness, insomnia, euphoria, dysphoria, tremor, headache; rarely, psychotic episodes at recommended doses.
Gastrointestinal: Dryness of the mouth, unpleasant taste, diarrhea, other gastrointestinal disturbances. Anorexia and weight loss may occurr as undersirable effects when amphetamines are used for other than the anorectic effect.
Allergic: Urticarta.
Endocrine: Impotence, changes in libido.

DOSAGE AND ADMINISTRATION

Regardless of indication, amphetamines should be administered at the lowest effective dosage and dosage should be individually adjusted. Late evening medication should be avoided because of the resulting insomnia.
1. Narcolepsy: Usual dose 5 to 60 milligrams per day in divided doses.
2. Minimal brain dysfunction:
a. Not recommended for children under 3 years of age.
b. Children from 3 to 5 years of age: 2.5 milligrams daily, rated in increments of 2.5 milligrams at weekly intervals until optimal response is obtained.
c. Children 6 years of age and older: 5 milligrams once or twice daily, increased in increments of 5 milligrams at weekly intervals. Only in rare cases will it be necessary to exceed a total of 40 milligrams per day.
3. Obesity: Usual adult dose 5 to 30 milligrams per day in divided doses.

OVERDOSAGE

Manifestations of acute overdosage with amphetamines include restlessness, confusion, assaultiveness, hallucinations, panic states. Fatigue and depression usually follow the central stimulation. Cardiovascular effects include arrythmia, hypertension or hypotension, and circulatory collapse. Gastrointestinal symptoms include nausea, vomiting, diarrhea, and abdominal cramps. Fatal poisoning usually terminates in convulsions and coma.
Management of acute amphetamine intoxication is largely symptomatic and includes lavage and sedation with a barbiturate. Experience with hemodialysis or peritoneal dialysis is inadequate to permit recommendations in this regard.
(5) Distribution of any such preparation currently on the market without an approved new-drug application may be continued provided that all the following conditions are met:
(i) Within 60 days following the date of publication of this section in the Federal Register, the labeling of any such preparation shipped within the jurisdiction of the act is in accord with the labeling conditions described in this section. After said 60 days any such preparation labeled or advertised contrary to this section will be regarded as misbranded within the meaning of section 502(f) (1) and (2) and (j) of the act and will be subject to regulatory proceedings. New drug charges will be included in appropriate cases.
(ii) The manufacturer, packer, or distributor of such drug submits to the Food and Drug Administration, within 1 year after the date of publication of this section in the Federal Register, a new-drug application providing substantial evidence derived from adequate and well-controlled clinical investigations that the drug is effective for each of its labeled indications. Since the treatment of obesity necessarily requires a prolonged period of time, data in support of the drug's long-range effectiveness in this condition must be based on studies conducted over periods exceeding a few weeks; intermittent administration of the drug may be required. Such studies should also include data on long-term toxicity; for example, cardiovascular and central nervous system. Such information is essential for an evaluation of the benefit-to-risk ratio.
(iii) The applicant submits within a reasonable time additional information required for the approval of the application as specified in a written communication from the Food and Drug Administration or in a notice published in the Federal Register.
(iv) The application has not been ruled incomplete or unapprovable.
(v) The Food and Drug Administration has not, by publication in the FEDERAL REGISTER, announced further conclusions concrening amphetamines based upon information submitted in new-drug applications or other information available.

(6) The labeling of any combination drug containing amphetamine or dextroamphetamine or their salts which includes any of the same indications for use as are listed in the labeling in this section should be revised to reflect the substance of those parts of the labeling set forth in this section that are applicable to the amphetamine component. Combination products labeled as required by this section are regarded as new drugs and must be subjects of approved new-drug applications.

(b) *Levamfetamine and its salts.* (1) Levamfetamine preparations currently on the market are represented to be useful in the treatment of obesity. The Food and Drug Administration finds there is neither substantial evidence of effectiveness nor a general recognition among qualified experts that these drugs are safe and effective for such use. Accordingly, these preparations are regarded as new drugs requiring approved new-drug applications.

(2) Regulatory proceedings based on section 505 of the act may be initiated with regard to any such drug shipped within the jurisdiction of the act for which an approved new-drug application is not in effect. Those products claiming exemption from the efficacy provisions of the Drug Amendments of 1962 (Public Law 87–781; 76 Stat. 780 et seq.) under the "grandfather" provisions (sec. 107(c)(4) of that act; 76 Stat. 789) will be considered on an individual basis.

(Secs. 502 (f), (j), 505, 701(a), 52 Stat. 1051–53, as amended, 1055; 21 U.S.C. 352 (f), (j), 355, 371(a))

Dated: July 30, 1970.

CHARLES C. EDWARDS,
Commissioner of Food and Drugs.

[F.R. Doc. 70-10353; Filed, Aug. 7, 1970; 8:47 a.m.]

[From the Federal Register, vol. 38, No. 28, Feb. 12, 1973, pp. 4249–50]

RULES AND REGULATIONS

Title 21—Food and Drugs

CHAPTER I—FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

SUBCHAPTER C—DRUGS

PART 130—NEW DRUGS

Amphetamines for Human Use

On August 8, 1970, there was published in the Federal Register (35 FR 12652) § 130.46 concerning amphetamines and their salts and levamfetamine and its salts. Section 130.46 required the submission of new drug applications for amphetamine or dextroamphetamine and their salts as a condition for continued marketing. The new drug aplications were to contain evidience of efficacy, including efficacy in the treatment of obesity.

Pursuant to that requirement 105 new drug applications for amphetamines or amphetamine-containing drugs were received. The analysis of the data submitted concerning the amphetamines and other, nonamphetamine anorectic drugs generally supported the efficacy of anorectic drugs. Use of the drug in obese patients was associated with more weight loss than was diet alone. The degree of extra weight loss was small (a few tenths of a pound a week in many cases), variations were great, and the rate of weight loss decreased after the first weeks of therapy.

On the basis of the currently available evidence, the Commissioner concludes that oral dosage forms of amphetamines and/or dextroamphetamines are effective in the management of exogenous obesity as a short term (a few weeks) adjunct in a regimen of weight reduction based on caloric restriction for patients in whom obesity is refractory to other measures. Appropriate notices concerning such drugs which have been reviewed in the Drug Efficacy Study will be published in the Federal Register.

Use of amphetamines for long periods of time may lead to drug dependence and abuse. Abuse of the amphetamines has been well known. Persistence of abuse

under conditions of marketing described herein may lead the Commissioner to take further steps to restrict the use of these drugs.

No data have been received providing substantial evidence of effectiveness of levamfetamine and its salts. Accordingly these preparations continue to be regarded as new drugs requiring approved full new drug applications.

On September 3, 1971, a Drug Efficacy Study Implementation notice was published in the Federal Register (35 FR 17669) stating that methamphetamine hydrochloride injection (intended for other than anoretic indications) was regarded as effective for some indications and less than effective for others. The Commissioner has now fully reviewed the evidence on the safety and effectiveness of this drug, and has concluded that the well-documented history of abuse of parenteral methamphetamine, together with the severe risk of dependence and the availability of safer and equally effective alternative drugs, creates an unfavorable balance of risk to benefit. A proposal to withdraw approval of those new drug applications as lacking evidence of safety is published elsewhere in this issue of the Federal Register. The Commissioner also concludes that, for the same reasons, parenteral preparations containing amphetamine, dextroamphetamine, or levamfetamine or their salts are lacking evidence of safety.

On August 8, 1970, a Drug Efficacy Study Implementation notice was published in the Federal Register (35 FR 12678) stating that various combination drugs containing an anorectic drug were regarded as possibly effective for their claimed anorectic effects and lacking substantial evidence of effectiveness for their other indications. Data were received concerning those drugs and also combination drugs which were subjects of new drug applications submitted as required by § 130.46. The combinations consisted of anoretic agents associated with, for example, sedatives, tranquilizers, rauwolfia derivatives, or vitamins. The data were reviewed and found not to fulfill the criteria set forth in the Statement of General Policy or Interpretation § 3.86 Fixed-combination prescription drugs for humans, published in the Federal Register of October 15, 1971 (36 FR 20037). Further, in view of the lack of substantial evidence of effectiveness of the drugs as fixed combinations, the recognized potential for abuse of the amphetamine dextroamphetamine, methamphetamine, and phenmetrazine components, and the availability of alternative therapeutic measures which are safer and effective, combinations containing such components, also lack proof of safety. Proceedings to withdraw approval of such applications are being initiated, and an appropriate notice is published elsewhere in this issue of the Federal Register.

In a forthcoming issue of the Federal Register, the Commissioner will set forth his policy with respect to anorectic agents in general.

On the basis of all of the data and information submitted pursuant to § 130.46 pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (sec. 502 (f), (j), 505, 701(a), 52 Stat. 1051–53; as amended, 1055; 21 U.S.C. 352(f), (j), 355, 371(a)), and under the authority delegated to him (21 CFR 2.120), the Commissioner of Food and Drugs hereby revises § 130.46 of Part 130, Subpart A to read as follows:

§ 130.46 Amphetamines (amphetamine, dextroamphetamine, and their salts and levamfetamine and its salts) for human use.

(a) Amphetamine and dextroamphetamine and their salts. (1) Pursuant to the drug efficacy requirements of the Federal Food, Drug, and Cosmetic Act, the National Academy of Sciences-National Research Council, Drug Efficacy Study Group, has evaluated certain dosage forms of amphetamines and other sympathomimetic stimulant drugs intended for use in the treatment of obesity and for other uses. The Academy found that such drugs as a class have been shown to have a generally short-term anorectic action. They further commented that clinical opinion on the contribution of the sympathomimetic stimulants in a weight reduction program varies widely, the anorectic effect of these drugs often plateaus or diminishes after a few weeks, most studies of them are for short periods, no available evidence shows that use of anorectic alters the natural history of obesity, some evidence indicates that anorectic effects may be strongly influenced by the suggestibility of the patient, and reservations exist about the adequacy of the controls in some of the clinical studies. Their significant potential for drug abuse was also cited.

(2) In addition to those dosage forms that were reviewed for efficacy by the Academy, other dosage forms of amphetamine drugs are on the market that were

not cleared through the new-drug procedures. While certain amphetamines were marketed prior to enactment of the Federal Food, Drug, and Cosmetic Act in 1938, some of the conditions of use subsequently prescribed, recommended, or suggested in their labeling (for example, for the treatment of obesity) differ from uses claimed for the amphetamines before said enactment. Such uses have not been cleared through the effectiveness provisions of the Drug Amendments of 1962 (Public Law 87-781 which amended the Federal Food, Drug, and Cosmetic Act). These drugs are very extensively used in the treatment of obesity. The extent of the use for such purposes as narcolepsy and minimal brain dysfunction in children is believed to be minor as compared with the total usage of these drugs. Because of their stimulant effect on the central nervous system, they have a potential for misuse by those to whom they are available through a physician's prescription, and their abuse by those who obtain them through illicit channels is well documented. Production data indicate that amphetamines have been produced and prescribed in quantities greatly in excess of demonstrated medical needs.

(3) Pursuant to a notice published in the FEDERAL REGISTER of August 8, 1970 (35 FR 12652), which required the submission of new drug applications as a condition for continued marketing of amphetamines, 106 new drug applications for amphetamines or amphetamine-containing drug products were received. The data submitted in those applications, and data obtained from other sources concerning anorectic drugs, generally supported the efficacy of anorectic drugs.

(b) On the basis of currently available evidence derived from short-term studies, the Commissioner concludes that single drug entity oral dosage forms of amphetamine or dextroamphetamine are effective in the management of exogenous obesity as a short-term (a few weeks) adjunct in a regimen of weight reduction, based on caloric restrictions, for patients in whom obesity is refractory to other measures. For purposes of this regulation, a mixture of dextroamphetamine and amphetamine is ordinarily regarded as a single drug entity.

(c) The Food and Drug Administration is not aware of data providing substantial evidence of the effectiveness of levamfetamine and its salts and regards these preparations as new drugs requiring approval full new-drug applications.

(d) In view of the well-documented history of abuse of parenteral amphetamines the severe risk of drug dependence, and the availability of safer alternative parenteral drugs which are equally effective for recognized non-anorectic indications, the Food and Drug Administration regards parenteral amphetamines as lacking evidence of safety.

(e) Any combination drug containing amphetamine or dextroamphetamine is regarded as a new drug requiring an approved full new-drug application as a condition for marketing. Data in new-drug applications are required to fulfill the criteria set forth in § 3.86 governing fixed combination prescription drugs for humans.

(f) New drug applications have been received from persons marketing orally administered single entity amphetamine or dextroamphetamine dosage forms. Any other person who intends to market such drug is required to submit to the Food and Drug Administration an abbreviated new drug application (§ 130.4 (f)) except that in addition, the application shall contain full information required under items 7 and 8 (composition and methods, facilities, and controls) of the new drug application form FD-356H (§ 130.4(c)).

(g) The labeling conditions for single entity oral dosage forms of amphetamine and dextroamphetamine and their salts are as follows:

(1) The label shall bear the statement "Caution: Federal law prohibits dispensing without prescription."

(2) The drug shall be labeled to comply with all requirements of the act and regulations. The labeling shall bear adequate information for safe and effective use of the drug. The indications for use are:

Narcolepsy.

Minimal brain dysfunction in children (hyperkinetic behavior disorders), as an aid to general management.

Management of exogenous obesity as short-term (a few weeks) adjunct in a regimen of weight reduction based on caloric restriction, for patients in whom obesity is refractory to other measures.

(3) Complete labeling guidelines are available from the Food and Drug Administration.

(h) Regulatory proceedings will be initiated with regard to any such drug within the jurisdiction of the act which is not in accord with this regulation.

Effective date. This regulation shall be effective on March 14, 1973.

Dated: February 7, 1973.

WILLIAM F. RANDOLPH,
Acting Associate Commissioner for Compliance.

[FR Doc. 73-2717 Filed 2-9-73; 8:45 am]

[From the Federal Register, vol. 38, No. 28, Feb. 12, 1973, pp. 4279-82]

NOTICES

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

FOOD AND DRUG ADMINISTRATION

[DESI 5378; Docket No. FDC-D-582; NDA No. 9-946 etc.]

CERTAIN COMBINATION ANORECTIC DRUGS

OPPORTUNITY FOR HEARING ON PROPOSAL TO WITHDRAW APPROVAL OF NEW DRUG APPLICATIONS

In a notice (DESI 5378) published in the FEDERAL REGISTER of August 8, 1970 (35 FR 12678), the Commissioner of Food and Drugs announced his conclusions pursuant to the evaluation of a report received from the National Academy of Sciences-National Research Council, Drug Efficacy Study Group, on the drugs described below stating that the drugs were regarded as possibly effective and lacking substantial evidence of effectiveness for the various labeled indications.

NDA No.	Drug	NDA Holder
9-946	Du-Oria tablets containing 10 mg methamphetamine hydrochloride, and 0.25 mg reserpine per sustained release tablet.	Formerly marketed by B. F. Ascher & Co., Inc., Post Office Box 827, Kansas City, Mo. 64130.
10-207	Dexserpine "5" tablets containing 5 mg dextroamphetamine sulfate and 0.1 mg reserpine per tablet.	Formerly marketed by Nysco Laboratories, Inc., 34-24 Vernon Blvd., Long Island City, N.Y. 11106.
11-280	Bamadex tablets containing 5 mg dextroamphetamine sulfate and 400 mg meprobamate per tablet.	Lederle Laboratories Division, American Cyanamid Co., Post Office Box 500, Pearl River, N.Y. 10965.
11-522	Obetrol-10 and Obetrol-20 tablets, respectively, containing 2.5 mg each or 5 mg each of methamphetamine saccharate, methamphetamine hydrochloride, amphetamine sulfate, dextroamphetamine sulfate per tablet.	Obetrol Pharmaceuticals, Division of Rexar Pharmacal Corp., 382 Schenck Ave., Brooklyn, N.Y. 11207.
11-538	Biphetamine-T "12½" capsules and Biphetamine-T "20" capsules, respectively, containing 6.25 mg each of dextroamphetamine and amphetamine, and 40 mg methaqualone per capsule, and 10 mg each of dextroamphetamine and amphetamine and 40 mg methaqualone per capsule, all as cation exchange resin complexes of sulfonated polystyrene.	Strasenburgh Pharmaceutical, Division Pennwalt Corp., 755 Jefferson Rd., Rochester N.Y. 11623.
12-042	Eskatrol Spansules containing 15 mg dextroamphetamine sulfate and 7.5 mg prochlorperazine (as the maleate) per sustained release capsule.	Smith Kline & French Laboratories, 1500 Spring Garden St., Philadelphia, Pa. 19101.
12-127	Appetrol tablets containing 5 mg dextroamphetamine sulfate and 400 mg meprobamate per tablet.	Wallace Pharmaceuticals, Division of Carter-Wallace, Inc., Half Acre Rd., Cranbury, N.J. 08512.
12-371	Prelu-Vite capsules containing 25 mg phenmetrazine hydrochloride, 2,000 USP units vitamin A, 200 USP units vitamin D, 2 mg thiamine mononitrate, 2 mg riboflavin, 20 mg niacinamide, 3 mg calcium pantothenate, 1 mg pyridoxine hydrochloride, 05. mg cobalamin concentrate, 37.5 mg ascorbic acid, 5 mg iron, 140 mg calcium, 108 mg phosphorus, 0.1 mg iodine and 1 mg copper per capsule.	Formerly marketed by Geigy Pharmaceuticals, Division of Ciba Geigy Co., Saw Mill River Rd., Ardsley, N.Y. 10502.
12-415	Delfeata-sed Stedytabs containing 30 mg dl-methamphetamine hydrochloride and 120 mg amobarbital per sustained-release tablet.	Eastern Research Laboratories Inc., 302 South Central Ave., Baltimore, Md. 21202.
12-570	Bamadex Sequels containing 15 mg dextroamphetamine sulfate and 300 mg meprobamate per sustained-release capsule.	Lederle Laboratories Division, American Cyanamid.
12-624	Appetrol-S.R. capsules containing 15 mg dextroamphetamine sulfate and 300 mg meprobamate per sustained-released capsule.	Wallace Pharmaceuticals.

Data submitted pursuant to the notice have been reviewed and found not to provide substantial evidence that the drugs are effective as fixed combinations for their claimed uses.

In view of the lack of substantial evidence of effectiveness of the drugs as fixed combinations, the recognized potential for abuse of the amphetamine, dextroamphetamine, methamphetamine, and phenmetrazine components, and the availability of alternative therapeutic measures which are safer and effective, the combination products are also regarded as lacking proof of safety. Data submitted in response to the notice of August 8, 1970, do not support a contention that the combination products decrease the incidence or severity of side effects associated with the single ingredient or that the addtional component(s) lessens the abuse potential as compared to that of the single entity anorectic drug. Also, the known adverse effects associated with phenothiazine drugs raises an additional question of safety of use of Eskatrol which contains dextroamphetamine sulfate in combination with prochlorperazine.

With further respect to Eskatrol, the Food and Drug Administration is aware of a study conducted by Dr. Carl Chambers relating to the abuse potential of the product, and for which no report has been submitted by the NDA holder pursuant to section 505(j) of the act and §§ 130.13 and 130.35 of the regulations (21 CFR 130.13 and 130.35).

Therefore, notice is given to the holder(s) of the new drug application(s) and to any other interested person that the Commissioner proposes to issue an order under section 505(e) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 355(e)) withdrawing approval of the listed new drug application(s) and all amendments and supplements thereto on the grounds that new information before him with respect to the drug(s), evaluated together with the evidence available to him at the time of approval of the application(s), shows that: (1) There is a lack of substantial evidence that the drug(s) will have all the effects they purport or are represented to have; and (2) the drugs are not shown to be safe for use under the conditions of use prescribed, recommended, or suggested in the labeling; and (3) further, in the case of Eskatrol tablets, the applicant has deliberately failed to make required reports in accordance with section 505(j) of the act (21 U.S.C. 355(j)) and § 130.13 and § 130.35 of the new drug regulations (21 CFR 130.13 and 130.35).

All identical, related, or similar products, not the subject of an approved new drug application, are covered by the new drug application(s) reviewed. See 21 CFR 130.40 (37 FR 23185, October 31, 1972). Any manufacturer or distributor of such an identical, related, or similar product is an interested person who may in response to this notice submit data and information, request that the new drug application(s) not be withdrawn, request a hearing, and participate as a party in any hearing. Any person who wishes to determine whether a specific product is covered by this notice should write to the Food and Drug Administration, Bureau of Drugs, Office of Compliance (BD–300), 5600 Fishers Lane, Rockville, MD 20852.

In accordance with the provisions of section 505 of the act (21 U.S.C. 355) and the regulations promulgated thereunder (21 CFR Part 130), the Commissioner hereby gives the applicant(s) and any other interested person an opportunity for a hearing to show why approval of the new drug application(s) should not be withdrawn.

The applicant(s) and any other interested person is required to file with the Hearing Clerk, Department of Health, Education, and Welfare, Room 6–88, 5600 Fishers Lane, Rockville, MD 20852, on or before March 14, 1973, a written appearance electing whether or not to avail himself of the opportunity for a hearing. Failure of an applicant or any other interested person to file a written appearance of election by March 14, 1973, will constitute an election by him not to avail himself of the opportunity for a hearing.

If no person elects to avail himself of the opportunity for a hearing, the Commissioner without further notice will enter a final order withdrawing approval of the application(s).

If an applicant or any other interested person elects to avail himself of the opportunity for a hearing, he must file, on or before March 14, 1973, a written appearance requesting the hearing, giving the reasons why approval of the new drug application(s) should not be withdrawn, together with a well-organized and full-factual analysis of the clinical and other investigational data he is

prepared to prove in support of his opposition. A request for a hearing may not rest upon mere allegations or denials, but must set forth specific facts showing that a genuine and substantial issue of fact requires a hearing (21 CFR 130.14(b)).

If review of the data submitted by an applicant or any other interested person warrants the conclusion that there exists substantial evidence demonstrating the effectiveness of the product(s) and evidence that the drug(s) is (are) safe for use for the labeling claims involved (and, in the case of NDA 12-042, that there has been no violation of section 505(j) of the act), the Commissioner will rescind this notice of opportunity for hearing.

If review of the data in the application(s) and data submitted by the applicant(s) or any other interested person in a request for a hearing, together with the reasoning and factual analysis in a request for a hearing, warrants the conclusion that no genuine and substantial issue of fact precludes the withdrawal of approval of the application(s), the Commissioner will enter an order of withdrawal making findings and conclusions on such data.

If, upon the request of the new drug applicant(s) or any other interested person, a hearing is justified, the issues will be defined, a hearing examiner will be named, and he shall issue, as soon as practicable after March 14, 1973, a written notice of the time and place at which the hearing will commence. All persons interested in identical, related, or similar products covered by the new drug application(s) will be afforded an opportunity to appear at the hearing, file briefs, present evidence, cross-examine witnesses, submit suggested findings of fact, and otherwise participate as a party. The hearing contemplated by this notice will be open to the public except that any portion of the hearing that concerns a method or process the Commissioner finds entitled to protection as a trade secret will not be open to the public, unless the respondent specifies otherwise in his appearance.

Requests for a hearing and/or elections not to request a hearing may be seen in the Office of the Hearing Clerk (address given above) during regular business hours, Monday through Friday.

This notice is issued pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (sec. 505, 52 Stat. 1052-53, as amended; 21 U.S.C. 355), and the Administrative Procedure Act (5 U.S.C. 554), and under authority delegated to the Commissioner (21 CFR 2.120).

Dated: February 7, 1973.

WILLIAM F. RANDOLPH,
Acting Associate Commissioner
for Compliance.

[FR Doc. 73-2716 Filed 2-9-73; 8:45 am]

[DESI 11673]

CERTAIN ORAL ANORECTIC PREPARATIONS; PHENTERMINE HYDROCHLORIDE; PHENDIMETRAZINE TARTRATE; BENZPHETAMINE HYDROCHLORIDE; DIETHYLPROPION HYDROCHLORIDE

DRUGS FOR HUMAN USE; DRUG EFFICACY STUDY IMPLEMENTATION

The Food and Drug Administration has evaluated reports received from the National Academy of Sciences-National Research Council, Drug Efficacy Study Group, on the following anorectic drugs:

1. Wilpo tablets, containing 8 mg. phentermine hydrochloride per tablet; Dorsey Laboratories, Division of Sandoz-Wander Inc., Northeast, U.S. 6 and Interstate 80, Lincoln, Nebr. 68501 (NDA 12-737).

2. Didrex tablets, containing 25 mg. and 50 mg. benzpetamine hydrochloride per tablet; The Upjohn Co., 7171 Portage Road, Kalamazoo, MI 49001 (NDA 12-427).

3. Plegine tablets, containing 35 mg. phendimetrazine tartrate per tablet; Ayerst Laboratories, Rouses Point, N.Y. 12979 (NDA 12-248).

4. Tepanil tablets, containing 25 mg. diethylpropion hydrochloride per tablet; The Merrell-National Drug Co., Division of Richardson-Merrell, Inc., 110 East Amity Road, Cincinnati, OH 45215 (NDA 11-673).

5. Tenuate tablets, containing 25 mg. diethylpropion hydrochloride per tablet; The Merrell-National Drug Co., Division of Richardson-Merrell, Inc. (NDA 11-722).

6. Preludin Endurets (prolonged-action tablets), containing phenmetrazine hydrochloride; Geigy Pharmaceuticals, Division of Ciba-Geigy Corp., Ardsley, N.Y. 10502 (NDA 11-752).

Although not specifically referred to the Academy for review, Preludin tablets, a conventional oral dosage form containing phenmetrazine hydrochloride (NDA 10-460, Geigy Pharmaceuticals) was approved on the basis of safety prior to 1962, was evaluated by the Academy, and is appropriately included herein.

Such drugs are regarded as new drugs (21 U.S.C. 321 (p)). Supplemental new drug applications are required to revise the labeling in and to update previously approved applications providing for such drugs. A new drug application is required from any person marketing such drug without approval.

I. Sustained-action, time-release, or other delayed or prolonged effect forms of Phenmetrazine Hydrochloride

The Food and Drug Administration has considered the Academy's report, as well as other available evidence, and concludes that phenmetrazine hydrochloride in prolonged-action tablet form is less than effective (possibly effective) with respect to any special claim for prolonged action when offered for the management of exogenous obesity as a short-term adjunct (a few weeks) in a regimen of weight reduction based on caloric restriction.

Any data submitted in response to this notice to support claims for which the drug is classified as other than effective must be previously unsubmitted and include data from adequate and well-controlled clinical investigations (identified for ready review) as described in § 130.12(a)(5) of the regulations published in the Federal Register of May 8, 1970 (35 F.R. 7250). Carefully conducted and documented clinical studies obtained under uncontrolled or partially controlled situations are not acceptable as a sole basis for approval of claims of effectiveness, but such studies may be considered on their merits for corroborative support of efficacy and evidence of safety.

II. Conventional tablet forms of Phenmetrazine Hydrochloride; Phentermine Hydrochloride; Benzphetamine Hydrochloride; Phendimetrazine Tartrate; or Diethylpropion Hydrochloride

A. *Effectiveness classification.*—The Food and Drug Administration has considered the Academy's reports, as well as other available evidence, and concludes that these drugs, administered in conventional oral dosage form, are effective in the management of exogenous obesity as a short-term adjunct (a few weeks) in a regimen of weight reduction based on caloric restriction.

B. *Conditions for approval and marketing.*—The Food and Drug Administration is prepared to approve abbreviated new drug applications and abbreviated supplements to previously approved new drug applications under conditions described herein.

1. *Form of drug.* Such preparations are in tablet dosage form suitable for oral administration.

2. *Labeling conditions.* The label bears the statement, "Caution: Federal law prohibits dispensing without prescription."

The drugs are labeled to comply with all requirements of the Act and regulations, and the labeling bears adequate information for safe and effective use of the drug(s). The "Indications" section is as follows:

INDICATIONS

(*Name of drug*) is indicated in the management of exogenous obesity as a short term adjunct (a few weeks) in a regimen of weight reduction based on caloric restriction. The limited usefulness of agents of this class (see Actions) should be measured against possible risk factors inherent in their use such as those described below.

In addition, the labeling contains the following "Actions" section and drug dependence warning the "Warnings" section:

ACTIONS

(*Name of drug*) is a sympathomimetic amine with pharmacologic activity similar to the prototype drugs of this class used in obesity, the amphetamines. Actions include central nervous system stimulation and elevation and blood pressure. Tachyphylaxis and tolerance have been demonstrated with all drugs of this class in which these phenomena have been looked for.

Drugs of this class used in obesity are commonly known as "anorectics" or "anorexigenics", it has not been established, however, that the action of such drugs in treating obesity is primarily one of appetite suppression. Other central nervous system actions, or metabolic effects, may be involved, for example.

Adult obese subjects instructed in dietary management and treated with "anorectic" drugs, lose more weight on the average than those treated with placebo and diet, as determined in relatively short-term clinical trials.

The magnitude of increased weight loss of drug-treated patients over placebo-treated patients is only a fraction of a pound a week. The rate of weight loss is greatest in the first weeks of therapy for both drug and placebo subjects and tends to decrease in succeeding weeks. The possible origins of the increased weight loss due to the various drug effects are not established. The amount of weight loss associated with the use of an "anorectic" drug varies from trial to trial, and the increased weight loss appears to be related in part to variables other than the drug prescribed, such as the physician-investigator, the population treated, and the diet prescribed. Studies do not permit conclusions as to the relative importance of the drug and non-drug factors on weight loss.

The natural history of obesity is measured in years, whereas the studies cited are restricted to a few weeks duration; thus, the total impact of drug-induced weight loss over that of diet alone must be considered clinically limited.

WARNINGS

Drug dependence: (*Name of drug*) is related chemically and pharmacologically to the amphetamines. Amphetamines and related stimulant drugs have been extensively abused, and the possibility of abuse of (*name of drug*) should be kept in mind when evaluating the desirability of including a drug as part of a weight reduction program. Abuse of amphetamines and related drugs may be associated with intense psychological dependence and severe social dysfunction. There are reports of patients who have increased the dosage to many times that recommended. Abrupt cessation following prolonged high dosage administration results in extreme fatigue and mental depression; changes are also noted on the sleep EEG. Manifestations of chronic intoxication with anorectic drugs include severe dermatoses, marked insomnia, irritability, hyperactivity, and personality changes. The most severe manifestation of chronic intoxications is psychosis, often clinically indistinguishable from schizophrenia.

3. *Marketing status.* Marketing of such drugs may be continued under the conditions described in the notice entitled Conditions for Marketing New Drugs Evaluated in Drug Efficacy Study, published in the Federal Register July 14, 1970 (35 FR 11273), as follows:

a. For holders of "deemed approved" new drug applications (i.e., an application which became effective on the basis of safety prior to October 10, 1962), the submission of a supplement for revised labeling and a supplement for updating information, including full manufacturing information with respect to items 7 and 8 of Form FD-356H (§ 130.4(c)), as described in paragraph (a)(1)(i) and (iii) of the notice of July 14, 1970.

b. For any person who does not hold an approved or effective new drug application, the submission of an abbreviated new drug application as described in paragraph (a)(3)(i) of that notice, except that full manufacturing information with respect to items 7 and 8 of Form FD-356H (§ 130.4(c)) is required.

c. For any distributor of the drug, the use of labeling in accord with this announcement for any such drug shipped within the jurisdiction of the Act as described in paragraph (b) of that notice.

Each of the above-named holders of the new drug applications for these drugs has been mailed a copy of the Academy's report. Communications forwarded in response to this announcement should be identified with the reference number DESI 11673, directed to the attention of the following appropriate office, and addressed to the Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20852:

Supplements (identify with NDA number): Office of Scientific Evaluation (BD-100), Bureau of Drugs.

Original abbreviated new drug applications (identify as such): Drug Efficacy Study Implementation Project Office (BD-60), Bureau of Drugs.

Requests for the Academy's report: Drug Efficacy Study Implementation Information Control (BD-66), Bureau of Drugs.

All other communications regarding this announcement: Drug Efficacy Study Implementation Project Office (BD–60), Bureau of Drugs.

All identical, related, or similar products, not the subject of an approved new drug application, are covered by the new drug applications reviewed and are subject to this notice. See 21 CFR 130.40 (37 FR 23185, October 31, 1972). Any person who wishes to determine whether a specific product is covered by this notice should write to the Food and Drug Administration, Bureau of Drugs, Office of Compliance (BD–300), 5600 Fishers Lane, Rockville, MD 20852.

This notice is issued pursuant to the Federal Food, Drug, and Cosmetic Act (secs. 502, 505, 52 Stat. 1050–53, as amended; 21 U.S.C. 352, 355) and the Administrative Procedure Act (5 U.S.C. 554), and under the authority delegated to the Commissioner of Food and Drugs (21 CFR 2.120).

Dated: February 7, 1973.

WILLIAM F. RANDOLPH,
Acting Associate Commissioner
for Compliance.

[FR Doc. 73–2718 Filed 2–9–73; 8:45 am]

[DESI 12101]

COMBINATION DRUG CONTAINING SYROSINGOPINE AND HYDROCHLOROTHIAZIDE

DRUGS FOR HUMAN USE; DRUG EFFICACY STUDY IMPLEMENTATION

The Food and Drug Administration has evaluated reports received from the National Academy of Sciences-National Research Council, Drug Efficacy Study Group on the following drug:

Singoserp-Esidrix Tablets (2 strengths) containing syrosingopine and hydrochlorothiazide; Ciba Pharmaceutical Company, Division of Ciga-Geigy Corp., 556 Morris Avenue, Summit, NJ 07901 (NDA 12–101).

Such drugs are regarded as new drugs (21 U.S.C. 321 (p)). The effectiveness classification is described below.

A. *Effectiveness classification.*—The Food and Drug Administration has considered the Academy's reports, as well as other available evidence, and concludes that the drug is less than effective (possibly effective) for its labeled indications.

B. *Submission of data.*—Any data submitted in response to this notice to support indications for which the drug is classified as less than effective must be previously unsubmitted and include data from adequate and well-controlled clinical investigations (identified for ready review) as described in § 130.12(a)(5) of the regulations published in the Federal Register of May 8, 1970 (35 FR 7250). Carefully conducted and documented clinical studies obtained under uncontrolled or partially controlled situations are not acceptable as a sole basis for approval of claims of effectiveness, but such studies may be considered on their merits for corroborative support of efficacy and evidence of safety.

A copy of the Academy's report has been furnished to the firm referred to above. Communications forwarded in response to this announcement should be identified with the reference number DESI 12101, directed to the attention of that appropriate office listed below, and addressed to the Food and Drug Administration, 5600 Fishers Lane Rockville, MD 20852.

Supplements (identify with NDA number): Office of Scientific Evaluation (BD–100), Bureau of Drugs.

Requests for the Academy's report: Drug Efficacy Study Information Control (BD–66), Bureau of Drugs.

All other communications regarding this announcement: Drug Efficacy Study Implementation Project Office (BD–60), Bureau of Drugs.

All identical, related, or similar products, not the subject of an approved new drug application, are covered by the new drug application(s) reviewed and are subject to this notice. See 21 CFR 130.40 (37 FR 23185, October 31, 1972). Any person who wishes to determine whether a specific product is covered by this notice should write to the Food and Drug Administration, Bureau of Drugs, Office of Compliance (BD–300), 5600 Fishers Lane, Rockville, MD 20852.

This notice is issued pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (secs. 502, 505, 52 Stat. 1050–53, as amended: 21 U.S.C. 352, 355) and

the Administrative Procedure Act (5 U.S.C. 554) and under the authority delegated to the Commissioner of Food and Drugs (21 CFR 2.120).

Dated: February 7, 1973.

WILLIAM F. RANDOLPH,
Acting Associate Commissioner for Compliance.

[FR Doc. 73-2714 Filed 2-9-73; 8:45 am]

[DESI 5504; Docket No. FDC-D-587; NDAs 5-674; 5-757]

METHAMPHETAMINE HYDROCHLORIDE (PARENTERAL)

OPPORTUNITY FOR HEARING ON PROPOSAL TO WITHDRAW APPROVAL OF NEW DRUG APPLICATIONS

The Food and Drug Administration published a notice (DESI 5504) in the Federal Register of February 23, 1971 (36 FR 3387), regarding the efficacy of the following drugs containing methamphetamine hydrochloride for parenteral use and classifying them as effective, probably effective, or lacking substantial evidence of effectiveness for certain indications.

NDA 5-674 (incorrectly listed as 5-504); Methedrine Injection; formerly marketed by Burroughs Wellcome & Co., Inc., 3030 Cornwallis Road, Research Triangle Park, NC 27709.

NDA 5-757; Drinalfa Injection: E. R. Squibb & Sons, Georges Road, New Brunswick, N.J. 08903.

Subsequent to that notice, a publication in the Federal Register of August 8, 1972 (37 FR 15946), further ruled on those indications that had initially been classified as probably effective.

The Food and Drug Administration has recently reviewed the entire class of drugs offered for use as anorectic agents and the available evidence pertaining to their safe and effective use, including their potential misuse and abuse. On the basis of this recent survey, the Commissioner of Food and Drugs concludes that the well-documented history of abuse of parenteral methamphetamine, together with the severe risk of dependence and the presence of effective alternative drugs, creates an unfavorable balance of risk to benefit.

Therefore, notice is hereby given to the holders of the new drug applications listed above and to any interested person who may be adversely affected, that the Commissioner of Food and Drugs proposes to issue an order under section 505(e) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(e)) withdrawing approval of the above new drug applications and all amendments and supplements thereto. It is proposed to withdraw approval of these applications on the grounds that new evidence, not contained in the new drug applications or not available to the Commissioner until after the applications were approved, evaluated together with the evidence available to him when the applications were approved, show that methamphetamine hydrochloride for parenteral administration is not shown to be safe for use under the conditions of use upon the basis of which the application was approved.

All identical, related, or similar products, not the subject of an approved new drug applications, are covered by the new drug applications reviewed. See 21 CFR 130.40 (37 FR 23185, October 31, 1972). Any manufacturer or distributor of such an identical, related or similar product is an interested person who may in response to this notice submit data and information, request that the new drug applications not be withdrawn, request a hearing, and participate as a party in any hearing. Any person who wishes to determine whether a specific product is covered by this notice should write to the Food and Drug Administration, Bureau of Drugs, Office of Compliance (BD- 300), 5600 Fishers Lane, Rockville, MD 20852.

In accordance with the provisions of section 505 of the Act (21 U.S.C. 355) and the regulations promulgated thereunder (21 CFR Part 130), the Commissioner hereby gives the applicant(s) and any other interested person an opportunity for a hearing to show why approval of the new drug application(s) should not be withdrawn.

The applicant(s) and any other interested person is required to file with the Hearing Clerk, Department of Health, Education, and Welfare, Room 6-88, 5600 Fishers Lane, Rockville, MD 20852, on or before March 14, 1973, a written appearance electing whether or not to avail himself of the opportunity for a hearing. Failure of an applicant or any other interested person to file a written appear-

ance of election before March 14, 1973, will constitute an election by him not to avail himself of the opportunity for a hearing.

If no person elects to avail himself of the opportunity for a hearing, the Commissioner without further notice will enter a final order withdrawing approval of the application(s).

If an applicant or any other interested person elects to avail himself of the opportunity for a hearing, he must file, on or before March 14, 1973, written appearance requesting the hearing, giving the reasons why approval of the new drug application(s) should not be withdrawn, together with a well-organized and full-factual analysis of the clinical and other investigational data he is prepared to prove in support of his opposition. A request for a hearing may not rest upon mere allegations or denials, but must set forth specific facts showing that a genuine and substantial issue of fact requires a hearing (21 CFR 130.14 (b)).

If review of the data submitted by the applicant or any other interested person warrants the conclusion that the drug is safe for use under the conditions of use prescribed, recommended, or suggested in its labeling, the Commissioner will rescind this notice of opportunity for hearing.

If review of the data in the application(s) and data submitted by the applicant(s) or any other interested person in a request for a hearing, together with the reasoning and factual analysis in a request for a hearing, warrants the conclusion that no genuine and substantial issue of fact precludes the withdrawal of approval of the application(s), the Commissioner will enter an order of withdrawal making findings and conclusions on such data.

If, upon the request of the new drug applicant(s) or any other interested person, a hearing is justified, the issues will be defined, a hearing examiner will be named, and he shall issue, as soon as practicable after March 14, 1973, written notice of the time and place at which the hearing will commence. All persons interested in identical, related, or similar products covered by the new drug application(s) will be afforded an opportunity to appear at the hearing, file briefs, present evidence, cross-examine witnesses, submit suggested findings of fact, and otherwise participate as a party. The hearing contemplated by this notice will be open to the public except that any portion of the hearing that concerns a method or process the Commissioner finds entitled to protection as a trade secret will not be open to the public, unless the respondent specifies otherwise in his appearance.

Requests for a hearing and/or elections not to request a hearing may be seen in the Office of the Hearing Clerk (address given above) during regular business hours, Monday through Friday.

This notice is issued pursuant to provisions of the Federal Food, Drug and Cosmetic Act (sec. 505, 52 Stat. 1052–53, as amended; 21 U.S.C. 355), and the Administrative Procedure Act (5 U.S.C. 554), and under authority delegated to the Commissioner (21 CFR 2.120).

Dated: February 7, 1973.

WILLIAM F. RANDOLPH,
Acting Associate Commissioner
for Compliance.

[FR Doc. 73–2715 Filed 2–9–73; 8:45 am]

[From the Federal Register, vol. 38, No. 61, Mar. 30, 1973, pp. 8240–41]

NOTICES

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

FOOD AND DRUG ADMINISTRATION

[DESI's 5378, 5504; Dockets Nos. FDC–D–582, FDC–D–587; NDA's 9–946, etc., 5–674, 5–757]

AMPHETAMINES FOR HUMAN USE

NOTICE OF WITHDRAWAL OF APPROVAL OF NEW DRUG APPLICATIONS

In the Federal Register of February 12, 1973 (38 FR 4249), the Commissioner of Food and Drugs revised § 130.46 of Part 130, Subpart A concerning amphetamines (amphetamine, dextroamphetamine, and their salts, and levamphetamine and its salts) for human use. That revision became effective March 14, 1973.

When published in the Federal Register on August 8, 1970 (35 FR 12652), § 130.46 permitted continued marketing of these amphetamines based upon receipt of a new drug application. In response to that regulation, 106 new drug applications were received and continued marketing of those products was permitted pending their detailed review in conjunction with a review of all anorectic drugs and consideration of any issues they presented.

Also published in the Federal Register on February 12, 1973 were notices of opportunity for a hearing to withdraw approval of all previously approved new drug applications providing for anorectic drugs in combination with other ingredients such as sedatives, tranquilizers, rauwolfia derivatives, or vitamins (38 FR 4279) and for parenteral methamphetamine hydrochloride (38 FR 4282). Thirty days were allowed for holders of the new drug applications or any interested person who manufactures or distributes a drug similar, related, or identical to a drug provided for in the approved new drug applications to file a written appearance requesting a hearing and giving the reasons why new drug application approval should not be withdrawn, together with a well-organized and full-factual analysis of the clinical and other investigational data they were prepared to prove in support of their opposition.

In accordance with the decision announced with the revision of § 130.46 published in the Federal Register of February 12, 1973 (38 FR 4249), each of the the new drug applications providing for a combination anorectic drug for oral administration or for parenteral methamphetamine hydrochloride, whether submitted pursuant to § 130.46 or the subject of a previous approval, has been the subject of a notice of opportunity for hearing, either in a letter mailed to the firm or through notice in the Federal Register, or both.

Pursuant to those notices, requests for hearings have been received with respect to the following combination drugs:

NDA No.	Drug	NDA holder
1-522	Obetrol-10 and Obetrol-20 tablets, containing methamphetamine saccharate, methamphetamine hydrochloride, amphetamine sulfate, and dextroamphetamine sulfate.	Obetrol Pharmaceuticals, Division of Rexar Pharmacal Corp., 382 Schenek Ave., Brooklyn, N.Y. 11207.
2-042	Eskatrol Spansules (sustained release capsules), containing dextroamphetamine sulfate and prochlorperazine (as the maleate).	Smith Kline & French Laboratories, 1500 Spring Garden St., Philadelphia, Pa. 19101.
12-570	Bamadex Sequels (sustained release capsules), containing dextroamphetamine sulfate and meprobamate.	Lederle Laboratories Division, American Cyanamid, Post Office Box 500, Pearl River, N.Y. 10965.
	Dexamyl Tablets, Dexamyl Elixir, Dexamyl Spansules (No. 1) (sustained release capsules), and Dexamyl Spansules (No. 2) (sustained release capsules), containing amobarbital and dextroamphetamine sulfate.	Smith Kline & French Laboratories.
	Delcobese Tablets, Delcobese Sustained Release Tablets, Delcobese Capsules, and Delcobese Sustained Release Capsules, containing dextroamphetamine sulfate, methamphetamine hydrochloride, methamphetamine adipate, and amphetamine sulfate.	Delco Chemical Co., Inc., 7 MacQuesten Parkway North, Mount Vernon, N.Y. 10550.

The products specifically named above may continue to be marketed pending a ruling on the requests for hearing.

Also, pursuant to the notice of opportunity for hearing for parenteral methamphetamine hydrochloride proposing to withdraw approval on the grounds that the drug is not shown to be safe, a request for hearing was received from Merle Diment, M.D. pertaining to all such products. Included in the request were the writer's opinion concerning the effectiveness of parenteral amphetamines in improving the mental status and well being of patients in their toleration of, and recovery from, anesthetic procedures, and his statements taking exception to the Commissioner's conclusion that the well-documented history of abuse of this dosage form, the severe risk on dependence, and the availability of effective, alternative drugs constitute lack of proof of safety. The contentions of Dr. Diment have been considered and the Commissioner of Food and Drugs concludes that there is no genuine and substantial issue of fact requiring a hearing. No charge was made in the notice of opportunity for hearing that parenteral methamphetamine hydrochloride lacks substantial evidence of effectiveness; rather, the notice stated that such products were considered effective. However, the use for which Dr. Diment recommends continued availability of the drugs has not been approved in the new drug applications, and no substantial evidence to support such

use accompanied the request. His comments concerning safety of the drug and espousing a principle that allows continued availability notwithstanding the known potential for misuse and abuse are testimonial at best and do not comprise adequate proof of safety. Thus, based on the information before him and a review of the statements made by Dr. Diment to support his contention that approval of the new drug applications should not be withdrawn, the Commissioner finds that there has been a failure to present adequate evidence of safety for parenteral methamphetamine hydrochloride and the request for a hearing is denied.

Comments were received from two physicians, Dr. William K. Hamilton, Professor and Chairman, Department of Anesthesia, School of Medicine, University of California, San Francisco, and Dr. Jack Moyers, Chief of Anesthesia, Professor and Head of Department of Anesthesia, University of Iowa, both objecting to the removal of a useful drug from the market because of its use and abuse for nontherapeutic purposes. No data accompanied the responses.

In response to the notices of opportunity for hearing published in the Federal Register of February 12, 1973 (33 FR 4279 and 4282), none of the holders of the following new drug applications named in those notices have filed a written appearance of election as provided by said notice. The failure to file such an appearance constitutes an election by such persons not to avail themselves of the opportunity for a hearing:

NDA No.	Drug	NDA holder
6-946	Du-Oria tablets containing methamphetamine hydrochloride and reserpine.	Formerly marketed by B. F. Asher & Co., Inc., Post Office Box 827, Kansas City, Mo. 64130.
10-207	Dexserpine "5" tablets containing dextroamphetamine sulfate and reserpine.	Formerly marketed by Nysco Laboratories, Inc., 34-24 Vernon Blvd., Long Island City, N.Y. 11106.
11-280	Bamadex tablets, containing dextrose amphetamine sulfate and meprobamate.	Lederle Laboratories Division, American Cynamamid Co., Post Office Box 500, Pearl River, N.Y. 10965.
11-538	Biphetamine-T "12½" capsules and Biphetamine-T "20" capsules, containing dextroamphetamine, amphetamine, and methaqualone, all as cation exchange resin complexes of sulfonated polystyrene.	Strasenburgh Pharmaceutical, Division Pennwalt Corp., 755 Jefferson Rd., Rochester, N.Y. 14623.
12-127	Appetrol tablets, cottaining dextroamphetamine sulfate and meprobamate.	Wallace Pharmaceuticals, Division of Carter-Wallace, Inc., Half Acre Rd., Cranbury, N.J. 08512.
12-371	Prelu-Vite capsules, containing phenmetrazine hydrochloride, Vitamine A, Vitamin D, thiamine mononitrate, riboflavin, niscinamide, calcium pantothenate, pyridoxine hydrochloride, cobalamin concentrate, ascorbic acid, iron, calcium, phosphorus, iodine, and copper.	Formerly marketed by Geigy Pharmaceuticals, Division of Ciba Geigy Co., Saw Mill River Rd., Ardsley, N.Y. 10502.
12-415	Delfeta-sed Stedytabs (sustained release tablets), containing di-methamphetamine hydrochloride and amobarbital.	Eastern Research Laboratories Inc., 302 South Central Ave., Baltimore, Md. 21202.
12-624	Appetrol-S.R. (sustained release capsules), containing dextroamphetamine sulfate and meprobamate.	Wallace Pharmaceuticals.
5-674	Methedrine Injection, containing methamphetamine hydrochloride.	Formerly marketed by Burroughs Wellcome & Co., Inc., 3030 Cornwallis Rd., Research Triangle Park, N.C. 27709.
5-757	Drinalfa, Injection, containing methamphetamine hydrochloride.	E. R. Squibb & Sons, Georges Rd., New Brunswick, N.J. 08903.

All identical, related, or similar products, not the subject of an approved new drug application, are covered by the new drug applications reviewed and are subject to this notice. See 21 CFR 130.40 (37 FR 23185, Oct. 31, 1972). Any person who wishes to determine whether a specific product is covered by this notice should write to the Food and Drug Administration, Bureau of Drugs, Office of Compliance (BD-300), 5600 Fishers Lane, Rockville, MD 20852.

The Commissioner of Food and Drugs, pursuant to the provisions of the Federal Food, Drug, and Cosmetic Act (sec. 505, 52 Stat. 1053, as amended; 21 U.S.C. 355), and the Administrative Procedure Act (5 U.S.C. 554), and under authority delegated to him (21 CFR 2.120) finds on the basis of new information before him, evaluated together with the evidence available to him at time of approval of the applications that, with respect to the above-listed combination preparations for which no hearing was requested: (1) there is a lack of substantial evidence that the drugs will have all the effects they purport or are represented to have; and (2) the drugs are not shown to be safe for use under the conditions of use prescribed, recommended, or suggested in their labeling; and with respect to the parenteral drug products containing methamphetamine hydrochloride, such products are not shown to be safe for use under the conditions of use prescribed, recommended, or suggested in their labeling.

Therefore, pursuant to foregoing findings, approval of the above new drug applications (except for those for which a request for hearing was received), and all amendments and supplements applying thereto is withdrawn effective on March 30, 1973. Shipment in interstate commerce of any combination drug product other than those few listed above that may continue to be marketed pending a ruling on the request for a hearing, or of any parenteral amphetamine product (e.g., amphetamine, dextroamphetamine, levamphetamine, or methamphetamine) is henceforth unlawful.

Dated: March 28, 1973

WILLIAM F. RANDOLF,
Acting Associate Commissioner
for Compliance.

[FR Doc. 73-6230 Filed 3-29-73; 8:45 am]

[From the Federal Register, vol. 38, No. 185, Sept. 25, 1973]

NOTICES

[DESI 5378; Docket No. FDC-D-582; NDA 11-522]

CERTAIN COMBINATION ANORECTIC DRUGS

FINAL ORDER ON OBJECTIONS AND REQUEST FOR A HEARING REGARDING WITHDRAWAL OF APPROVAL OF NEW DRUG APPLICATIONS

In the Federal Register of August 8, 1970 (35 FR 12652) the Commissioner of Food and Drugs published a statement of policy (21 CFR 130.46) concerning amphetamines for human use. The statement contained the findings of the Food and Drug Administration based upon reports received from the National Academy of Sciences-National Research Council (NAS-NRC) Drug Efficacy Study Group. Also published in the Federal Register of August 8, 1970 (35 FR 12678) was a notice (DESI 5378) on drugs containing amphetamines and their salts, stating that the drugs were regarded as possibly effective for their claimed anorectic effect and lacked substantial evidence of effectiveness for their other labeled indications. The statement of policy also contained the findings of the Commissioner that because of the extensive use of the drugs in the treatment of obesity, and their stimulant effect on the nervous system, they have a potential for misure and actual abuse, and production data indicated that amphetamines are produced and prescribed in quantities greatly in excess of demonstrated medical needs. As a condition for continued marketing of amphetamines, the statement of policy required relabeling as specified and the submission of a new drug application (NDA) within one year for all such drugs not then the subject of NDA approval. Holders of approved NDAs were required to submit additional evidence of safety and substantial evidence of efficacy in the form of adequate and well-controlled clinical investigations.

On February 12, 1973, the Commissioner published in the Federal Register (38 FR 4249) a final order stating that there was a lack of substantial evidence of effectiveness for, and a recognized potential for the abuse of, fixed combination drugs for anorectic use which contained, among other ingredients, amphetamine, methamphetamine, or dextroamphetamine. In addition, the Commissioner found that alternative therapeutic measures which are safe and effective are available for use. The Commissioner also stated in the final order that a mixture of dextroamphetamine and amphetamine is ordinarily regarded as a single drug entity. A similar conclusion as to a mixture of dextroamphetamine and methamphetamine, and/or amphetamine and methamphetamine, was not made. In § 3.86 (21 CFR 3.86) the Food and Drug Administration set forth a policy on fixed-combination drugs for prescription use requiring that each drug in a fixed-combination drug contribute to the claimed effect of the drug; section IV, infra. Therefore, drugs containing combinations of amphetamine and methamphetamine and/or dextroamphetamine and methamphetamine, are fixed combination drugs. The final order also stated that a proposal to withdraw approval of such combination drugs for anorectic use was published elsewhere in the same issue of the Federal Register.

In a notice in the Federal Register of February 12, 1973 (38 FR 4279), the Commissioner announced an opportunity for hearing on his proposal to withdraw approval of new drug applications for the combination amphetamine or other

anorectic drugs. This notice was based on evaluation of data submitted pursuant to the Federal Register notice of August 8, 1970 (35 FR 12678). This data was found, after review, not to provide substantial evidence that the drugs named in the Federal Register notice of February 12, 1973, were effective as fixed combination for their claimed anorectic uses. Based on this lack of substantial evidence of effectiveness of the drugs as fixed combinations, the recognized potential for abuse of these combination drugs, and the availability of alternative therapeutic measures which are safe and effective, the named drugs were also found to be lacking in proof of safety. The Commissioner further found that the data submitted in response to the Federal Register notice of August 8, 1970, did not support a contention that the combination products decrease the incidence or severity of side effects associated with the abuse potential of the single entity anorectic drug. Notice was therefore given to holders of the named new drug applications and all other interested persons, including those marketing similar, identical or related drugs (§ 130.40 (21 CFR 130.40) that the Commissioner proposed to withdraw approval of these new drug applications based on a lack of substantial evidence of effectiveness and a lack of proof of safety. All holders of the NDA's and persons marketing similar, identical or related drugs, and other interested persons were invited to request a hearing on the proposed withdrawals and to submit with such request a well organized and full-factual analysis of the clinical and other investigational data they were prepared to prove in support of their opposition to the withdrawal of the named NDA's and any such similar, identical or related drugs. The notice stated that if substantial evidence of effectiveness and evidence if safety was received for any of the named drugs, or for similar, identical and related drugs, the notice would be rescinded as to such drugs.

In response to the notice in the Federal Register of February 12, 1973, requests for a hearing were received from four persons for five drugs. The persons and the drugs were named in the Federal Register notice of March 30, 1973 (38 FR 8290). The subject final order concerns only two of those persons requesting hearings.

Rexar Pharmacal Co., 396 Rockaway Ave., Valley Stream, NY 11582, requested a hearing for the drugs Obetrol-10 and Obetrol-20 Tablets (NDA 11-522). These drugs are the subject of an NDA which was made conditionally effective on July 24, 1959, and fully effective on February 23, 1960. The Obetrol drugs had been reviewed by the NAS-NRC and found to be possibly effective as an adjunct in the management of some forms of obesity in which an appetite depressant is indicated. The NAS-NRC finding was incorporated into the August 8, 1970 Federal Register notice discussed above (35 FR 12678).

Delco Chemical Co., 7 McQuesten Parkway North, Mount Vernon NY 10550, requested a hearing for the drugs Delcobese Sustainted Release Tablets and Capsules and Delcobese Tablets and Capsules. Pursuant to the August 8, 1970 Federal Register order, the Commissioner received from Barrows Pharmacal Inc., 300 Prospect St., Inwood, NY 11696, four new drug applications on the following dates for the following drugs: March 15, 1971, NDA 17-162, Delcobese Tablets, 5 mg., 10 mg., 15 mg., and 20 mg.; March 15, 1971, NDA 17-161, Delcobese Capsules, 5 mg., 10 mg., 15 mg., and 20 mg.; March 26, 1971, NDA 17-160, Delcobese Sustained Release Capsules, 5 mg., 10 mg., 15 mg., and 20 mg., and June 24, 1971, NDA 17-159. Delcobese Sustained Release Double-Layer Tablets, 5 mg., 10 mg., 15 mg., and 20 mg. All four of the drugs consist of a combination of amphetamines and methamphetamines. No data was submitted in support of the efficacy of these combination drugs: the sponsor merely paraphrased the conclusions stated in the August 8, 1970 Federal Register notice in support of the stafety and efficacy of the drugs for use as anorectics and in treating narcolepsy and minimal brain dysfunction in children.

Due to the large number of new drug applications received pursuant to the August 8, 1970 Federal Register order, a review and evaluation of the new drug applications submitted by Barrows was delayed. Barrows was notified of this delay by a letter from the Food and Drug Administration on February 25, 1972. On January 15, 1973, a letter was sent to Barrows from J. Richard Crout, M.D., Acting Director, Office of Scientific Evaluation, Bureau of Drugs, stating the conclusion of the Food and Drug Administration that the four new drug applications submitted by Barrows could not be approved because the submissions

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[From the Federal Register, vol. 39, No. 140, July 19, 1974, pp. 26459—62]

NOTICES

[DESI 5378; Docket No. FDC-D-687; NDA 5-378, etc.]

DRUGS FOR HUMAN USE—DRUG EFFICACY STUDY IMPLEMENTATION CERTAIN SINGLE ENTITY ORAL ANORECTIC DRUGS IN CONVENTIONAL OR CONTROLLED RELEASE DOSAGE FORMS

FOLLOW-UP NOTICE AND OPPORTUNITY FOR HEARING

The Food and Drug Administration published an announcement in the Federal Register of August 8, 1970 (35 FR 12678) regarding the efficacy of the following single entity oral anorectic drugs:

1. Biphetamine "7½" Capsules, Biphetamine "12½" Capsules, and Biphetamine "20" Capsules, respectively, containing 3.75 milligrams, 6.25 milligrams, and 10 milligrams each of dextroamphetamine and amphetamine per capsule, all as cation exchange resin complexes of sulfonated polystyrene; Strasenburgh Laboratories, Division of Wallace and Tiernan Inc., Post Office Box 1710, Rochester, NY 14603 (NDA 10-093).

2. Ionamin "15" Capsules and Ionamin "20" Capsules, containing, respectively, 15 milligrams phentermine and 30 milligrams phentermine per capsule, both as cation exchange resin complexes of sulfonated polystyrene; Strasenburgh Laboratories Division of Wallace and Tiernan Inc. (NDA 11-613).

3. Methedrine Tablets containing 5 milligrams methamphetamine hydrochloride per tablet; formerly marketed by Burroughs Wellcome & Co., Inc., 3030 Cornwallis Road, Research Triangle Park, NC 27709 (NDA 5-504).

4. Amphedroxn Hydrochloride Tablets containing 5 milligrams methamphetamine hydrochloride per tablet; Eli Lilly and Co., Post Office Box 618, Indianapolis, Ind. 46206 (NDA 6-390).

5. Delfetamine Stedytabs containing 30 milligrams di-methamphetamine hydrochloride per controlled release tablet; Eastern Research Laboratories, Inc., 302 South Central Ave., Baltimore, MD 21202 (NDA 12-416).

6. Desoxyn Tablets containing 2.5 milligrams or 5 milligrams methamphetamine hydrochloride per tablet, Desoxyn Gradumet Tablets containing 5, 10, or 15 milligrams methamphetamine hydrochloride per tablet, and Desoxyn Elixir containing 20 milligras methamphetamine hydrochloride per 30 milliters; Abbott Laboratories, 14th and Sheridan Road, North Chicago, Ill. 60064 (NDA 5-378).

7. Drinalfa Tablets containing 5 milligrams methamphetamine hydrochloride per tablet; E. R. Squibb, P.O. Box 400, Princeton, NJ 08544 (NDA 5-756).

8. Tenuate Dospan Tablets containing 75 milligrams diethylpropion hydrochloride per controlled release tablet; Merrell-National Laboratories, Division of Richardson-Merrell, Inc., 1100 East Amity Road, Cincinnati, OH 45215 (NDA 12-546).

9. Racemic Desoxyephedrine Hydrochloride Tablets containing 5 milligrams dimethamphetamine hydrochloride per tablet; High Chemical Co., 1760 North Howard Street, Philadelphia, PA 19122 (NDA 5-969).

10. Miller-Drine Tablets containing 10 milligrams di-methamphetamine hydrochloride per tablet; Smith, Miller and Patch, Inc., 401 Joyce Kilmer Avenue, New Brunswick, NJ 08902 (NDA 6-003).

11. Norodin Tablets containing 5 milligrams methamphetamine hydrochloride per tablet; Endo Laboratories, 1000 Stewart Avenue, Garden City, Long Island, NY 11733 (NDA 6-632).

12. D-O-E Tablets containing 5 milligrams methamphetamine hydrochloride per tablet, Tilden-Yates Laboratories, Inc., 295 Lafayette Street, New York, NY 10012 (NDA 5-603).

Of the new drug applications listed above, approval of the following applications and supplements thereto, was withdrawn August 8, 1972 (37 FR 15948) on the grounds that the applicants had not made required reports under section 505(j) of the Act (21 U.S.C. 355(j)) and §§ 310.300 or 310.302 (e) and (f) of the new-drug regulations (21 CFR 310.300, 310.302):

NDA 5-632, Norodin Tablets (methamphetamine hydrochloride); Endo Laboratories.

NDA 6-390, Amphedroxyn Hydrochloride Tablets (methamphetamine hydrochloride); Eli Lilly and Company.

Other drugs (combination anorectic drugs) were also included in the notice of August 8, 1970. They are not affected by this notice.

In addition to the holder(s) of the new drug application(s) specifically named above, this notice applies to all persons who manufacture or distribute a drug product, not the subject of an approved new drug application, which is identical, related, or similar to a drug product named above, as defined in 21 CFR 310.6. It is the responsibility of every drug manufacturer or distributor to review this notice to determine whether it covers any drug product he manufactures or distributes. Any person may request an opinion of the applicability of this notice to a specific drug product he manufactures or distributes that may be identical, related, or similar to a drug product named in this notice by writing to the Food and Drug Administration, Bureau of Drugs, Office of Compliance (HFD-300), 5600 Fishers Lane, Rockville, MD 20852.

The August 8, 1970 notice stated that the above-listed drugs were regarded as lacking substantial evidence of effectiveness for specific indications; and possibly effective for their claimed anorectic effects, for their claims for prolonged, continuous or sustained release, and for certain other claims.

Based on information submitted by the manufacturers of anorectic drugs and a review of available evidence, the Commissioner of Food and Drugs finds it appropriate to amend the announcement of August 8, 1970 insofar as it pertains to the drugs listed above, as set forth below.

Such drugs are regarded as new drugs (21 U.S.C. 321(p)). Supplemental new drug applications are required to revise the labeling in and to update previously approved applications providing for such drugs. A new drug application is required from any person marketing such drug without approval.

A. *Effectiveness classification.*—The Food and Drug Administration has considered the Academy's reports as well as other available evidence and concludes that:

1. All of the drugs listed above are effective in the management of exogenous obesity as a short-term (a few weeks) adjunct in a regimen of weight reduction based on caloric restriction.

2. Dextroamphetamine and amphetamine are also effective for narcolepsy and for minimal brain dysfunction in children (hyperkinetic behavior disorders), as an aid to general management.

3. All of the drugs lack substantial evidence of effectiveness for all other of their claims.

B. *Conditions for approval and marketing.*—The Food and Drug Administration is prepared to approve abbreviated new drug applications and abbreviated supplements to previously approved new drug applications under conditions described herein.

1. *Form of drug.* The preparations are in capsule, tablet, or liquid form as indicated above, suitable for oral administration.

2. *Labeling conditions.* a. The label bears the statement, "Caution: Federal law prohibits dispensing without prescription."

b. The drug is labeled to comply with all requirements of the Act and regulations, and the labeling bears adequate information for safe and effective use of the drug. The Indications, Actions, and the Drug Dependence portions of the Warnings sections are as follows (Complete labeling guidelines are available on request):

FOR PHENTERMINE AND DIETHYLPROPION HYDROCHLORIDE

Indication

(Name of drug) is indicated in the management of exogenous obesity as a short-term (a few weeks) adjunct in a regimen of weight reduction based on caloric restriction. The limited usefulness of agents of this class (see Actions) should be measured against possible risk factors inherent in their use such as those described below.

Actions

(Name of drug) is a sympathomimetic amine with pharmacologic activity similar to the prototype drugs of this class used in obesity, the amphetamines. Actions include central nervous system stimulation and elevation of blood pressure. Tachyphylaxis and tolerance have been demonstrated with all drugs of this class in which these phenomena have been looked for.

Drugs of this class used in obesity are commonly known as "anorectics" or "anorexigenics". It has not been established, however, that the action of such

drugs in treating obesity is primarily one of appetite suppression. Other central nervous system actions, or metabolic effects may be involved, for example.

Adult obese subjects instructed in dietary management and treated with "anorectic" drugs, lose more weight on the average than those treated with placebo and diet, as determined in relatively short-term clinical trials.

The magnitude of increased weight loss of drug-treated patients over placebo-treated patients is only a fraction of a pound a week. The rate of weight loss is greatest in the first weeks of therapy for both drug and placebo subjects and tends to decrease in succeeding weeks. The possible origins of the increased weight loss due to the various drug effects are not established. The amount of weight loss associated with the use of an "anorectic" drug varies from trial to trial, and the increased weight loss appears to be related in part to variables other than the drugs prescribed, such as the physician-investigator, the population treated, and the diet prescribed. Studies do not permit conclusions as to the relative importance of the drug and non-drug factors on weight loss.

The natural history of obesity is measured in years, whereas the studies cited are restricted to a few weeks duration; thus, the total impact of drug-induced weight loss over that of diet alone must be considered clinically limited.

Drug Dependence Section of Warnings Section

Drug Dependence. (Name of drug) is related chemically and pharmacologically to the amphetamines. Amphetamines and related stimulant drugs have been extensively abused, and the possibility of abuse of (name of drug) should be kept in mind when evaluating the desirability of including a drug as part of a weight reduction program. Abuse of amphetamines and related drugs may be associated with intense psychological dependence and severe social dysfunction. There are reports of patients who have increased the dosage to many times that recommended. Abrupt cessation following prolonged high dosage administration results in extreme fatigue and mental depression; changes are also noted on the sleep EEG. Manifestations of chronic intoxication with anorectic drugs include severe dermatoses, marked insomnia, irritability, hyperactivity, and personality changes. The most severe manifestation of chronic intoxication is psychosis, often clinically indistinguishable from schizophrenia.

For Amphetamine, Dextroamphetamine, Methamphetamine Hydrochloride and Didimethamphetamine Hydrochloride

Indication

Exogenous obesity as a short term (a few weeks) adjunct in a regimen of weight reduction based on caloric restriction, for patients in whom obesity is refractory to alternative therapy, e.g., repeated diets, group programs, and other drugs. The limited usefulness of (name of drug) (see ACTIONS) should be weighed against possible risks inherent in use of the drug, such as those described below.

For amphetamine and dextroamphetamine, additional indications are:

Narcolepsy—Mineral Brain Dysfunction in Children as adjunctive therapy to other remedial measures (psychological, educational, social).

Special Diagnostic Considerations:

Special etiology of Minimal Brain Dysfunction (MGD) is unkown ,and there is no single diagnosic test. Adequate diagnosis requires the use not only of medical but of special psychological, eduentional, and social resources.

The characteristic signs most often observed are chronic history of short attention span, distractibility, emotional liability, impulsivity, moderate to severe hyperactivity, minor neurological signs and abnormal EEG. Learning disabilities may or may not be present. The diagnosis of MBD must be based upon a complete history and evaluation of the child and not solely on the presence of one or more of these signs.

Drug treatment is not indicated for all children with MBD. Appropriate educational placement is essential and psychological or social intervention may be necessary. When remedial measures alone are insufficient, the decision to prescribe stimulant medication will depend upon the physician's assessment of the chronicity and severity of the child's symptoms.

Drug treatment is not intended for use in the child whose hyperactivity is due to environmental factors and/or primary psychiatric disorders.

Actions

(Name of drug) is a sympathomimetic amine with CNS stimulant activity. Peripheral actions include elevation of systolic and diastolic blood pressures and weak bronchodilator and respiratory stimulant action. Drugs of this class used in obesity are commonly known as "anorectics" or "anorexigenics". It has not been established, however, that the action of such drugs in treating obesity is primarily one of appetite suppression. Other central nervous system actions, or metabolic effects, may be involved, for example.

Adult obese subjects instructed in dietary management and treated with "anorectic" drugs, lose more weight on the average than those treated with placebo and diet, as determined in relatively short-term clinical trials.

The magnitude of increased weight loss of drug-treated patients over placebo-treated patients is only a fraction of a pound a week. The rate of weight loss is greatest in the first weeks of therapy for both drug and placebo subjects and tends to decrease in succeeding weeks. The origins of the increased weight loss due to the various possible drug effects are not established. The amount of weight loss associated with the use of an "anorectic" drug varies from trial to trial, and the increased weight loss appears to be related in part to variables other than the drug prescribed, such as the physician-investigator, the population treated, and the diet prescribed. Studies do not permit conclusions as to the relative importance of the drug and non-drug factors on weight loss.

The natural history of obesity is measured in years, whereas the studies cited are restricted to a few weeks duration; thus, the total impact of drug-induced weight loss over that of diet alone must be considered clinically limited.

DRUG DEPENDENCE SECTION OF WARNINGS SECTION

Drug Dependence. (Name of drug) has been extensively abused. Tolerance, extreme psychological dependence, and severe social disability have occurred. There are reports of patients who have increased the dosage to many times that recommended. Abrupt cessation following prolonged high dosage administration results in extreme fatigue and mental depression; changes are also noted on the sleep EEG. Manifestations of chronic intoxication with (name of drug) include severe dermatoses, marked insomnia, irritability, hyperactivity, and personality changes. The most severe manifestation of chronic intoxication is psychosis, often clinically indistinguishable from schizophrenia.

3. *Marketing status.* Marketing of such drugs may be continued under the conditions described in the notice entitled Conditions for Marketing New Drugs Evaluated in Drug Efficacy Study, published in the Federal Register July 14, 1970 (35 FR 11273), as follows:

a. For holders of "deemed approved" new drug applications (i.e., an application which became effective on the basis of safety prior to October 10, 1962), the submission of a supplement for revised labeling and a supplement for updating information, including full manufacturing information with respect to items 7 and 8 of Form FD-356H (§ 314.1(c)), as described in paragraphs (a)(1) (i) and (iii) of the notice of July 14, 1970. For preparations claiming controlled release, such supplement should contain studies comparing blood levels occurring with the controlled release form with blood levels occurring with single units of the conventional form given multiple times. For example, when comparing a 30 mg. controlled release form normally given every 12 hours with a 10 mg. conventional form normally given every 4 hours, the comparison should involve 1 unit of the controlled release form given once and one unit of the 10 mg. form given every 4 hours.

b. For any person who does not hold an approved or effective new drug application, the submission of an abbreviated new drug application as described in paragraph (a)(3)(i) of that notice, except that full manufacturing information with respect to items 7 and 8 of Form FD-356H (§ 314.1(c)) is required. For preparations claiming controlled release such supplement should contain studies comparing blood levels occurring with the controlled release form with blood levels occurring with single units of the conventional form given multiple times. For example, when comparing a 30 mg. controlled release form normally given every 12 hours with a 10 mg. conventional form normally given every 4 hours, the comparison should involve 1 unit of the controlled release form given once and one unit of the 10 mg. form given every 4 hours.

c. For any distributor of the drug, the use of labeling in accord with this announcement for any such drug shipped within the jurisdiction of the Act as described in paragraph (b) of that notice.

C. *Notice of opportunity for hearing.*—On the basis of all the data and information available to him, the Director of the Bureau of Drugs is unaware of any adequate and well-controlled clinical investigation, conducted by experts qualified by scientific training and experience, meeting the requirements of section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) and 21 CFR 314.111 (a) (5), demonstrating the effectiveness of drug(s) for the indication(s) lacking substantial evidence of effectiveness referred to in paragraph A.3 of this notice.

Notice is given to the holder(s) of the new drug application(s), and to all other interested persons, that the Director of the Bureau of Drugs proposes to issue an order under section 505(e) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(e)), withdrawing approval of the new drug application(s) (or, if indicated above, those parts of the application(s) providing for the drug product(s) listed above) and all amendments and supplements thereto providing for the indication(s) lacking substantial evidence of effectiveness referred to in paragraph A.3 of this notice on the ground that new information before him with respect to the drug product(s), evaluated together with the evidence available to him at the time of approval of the application(s), shows there is a lack of substantial evidence that the drug product(s) will have all the effects it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling. An order withdrawing approval will not issue with respect to any application(s) supplemented, in accord with this notice, to delete the claim(s) lacking substantial evidence of effectiveness.

In addition to the ground for the proposed withdrawal of approval stated above, this notice of opportunity for hearing encompasses all issues relating to the legal status of the drug products subject to it (including identical, related, or similar drug products as defined in § 310.6), e.g., any contention that any such product is not a new drug because it is generally recognized as safe and effective within the meaning of section 201(p) of the act or because it is exempt from part or all of the new drug provisions of the act pursuant to the exemption for products marketed prior to to June 25, 1938, contained in section 201(p) of the act, or pursuant to section 107(c) of the Drug Amendments of 1962; or for any other reason.

In accordance with the provisions of section 505 of the act (21 U.S.C. 355) and the regulations promulgated thereunder (21 CFR 310, 314), the application(s) and all other persons who manufacture or distribute a drug product which is identical, related, or similar to a drug product named above (21 CFR 310.6), are hereby given an opportunity for a hearing to show why approval of the new drug application(s) providing for the claim(s) involved should not be withdrawn and an opportunity to raise, for administrative determination, all issues relating to the legal status of a drug product named above and all identical, related, or similar drug products.

If an applicant or any person subject to this notice pursuant to 21 CFR 310.6 elects to avail himself of the opportunity for a hearing, he shall file (1) on or before August 19, 1974, a written notice of appearance and request for hearing, and (2) on or before September 17, 1974, the data, information, and analyses on which he relies to justify a hearing, as specified in 21 CFR 314.200. Any other interested person may also submit comments on this proposal to withdraw approval. The procedures and requirements governing this notice of opportunity for hearing, a notice of appearance and request for hearing, a submission of data, information, and analyses to justify a hearing, other comments, and a grant or denial of hearing, are contained in 21 CFR 130.14 as published and discussed in detail in the Federal Register of March 13, 1974 (39 FR 9750), recodified as 21 CFR 314.200 on March 29, 1974 (39 FR 11680).

The failure of an applicant or any other person subject to this notice pursuant to 21 CFR 310.6 to file timely written appearance and request for hearing as required by 21 CFR 314.200 constitutes an election by such person not to avail himself of the opportunity for a hearing concerning the action proposed with respect to such drug product and a waiver of any contentions concerning the legal status of such drug product. Any such drug product labeled for the indication(s) lacking substantial evidence of effectiveness referred to in paragraph A.3 of this notice may not thereafter lawfully be marketed, and the Food and Drug Administration will initiate appropriate regulatory action to remove such drug products from the market. Any new drug product marketed without an approved NDA is subject to regulatory action any time.

side effects attributable to the dextroamphetamine component. Lederle also argues that Bamadex Sequels must be found effective because meprobamate and dextroamphetamine have each been found by the FDA to be effective as single entities, and that its product must be found safe because Bamadex Sequels were approved on the basis of safety in August 1960 and there has been no clinical experience to the contrary since that time. Lederle contends that the addition of meprobamate, a schedule IV controlled substance under the Controlled Substances Act (21 U.S.C. 801 et seq.) to dextroamphetamine, a schedule II substance under the same act, results in a combination with significantly lower potential for abuse than dextroamphetamine alone, within the meaning of 21 CFR 3.86(a)(2).

Finally, Lederle claims that the FDA interpreted certain data in its investigations in a manner contrary to the observations and reports of the investigators who conducted the studies.

The Commissioner has considered all of the material submitted by Lederle and has concluded that there is no genuine issue of material fact requiring a hearing and that the legal objections offered are insubstantial. A full discussion follows:

I. The drug

Bamadex Sequels contains (each capsule) a fixed combination of milligrams dextroamphetamine sulfate and 300 milligrams meprobamate.

II. Recommended uses and dosage; rationale for the combination

The labeling reviewed by the NAS/NRC, Drug Efficacy Study Group, claimed that Bamadex Sequels was useful in the management of obesity, curbed appetite with minimal overstimulation of the central nervous system, and provided a sustained release of active ingredients. Lederle's present labeling retains the claims with respect to sustained release and minimal overstimulation of the central nervous system, but incorporates the changes required by 21 CFR 310.504 and recommends Bamadex only for use in exogenous obesity as a short term (a few weeks) adjunct in a regimen of weight reduction based on caloric restriction. The usual adult dosage of Bamadex Sequels is one capsule daily in the morning.

Lederle's rationale for the combination is twofold: (1) The dextroamphetamine results in a drug with a lower abuse potential than dextromphetamine counteracts the overstimulation which frequently accompanies the use of dextroamphetamine sulfate, and (2) the addition of meprobamate to dextroamphetamine results in a drug with a lower abuse potential than dextroemphetamine alone.

III. Data submitted to support claims of effectiveness

A. *Bamadex Sequels studies.*—Lederle submitted three clinical studies in support of the claimed effectiveness of Bamadex Sequels. These studies, with the exceptions noted below, followed substantially identical protocols; they are evaluated as follows:

1. Noble, Rudolph E., "A Comparison of Bamadex Sequels (15 mg dextroamphetamine and 300 mg meprobamate), Bamadex Sequels Minus Meprobamate (15 mg dextroamphetamine) and Placebo on Weight Loss and Side Effects in 90 Overweight Patients," unpublished study, 1971. In an attempt to establish, inter alia, that patients on Bamadex Sequels experience fewer adverse reactions than those who receive dextroamphetamine alone (i.e., that meprobamate reduces the side effects attributable to dextroamphetamine), the investigator selected 90 patients who were 20 percent overweight according to Metropolitan Life Insurance Company standards. These were divided into three equal groups and randomly assigned to one of three treatment regimens of Bamadex Sequels, dextroamphetamine, or placebo. The first group received Bamadex Sequels for 21 days, placebo for 21 days, and then Bamadex Sequels for the final 21 days; the second received dextroamphetamine for 21 days, placebo for 21 days, and dextroamphetamine for 21 days; the third received a placebo for the entire 9-week period. Each patient was instructed to take one capsule each day at least 1 hour before breakfast. Male patients were placed on a 1,500 calorie daily diet; females on a 1,200 calorie daily diet. Prior to entrance in the study and at 3, 6, and 9 weeks after entry into the study, patients' height, weight, pulse, and blood pressure were recorded and compared.

This study is not adequate and well-controlled within the meaning of 21 CFR 314.111(a)(5)(ii)(a)(2)(*iii*) in that it fails to assure that test and control groups were comparable with respect to the use of drugs other than the test drug. Thus, although the investigator undertook statistical analysis to assure the

groups were comparable with respect to age, sex, percent overweight distribution, and the mean dosage duration, no such analysis was performed with respect to the use of concomitant medication. This is always a pertinent variable and particularly so in this study where patients were taking diuretics (which could interfere with the effect of test medication on weight loss) and major tranquilizers, analgesics, and antihistamines with sedative effects (which could interfere with adverse reactions related to the central nervous system).

The study fails to explain the methods of observation and recording of results with respect to side effects (21 CFR 314.111(a)(5)(ii) (*a*)(*3*)). Thus, no details are given as to whether subjects were questioned as to whether they experienced side effects or whether only the investigator's observations were counted. If the subjects were questioned regarding side effects, no details are given as to the nature of the questions asked. Were the questions only designed to elicit dextroamphetamine-like side effects or were they also directed at uncovering meprobamate-type side effects? Obviously, it makes no sense to claim that the side effects of dextroamphetamine are reduced if the other component, meprobamate, is responsible for equally serious side effects of its own. Without details as to how adverse reaction data were elicited, it is impossible to determine if the investigators took such a possibility into account. Indeed, without any knowledge as to how data were observed and/or recorded, it is impossible to make any meaningful evaluation as to the realiability of the study's findings.

Even if it could be shown that the groups were comparable and that the data had been assembled and recorded in a proper manner, the results do not support Lederle's contention that the addition of meprobamate to the combination decreases the incidence or severity of side effects associated with the primary ingredient, dextroamphetamine sulfate. Thus, although the raw data showed that there were numerically slightly fewer side effects associated with patients on Bamadex Sequels (10) than there were with patients who used dextroamphetamine alone (13), Lederle's own statistical analysis demonstrated that this difference was not statistically significant since Lederle stated that the proportion of subjects reporting side effects was not significantly different for the three groups. In other words, there was no assurance that the observed difference was not due to chance. Lederle has failed to show that meprobamate significantly reduces the number of side effects attributable to dextroamphetamine and consequently has failed to demonstrate that meprobamate enhances the safety of the principal ingredient, dextroamphetamine, within the meaning of, and as required by, 21 CFR 3.86(a)(1), and as claimed in its labeling.

The study is incapable of scientifically demonstrating the anorectic effectiveness, or lack thereof, of Bamadex Sequels because, as shown above, the investigator failed to assure group comparability with respect to the use of concurrent medications (21 CFR 314.111(a)(5)(ii)(*a*)(*2*)(*iii*)).

The study also fails to explain the methods of observation and recording of weight loss data (21 CFR 314.111(a)(5)(ii) (*a*)(*3*)). Thus the author does not explain whether patients were always weighed at the same time of day, whether the menstrual cycles of female subjects was taken into account and, more importantly, whether any analysis was done to determine which patients, if any, followed their diets. These factors cannot be overlooked in a study designed to measure weight loss.

Using Lederle's criterion for satisfactory weight loss (5 or more pounds in both active drug phases), Lederle's statistical analysis showed that Bamadex Sequels patients did not lose significantly more weight than patients who took the placebo. Lederle also conducted a statistical analysis of the difference in mean weight losses. The difference between the Bamadex and placebo groups were statistically significant only at the end of 3 weeks; there was no statistically significant difference either for the second on-drug period (7 to 9 weeks) or overall (1 to 9 weeks). Thus, Lederle's own findings are inconclusive, and even if they weren't, they would be scientifically meaningless because of the defects pointed out.

2. Schein, M., "A Comparison of Bamadex Sequels, Dextroamphetamine and Placebo on Weight Loss and Number and Types of Side Effects in 90 Overweight Patients," unpublished study, 1971. To exclude climatic conditions as a factor, this investigator had all 90 patients begin the study during the same week. Otherwise, this study followed the same protocol as the just-reviewed Noble study. Accordingly, it too failed to assure comparability with respect to the use of other drugs (21 CFR 314.111(a)(5)(ii)(*a*)(*2*)(*iii*)). Thus, 13 of the 30 patients in the Bamadex group were receiving concomitant medication, while 6 in the amphetamine and 8 in the placebo groups were concurrently using other drugs. As in the

A request for a hearing may not rest upon mere allegations or denials, but must set forth specific facts showing that there is a genuine and substantial issue of fact that requires a hearing. If it conclusively appears from the face of the data, information, and factual analyses in the request for the hearing that there is no genuine and substantial issue of fact which precludes the withdrawal of approval of the application, or when a request for hearing is not made in the required format or with the required analyses, the Commissioner will enter summary judgment against the person(s) who requests the hearing, making findings and conclusions, denying a hearing.

All submissions pursuant to this notice of opportunity for hearing shall be filed in quintuplicate. Such submissions, except for data and information prohibited from public disclosure pursuant to 21 U.S.C. 331(j) or 18 U.S.C. 1905, may be seen in the office of the Hearing Clerk (address given below) during regular business hours, Monday through Friday.

Communications forwarded in response to this announcement should be identified with the reference number DESI 5378, directed to the attention of the appropriate office listed below, and addressed to the Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20852:

Supplements (identify with NDA number): Office of Scientific Evaluation (HFD–100), Bureau of Drugs.

Original abbreviated new drug applications (identify as such): Generic Drug Staff (HFD–107), Office of Scientific Evaluation, Bureau of Drugs.

Submissions pursuant to the notice of opportunity for hearing (identify with docket number): Hearing Clerk, Food and Drug Administration (HFC–20), Room 6–86, Parklawn Building.

Requests for the Academy's report: Drug Efficacy Information Activity (HFD–8), Bureau of Drugs.

All other communications regarding this announcement: Drug Efficacy Study Implementation Project Manager (HFD–101), Bureau of Drugs.

This notice is issued pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (secs. 502, 505, 52 Stat. 1050–53, as amended; 21 U.S.C. 352, 355) and under the authority delegated to the Director, Bureau of Drugs (21 CFR 2.121).

Dated: July 3, 1974.

J. RICHARD CROUT,
Director, Bureau of Drugs.

[FR Doc. 74–16522 Filed 7–18–74; 8:45 a.m.]

[From the Federal Register, vol. 40, No. 101, May 23, 1975, pp. 22570–75]

NOTICES

[DESI 5378; Docket No. FDC–D–582; NDA 12–570]

BAMADEX SEQUELS

DENIAL OF HEARING AND WITHDRAWAL OF APPROVAL OF NEW DRUG APPLICATION

The Commissioner of Food and Drugs denies hearing and withdraws approval of new drug application for Bamadex Sequels, effective June 2, 1975.

In a notice published in the FEDERAL REGISTER of August 8, 1970 (35 FR 12678), the Food and Drug Administration (FDA) announced its evaluation of 23 anorectic drugs, including Bamadex Sequels and Bamadex Tablets, NDAs 12–570 and 11–280, held by Lederle Laboratories, Division of American Cyanamid Co., Pearl River, NY 10965, hereafter Lederle.

The announcement stated that the FDA had considered the reports of the National Academy of Sciences-National Research Council (NAS/NRC), Drug Efficacy Study Group, together with other evidence and concluded that there was a lack of substantial evidence for several claims but that the listed drugs were regarded as possibly effective for their anorectic (appetite-suppressant) claims and for their prolonged, continuous or sustained release claims. Manufacturers were given 60 days to revise their labeling to delete those indications for which no substantial evidence of effectiveness had been found and 6 months to provide substantial evidence of effectiveness for the anorectic and sustained release claims. Finally, the notice advised that at the end of the 6-month period, the data

would be evaluated to determine whether or not the existence of substantial evidence of effectiveness had been demonstrated, and if it had not, procedures would be initiated to withdraw approval of the new drug applications pursuant to section 505(e) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355 (e)).

In the same issue of the FEDERAL REGISTER of August 8, 1970 (35 FR 12652), the Commissioner of Food and Drugs issued a Statement of Policy (21 CFR 310.504, formerly 21 CFR 130.46) regarding amphetamine containing drugs, including dextroamphetamine. The order stated that the NAS/NRC had found, inter alia, that this class of drugs had a generally short term (a few weeks) anorectic effect, that there was no evidence that they altered the natural history of obesity, and that they had a significant potential for abuse. The FDA concurred with the NAS/NRC report and, in addition, noted that production data indicated that amphetamines were manufactured and used in quantities greatly in excess of demonstrated medical needs. Accordingly, the order required that such drugs be relabeled to reflect the present state of knowledge concerning amphetamines, their potential for misuse and abuse, and their limited medical usefulness. The order was made specifically applicable to combination drugs which contained dextroamphetamine.

In response to the notice (DESI 5378) of August 8, 1970, Lederle submitted three clinical studies for Bamadex Sequels (Noble, Miller, and Schein) and three clinical studies for Bamadex Tablets (Trodella, Parsons, and Bowlan), together with a list of side effects and combined statistical analysis for all six studies and a combined statistical analysis for the three clinical studies of Bamadex Sequels.

Subsequently, the Commissioner issued a notice of opportunity for hearing, published in the Federal Register of February 12, 1973 (38 FR 4279), covering [redacted] anorectic combinations including Bamadex Tablets and Bamadex Sequels. The notice stated that the submitted data had been reviewed and found not to provide substantial evidence that the drugs were effective as fixed combinations for their claimed uses. Neither, the notice continued, did the submitted data support the contention that the combination products decrease the incidence or severity of side effects or lessen the abuse potential associated with the single anorectic ingredient. Accordingly, the Commissioner proposed to withdraw approval of the named new drug applications and invited holder(s) of new drug applications and other interested persons, including manufacturers and distributors of identical, related, or similar products, to submit on or before March 14, 1973, a written notice requesting an opportunity for hearing. Those requesting a hearing were instructed to state the reasons why approval of the new drug application should not be withdrawn and to provide a well-organized and full factual analysis of the clinical and other investigational data that they were prepared to prove in support of the requested hearing.

In the same issue of the Federal Register of February 12, 1973 (33 FR 4249), the Statement of Policy regarding amphetamines for human use (21 CFR 310.504, formerly 21 CFR 130.46) was revised to reflect that while sufficient data had been submitted (in response to the previous Statement of Policy) to generally support the anorectic efficacy of single entity amphetamine drugs, the degree of extra weight loss was small) a few tenths of a pound a week in many cases), variations were great, and the rate of weight loss decreased after the first weeks of therapy. Accordingly, the Commissioner concluded that single entity oral dosage forms of amphetamine or dextroamphetamine were effective in the management of exogenous obesity as a short term (a few weeks) adjunct in a regimen of weight reduction based on caloric restriction for patients in whom obesity is refractory to other measures. The notice advised that anorectic combinations containing sedatives or tranquilizers were regarded as new drugs requiring approved new drug applications and that the data in such applications must meet the requirements of 21 CFR 3.86, fixed combination prescription drugs for human use.

On March 9, 1973, Lederle requested a hearing for NDA 12-570 covering Bamadex Sequels. Lederle did not request a hearing for Bamadex Tablets, and the Commissioner withdrew the approval of the NDA for Bamadex Tablets (NDA 11-280), notice of which was published in the Federal Register of March 30, 1973 (38 FR 8290).

In its hearing request, Lederle contends that its submissions demonstrate (a) that, with respect to weight loss, Bamadex Sequels are significantly better than placebo and not significantly inferior to dextroamphetamine alone, and (b) that the meprobamate component significantly reduces the central nervous system

Noble study, there were patients receiving anti-inflammatory agents with analgesic properties, antihistamines with sedative properties, and major tranquilizers, any of which could interfere with central nervous system side effects. Similarly, patients in the Bamadex group also used thyroid and diuretic drugs which could also influence weight reduction.

This study also fails to explain the methods of observation and/or recording of results as required by 21 CFR 314.111(a)(5)(ii)(*a*)(*3*). No details are given as to whether subjects were questioned as to whether they experienced side effects or whether only the investigator's observations were counted. Thus, as before, there is no way to determine the accuracy or quality of the data relating to adverse reactions, and hence there is no way to scientifically assess the result. Although the investigator reported only one side effect for the Bamadex group, a check of the patient reports showed that an additional patient, No. 222, experienced depression and had to be switched to other medications. This indicates that the investigator had not accurately observed and/or recorded the results (21 CFR 314.111(a)(5)(ii)(*a*)(*3*)). There were 6 patients in the dextroamphetamine group who experienced side effects.

Even if these deficiencies are ignored, Lederle's own statistical analyst admits that there was no statistically significant difference found in the side effects reported for the three groups. This study, therefore, fails to provide evidence that meprobamate contributes to the claimed effects within the meaning of and as required by 21 CFR 3.86(a)(1).

With respect to the claimed anorectic effect, this study shares the identical defects as the just-reviewed Noble study, i.e., the author failed to assure group comparability with respect to the use of concomitant medication (21 CFR 314.111(a)(5)(ii)(*a*)(*2*)(*iii*)) and failed to explain the methods of observation and recording of results (21 CFR 314.111(a)(5)(ii)(*a*)(*3*)).

The investigator initially defined a "satisfactory" response as a loss of at least 9 pounds for the 9-week period. Under this definition, he found no statistically significant difference between the three groups, i.e., the placebo group did as well as the Bamadex group. Accordingly, a second, less stringent, standard was adopted which defined "satisfactory" response to be a loss of at least 6 pounds for the first and last 3-week periods. Using this criterion, the results of the Bamadex and dextroamphetamine groups were found to be satistically significant when compared to the placebo group, and the differences between the Bamadex and dextroamphetamine groups were not statistically significant. Lederle's statistical analysis of the mean weight losses claimed statistically significant differences for the Bamadex and dextroamphetamine groups over the placebo group for the end of both active treatment periods (1 to 3 and 7 to 9 weeks) and overall (weeks 1 to 9). However, since the study was not adequate and well-controlled, as discussed above, these reported results are not reliable or scientifically evaluable.

3. Miller, Jerome, "A Comparison of Bamadex Sequels, Dextroamphetamine, and Placebo on Weight Loss and Side Effects in 90 Patients", unpublished study, 1971. This study also followed the basic protocol used in the Noble and Schein studies with only one exception: To assure more reliable weight-loss data, followup weighings were done in circumstances similar to the original weighings with respect to time of day, scales, and clothing.

As with the previous studies, this study failed to assure group comparability with respect to the concurrent use of other drugs which could have interferred with the central nervous system side effects and the claimed anorectic effects (21 CFR 314.111(a)(5)(ii)(*a*)(*2*)(*iii*)). Although the author did explain that he conducted the weighings at the same time of day and under similar conditions with regard to scales and clothing, he failed to explain whether or not, and if so how, he took into account such variables as caloric intake and menstrual cycles (21 CFR 314.111(a)(5)(ii)(*a*)(*3*)).

For the third consecutive time, Lederle's statistical analysis showed that there was no statistically significant difference between the three groups with respect to the incidence of side effects. Therefore, this study, too, fails to provide evidence that meprobamate contributes to the claimed effects within the meaning of and as required by 21 CFR 3.86(a)(1).

With respect to anorectic effects, the investigator's own clinical evaluation showed that the number of Bamadex-treated patients with an overall satisfactory clinical (weight loss) response was strikingly similar to the number for the placebo group and smaller than the dextroamphetamine group (Bamadex Sequels, 12; dextroamphetamine, 20; placebo, 10). Since the placebo and Bamadex groups were nearly identical with respect to this variable, if anything, the

evidence suggests that Bamadex is no better than a placebo with respect to the claimed anorectic effect. While the statistical analysis of mean weight losses based on averaging total weight loss over all subjects shows that the difference between Bamadex and placebo was statistically significant, this result is at odds with the investigator's evaluation of the overall clinical response based on number of subjects who lost weight and, in any event, is rendered scientifically unreliable by the study's failure to meet the regulatory criteria for an adequate and well-controlled clinical investigation (21 CFR 314.111(a)(5)(ii)).

Lederle's own investigations and analyses of the Bamadex Sequels studies not only fail to substantiate its rationale for the combination, but affirmatively demonstrate that meprobamate does not reduce the incidence of side effects attributable to the principal ingredient, dextroamphetamine. Moreover, using the clinical response data, only one study (Schein) shows that the difference in anorectic effect between Bamadex and placebo was statistically significant, and in that case the investigator was forced to lower his initial criterion of "satisfactory" to find a statistically significant difference.

B. *Bamadex Tablets studies.*—Lederle also conducted three clinical studies with Bamadex Tablets (5 mg dextroamphetamine and 400 mg meprobamate). Since both Bamadex Tablets and Bamadex Sequels contain the same active ingredients and are recommended by their respective labels for the same indication, i.e., as a short term adjunct in the treatment of exogenous obesity, and since Lederle in its request for hearing dated March 9, 1973, relied upon a listing of side effects and a combined statistical analysis of data from the three Bamadex Sequels studies and three studies of Bamadex Tablets, the three Bamadex Tablets studies are relevant to Lederle's request for a hearing. With the exception of the dosage schedule (one tablet three times daily), these studies followed the protocol used in the Bamadex Sequels studies. The results are summarized as follows:

1. Parsons, W. B., "Comparative Efficacy of Bamadex Tablets (400 mg meprobamate and 5 mg dextroamphetamine), Bamadex Minus Meprobamate, and Placebo in the Control of Obesity and Measurement of Side Effects," unpublished study, 1971. This study is not adequate and well-controlled within the meaning of 21 CFR 314.111(a)(5)(ii) (*a*)(*2*)(*iii*) in that it failed to assure that the test and control groups were comparable with respect to the use of drugs other than the test drug. Seventeen of 28 patients in the Bamadex group, 18 of 27 patients in the dextroamphetamine group, and 15 of 29 patients in the placebo group were concurrently using drugs other than the test drug. Concurrent medication included diuretics and transquilizers which could affect the results of a study designed to measure the anorectic effect and the incidence of adverse reactions related to the central nervous system.

The investigators failed to explain the methods of observation and recording of results with respect to side effects (21 CFR 314.111(a)(5)(ii)(*a*)(*3*)). No details are given as to whether subjects were questioned, as to whether they experienced side effects, or whether only the investigators' observations were counted.

This study also fails to provide any statistical analysis of the anorectic data and thus does not comply with 21 CFR 314.111(a)(5)(ii)(*a*)(*5*).

Even if the defects above, which render the study not adequate and well-controlled within the meaning of 21 CFR 314.111(a)(5)(ii), are ignored, the results do not support Lederle's contention that the addition of meprobamate to the combination decreases the incidence or severity of side effects associated with the primary ingredient, dextroamphetamine sulfate.

The results of this study showed a markedly higher occurrence of side effects with Bamadex than with either dextroamphetamine alone or placebo. Of the patients who took Bamadex Tablets, 10 reported side effects while only one in the dextroamphetamine and 4 in the placebo group showed adverse reactions. Since the Bamadex Tablets contain more meprobamate and less dextroamphetamine than the Bamadex Sequels (300 mg meprobamate and 15 mg dextroamphetamine), these results directly contradict Lederle's rationale for the inclusion of meprobamate with dextroamphetamine. If, as the sponsor claims, meprobamate decreases the incidence of adverse effects associated with dextroamphetamine, this decrease should be more evident in the tablet formulation which utilizes a higher ration of meprobamate to dextroamphetamine. As shown above, however, this was not the case. Since there were 10 times as many side effects associated with the use of Bamadex, there is no support whatever for

the contention that meprobamate enhances the safety of the primary ingredient, dextroamphetamine (21 CFR 3.86(a)(1)).

2. Trodella, G. P., "Comparative Efficacy of Bamadex Tablets, Bamadex Minus Meprobamate, and Placebo in the Control of Obesity and Measurement of Side Effects," unpublished study, 1971. The results of this study with respect to side effects were very similar to those in the Parsons' study. The investigator reported three side effects in the Bamadex group, one in the dextroamphetamine group, and two in the placebo group. Since Lederle's own statistical analysis concluded that the differences in the incidence of side effects for the three groups were not statistically significant, the results of this study do not support Lederle's contention that meprobamate significantly decreases the adverse reactions associated with dextroamphetamine, as required by 21 CFR 3.86(a)(1).

This study shares the same defect as the Parsons' study previously described in that the investigator failed to explain the methods of observation and recording of results with respect to side effects, 21 CFR 314.111(a)(5)(ii)(*a*)(*3*). No details are given as to whether subjects were questioned as to whether they experienced side effects, or whether only the investigator's observations were counted.

With respect to weight loss (both overall clinical response and average weight loss), Lederle admitted that at the end of the second 21-day period, Bamadex was inferior (both overall clinically and in average weight loss) to the placebo, and at the end of the first 21-day period Bamadex was only equal to a placebo in average weight loss.

3. Bowlan, W. L., "Comparative Efficacy of Bamadex Tablets, Bamadex Minus Meprobamate and Placebo in the Control of Obesity and Measurement of Side Effects," unpublished study, 1971. In this study the incidence of side effects was low for all three groups (one on Bamadex, two on dextroamphetamine, and four on placebo). Statistical analysis failed to demonstrate any statistically significant differences between the active medication with respect to side effects. Consequently, this study fails to support Lederle's contention that meprobamate decreases the side effects associated with dextroamphetamine and therefore, fails to provide evidence that meprobamate enhances the safety of the principal active component of Bamadex as required by 21 CFR 3.86(a)(1).

Lederle did not attempt to perform any statistical analysis on the anorectic data (21 CFR 314.111(a)(5)(ii)(*a*)(*5*)).

No details are given as to whether the subjects were questioned as to whether they experienced side effects or whether only the investigator's observations were counted. Therefore, this study fails to explain the methods of observations and recording of result as is required by 21 CFR 314.111(a)(5)(ii)(*a*)(*3*).

The three tablet studies, whether taken individually or together, failed to show a significant decrease in side effects for Bamadex patients when compared to patients who used dextroamphetamine alone. In fact, the combined results for the tablet studies show more side effects for Bamadex patients (14) than for the dextroamphetamine patients (4).

C. *Combined statistical analyses.*—Lederle submitted a combined statistical analysis of the side effects and mean weight loss for the Bamadex, dextroamphetamine, and placebo groups in the six studies reviewed above and a combined statistical analysis of the three sequel studies alone. Since these analyses are dependent upon the data obtained from the individual studies, and since the individual studies have been shown to be not adequate, and well-controlled within the meaning of 21 CFR 314.111(a)(5)(ii), any analysis of such data can only yield results that have no scientific validity.

The tabulation for the sequel studies shows discrepancies between the number of side effects recorded by Lederle and the number disclosed by examination of the individual case reports. In the Schein study, Lederle noted only one side effect for the Bamadex group while the case reports reveal that patient No. 222 experienced depression. In the Miller study, Lederle noted only three side effects for the Bamadex group, whereas both Lederle's initial analysis and the case reports show four side effects. Any statistical analysis which is based upon inaccurate reporting of data cannot provide substantial evidence to support drug effectiveness (21 CFR 314.111(a)(5)(ii)(*a*)(*2*)(*iii*).

Lederle has failed to show that it was justified in pooling the results of the three sequel studies. Thus no details were provided as to whether or not the groups in each study were comparable with respect to concurrent drug use and whether each investigator observed and recorded his data in the same manner. The scanty information that was provided shows that theer were differences in

study methodology; thus, while Dr. Miller was careful to conduct followup weighings at the same time as the initial weighings, neither Dr. Schein nor Dr. Noble did so. Dr. Schein had all his subjects begin the study during the same week; it does not appear that either Dr. Noble or Dr. Miller followed this procedure. It is, therefore, not at all clear that the data from the three studies are sufficiently homogeneous to warrant pooling.

With respect to the combined statistical analysis for all studies, the discrepancies in the tablet studies are even more striking. In the Bowlan study, Lederle reported only one side effect for the Bamadex group whereas the case reports showed seven patients had side effects (No. 401—"nervous," No. 419—"no energy," No. 427—"dry mouth," No. 436—"irritable," No. 442—"increased voiding," No. 449—"emotionally upset," and No. 468—"constipated"). Similarly, while Lederle included only 21 patients in the dextroamphetamine group and 20 patients in each of the Bamadex and placebo groups, FDA's check of the case reports showed that the following patients returned for at least one visit after the initial interview and should have been included in the calculation; the Bamadex group, 30 patients; the dextroamphetamine group, 28 patients; and the placebo group, 28 patients. In studying side effects, it is essential to use all data available. To exclude patients who had only one followup and/or who were dropped from the study is to eliminate from consideration the very patients who may have discontinued because of side effects.

In the Trodella study, Lederle reported three, one and two side effects respectively for the Bamadex, dextroamphenamine and placebo groups while the report forms submitted by the investigator showed the Bamadex group had seven side effects (Nos. 508, 510, 522, and 539—"fatigue," No. 545—"irritable," No. 568—"rash and swelling," and No. 576—"marked increase in blood pressure and headaches"); the dextroamphetamine group, four (No. 507—"constipation," No. 521—"swelling of feet," No. 529—"falls asleep," No. 594—"trouble sleeping if took all three pills"; and the placebo, four (No. 525—"headaches," No. 533—"nauseated and upset," No. 540—"very tired," and No. 590—"sleepy").

Finally, in the Parsons study Lederle based its calculations on 26 patients in the Bamadex and dextroamphetamine gorups and 25 patients in the placebo group. A check of the patient report forms, however, shows that 27 patients should have been evaluated in the Bamadex group (only No. 610 failed to show up after initial visit), 28 in the dextroamphetamine group (all patients evaluated through at least first phase), and 28 in the placebo group (only No. 648 failed to show up after initial visit).

Using Lederle's interpretation in the patient report forms, the results for all six studies show that the identical number of side effects (28) occurred for both the Bamadex and dextroamphetamine groups. There is no basis for the contention that meprobamate significantly reduces the number of side effects associated with dextroamphetmine. In addition, Lederle's statistical analysis of the reduction in the total number of side effects of Bamadex when compared to the total number of side effects for dextroamphetamine only "approached significance."

These data provide no evidence that meprobamate contributes to the combination's claimed effect. Lederle has clearly failed to come forward with any evidence derived from adequate and well-controlled studies showing that meprobamate reduces the number of side effects attributable to dextroamphetamine within the meaning of, and as required by, 21 CFR 3.86(a)(1).

It is also important to note that with respect to the claimed anorectic effect, the primary indication for Bamadex, all individual studies failed to show that the differences between the Bamadex and placebo groups for the 9-week study were statistically significant. Similarly, two of the three tablet studies also failed to show that Bamadex was any better than a placebo.

Since, as shown above, the studies upon which both of the analyses are based are not adequate and well-controlled within the meaning of 21 CFR 314.111(a)(5)(ii), and since the analyses themselves incorrectly and inaccurately report results from the studies, any data from the combined statistical analyses would be scientifically meaningless.

IV. Summary

For the foregoing reasons, the medical evidence submitted by Lederle fails to meet either the statutory standard, section 505(d) of the act (21 U.S.C. 355(d)), for "adequate and well-controlled investigations" as set forth by 21 CFR 314.111(a)(5)(ii) or the requirements established in 21 CFR 3.86 for a fixed combination prescription drug for human use.

All three of the clinical studies submitted by Lederle in support of the effectiveness of the sequels shared the same basic defects: They each fail to assure that the test and control groups were comparable with respect to the concurrent use of other drugs, a requirement of 21 CFR 314.111(a)(5)(ii)(*a*)(*2*)(*iii*); and they each failed to explain the method of observation and recording of results (21 CFR 314.111(a)(5)(ii)(*a*)(*3*)). These defects conclusively render these submissions inadequate and not well-controlled on their face. As pointed out above, even when these critical defects are ignored, the results, as interpreted by Lederle, of each of the sequel studies taken separately failed to support the contention that meprobamate significantly reduces the incidence of side effects attributable to dextroamphetamine. The combined statistical analyses submitted by Lederle further support this conclusion since Lederle's analysts were unable to conclude that meprobamate reduced the number of side effects in a statistically significant manner (21 CFR 3.86(a)(1)).

None of Lederle's initial statistical analyses for the three sequel studies showed Bamadex to be a significantly better anorectic (overall clinical response) than placebo. Only in the Schein study, when a second analysis was performed and the standard for "satisfactory" clinical response was lowered, did the results show Bamadex Sequels to be significantly better than a placebo. However, these results are not scientifically evaluable since the Schein study is not adequate and well-controlled. Similarly, two of the tablet studies (Parsons and Trodella) also failed to show that Bamadex was significantly better than placebo as an anorectic. While the Bowland study suggests that Bamadex is a significantly better anorectic than placebo, Lederle did not submit any statistical analysis on the anorectic data.

Lederlie's statistical analyst, when confronted with the combined data for all three sequel studies concluded that "Bamadex Sequels may have slightly less efficacy in terms of weight loss than dextroamphetamine". Thus, the clinical studies suggest that meprobamate reduces the anorectic effect of dextroamphetamine.

Lederle failed to submit any evidence to support its claim under 21 CFR 3.86(a)(2) in its March 9, 1973 request for hearing that the addition of meprobamate enhances the safety of the principal active ingredient, dextroamphetamine, by lowering its abuse potential.

Finally, although Lederle's current labeling does not claim that Bamadex is safe and effective for the treatment of exogenous obesity with concomitant anxiety and tension, the argument is raised in Lederle's March 9, 1973 request for a hearing and, as stated above, the claim was made in Lederle's earlier Bamadex labeling. However, Lederle has not submitted any evidence to demonstrate the existence of a significant population which fits this description and which requires the dosage of both dextroamphetamine and meprobamate contained in Bamadex for a comparable period of time, as is required by 21 CFR 3.86. To show that such a patient population does exist, it would have been necessary for investigators trained in the use of evaluation of standardized psychological rating scales to have applied the scales to the patient population being studied. Neither investigators with the requisite qualifications nor the rating scales were present in any of these studies.

V. Legal arguments

In its March 9, 1973 request for a hearing, Lederle argues that the three sequels studies demonstrate a statistically significant anorectic superiority of Bamadex Sequels over the placebo and no significant difference from dextroamphetamine. Inasmuch as Bamadex Sequels contains dextroamphetamine, a recognized anorectic, it would not be at all surprising if the data did demonstrate significant superiority for this indication when compared to a placebo. As shown above, however, this is not the case.

Lederle's major argument is that the sequel studies, the list of side effects and the combined statistical analysis, demonstrate that a satistically significant reduction in the central nervous system side effects is achieved by meprobamate, i.e., that meprobamate enhances the safety of the principal active ingredient within the meaning of 21 CFR 3.86(a)(1). As shown above, this contention is not supported by Lederle's evidence. In the first place, none of the submitted studies are adequate and well-controlled clinical investigations within the meaning of section 505(d) of the act (21 U.S.C. 355(d)) and 21 CFR 314.111(a)(5)(ii). Next, even assuming, arguendo, that the studies were adequate and well-controlled, Lederle inaccurately recorded the data from its own patient report

forms so that the analysis is based on unreliable data. FDA's interpretation and statistical analysis of the patient report forms shows there was no statistically significant reduction in side effects with Bamadex. It should be emphasized, however, that FDA does not rely on its analysis for its action but rather on the failure of Lederle's data to meet the statutory and regulatory criteria for adequate and well-controlled studies (section 505(d) of the act (21 U.S.C. 355(d)) and (21 CFR 314.111(a)(5)(ii))).

Finally, even if all these discrepancies are ignored, Lederle's statistical analysis based on Lederle's interpretation of the patient report forms fails, with equal conclusiveness, to demonstrate any significant reduction in side effects for Bamadex. This judgment holds true whether the three sequel studies are judged individually or collectively, whether the three tablet studies are judged individually or collectively, and whether all six studies are combined. It is obvious that the unanalyzed list of side effects, by itself, is of no evidentiary value. Since this data is incorporated into Lederle's combined statistical analysis, its significance stands or falls with the evaluation of that report.

With respect to the interpretation of the patient report forms, Lederle contends that FDA incorrectly characterized the incidence of side effects. This is simply not the case. Lederle's carelessness in tabulating its own data is clearly evidenced by two instances: (1) Lederle's table, which summarizes the combined number of side effects (and upon which Lederle bases its overall statistical analysis), does not even square with its own earlier reported findings for each individual study; Lederle lists three side effects in its summary table for the Bamadex group in the Miller study, and Dr. Miller's summary lists four side effects; and (2) in the Parson tablet study, no side effect was recorded by Lederle for patient No. 632 despite the investigator's comment, "Didn't find medication very helpful. Too much of a tranquilizer—a hindrance in his work. Didn't alter appetite. Also seemed to cause impotence (no previous trouble)."

There were many similar instances throughout the studies where the investigator's comment regarding adverse reactions went unnoticed by Lederle. The issue of correctness of interpretation of patient report forms need never be reached since Lederle's own analysis fails to demonstrate any statistically significant reduction of side effects for Bamadex compared to dextroamphetamine.

Lederle also contends that since meprobamate has been found effective for the relief of anxiety and tension and in the treatment of diseases in which anxiety and tension are manifest, and since dextroamphetamine has been found effective in the management of weight reduction, that Bamadex Sequels, which contains both of these ingredients, must be recognized as effective for its claimed effect: the management of obesity with minimal overstimulation of the central nervous system.

This reasoning is fallacious because (1) that meprobamate is effective for anxiety and tension or in the treatment of diseases accompanied by anxiety and tension is irrelevant to the issue of its effectiveness, or lack thereof, for its claimed effect in Bamadex since there is no proof that central nervous system side effects are related to the conditions of anxiety and tension; and (2) Lederle's argument is, as a matter of law, insufficient since although each of the components of a drug may be safe and effective, it does not necessarily follow that a combination of the same ingredients will be effective. (See 21 CFR 310.3(h); *United States* v. *An article of drug* * * * *Ferestrol*, 294 F. Supp. 1307 (N.D. Ga., 1968), aff'd 415 F. 2d 390 (C.A. 5, 1969); *United States* v. *41 Cases* * * *, 420 F. 2d 1126 (C.A. 5, 1970); *United States* v. * * * *Nerac Alcohol Acne Gel*, CCH F.D. Cosm. L. Rep. ¶40,836 (N.D. Ill., 1971); *United States* v. *An article of drug* * * * *Patrol C. Medicated*, 362 F. Supp. 424 (S.D. Cal., 1973); *United States* v. *An article of drug* * * * *"Mykocert"*, 345 F. Supp. 571 (N.D. Ill., 1972); *United States* v. * * * *"Asper Sleep"*, CCH F.D. Cosm. L. Rep. ¶40,832 (N.D. Ill., 1971). The reasoning behind these cases is particularly cogent where, as here, one of the ingredients, meprobamate, is recommended by the labeling for the combination for a use different from that for which it has been found effective. In such a case, there can be no basis for a claim that the effectiveness of meprobamate is established for its role in the combination. Thus, the clinical evidence must be the determinant of whether meprobamate contributes to the effect of Bamadex or makes the principal ingredient safer. However, as shown above, the clinical evidence submitted by Lederle not only fails to demonstrate that meprobamate makes a contribution to the claimed effect, but suggests that it reduces the effectiveness of the principal ingredient, dextroamphetamine.

Lederle next argues that Bamadex Sequels must be found safe because the product was approved on the basis of safety in 1960, and there has been no clini-

cal experience to the contrary since that time. This argument is irrelevant in the absence of evidence showing that the drug is effective as a fixed combination. As has been shown, Lederle has totally failed to provide such evidence. No drug can be considered safe if it is not effective. Moreover, it is now clear that the marketing history of a product, standing alone, cannot meet the standards of substantial evidence. *Upjohn* v. *Finch*, 422 F. 2d 944, 954 (C.A. 6, 1970).

Lederle's last argument is that by combining meprobamate, a Schedule IV controlled substance (under the Drug Abuse Prevention and Control Act, 21 U.S.C. 801 et seq.), with dextroamphetamine, a Schedule II controlled substance under the same act, the abuse potential of the latter drug is reduced, and therefore, the safety of the principal ingredient is enhanced within the meaning of 21 CFR 3.86(a)(2). It is significant to note that the Attorney General placed Bamadex drug products under Schedule II, the same as for dextroamphetamine, rather than in the less restrictive Schedule IV in which meprobamate is placed. A claim of decreased abuse potential, like other claims, must be supported by evidence, not speculation. No such evidence is offered by Lederle. Lederle does not support its contention that the abuse potential of a drug is lowered by combining it with another drug with an intrinsic abuse potential of its own.

VI. Findings

On the basis of the foregoing review of Lederle's evidence and legal arguments, the Commissioner finds that: (1) There is a lack of substantial evidence that this drug has the effects it is represented to have under the conditions of use recommended, suggested, or prescribed in its labeling and (2) new evidence of clinical experience, not contained in the application and not available to the Commissioner until after the application was approved, evaluated together with the evidence available to the Commissioner when the application was approved, shows that Bamadex Sequels have not been shown to be safe for use under the conditions of use upon the basis of which the application was approved. The evidence fails to show either that each component of the combination contributes to the total effects claimed or that meprobamate enhances the safety or minimizes the abuse potential of the principal active ingredient, dextroamphetamine. Therefore, Bamadex fails to meet the requirements of 21 CFR 3.86. Furthermore, Lederle has not submitted any evidence to show that there exists a significant patient population requiring the concurrent therapy for exogenous obesity together with anxiety and tension or that Bamadex is effective for that indication as required by 21 CFR 3.86.

Lederle has failed to offer a substantial legal argument or to set forth facts showing there is a genuine and substantial issue of fact requiring a hearing.

Therefore, pursuant to provisions of the Federal Food, Drug and Cosmetic Act (sec. 505(e), 52 Stat. 1052, as amended (21 U.S.C. 355(e))) and under authority delegated to the Commissioner (21 CFR 2.120), the request for a hearing is denied, and the approval of the new drug application (NDA 12-570) for Bamadex Sequels, including all amendments and supplements thereto, is withdrawn, effective June 2, 1975.

Dated: May 15, 1975.

A. M. Schmidt,
Commissioner of Food and Drugs.

[FR Doc. 75-13548 Filed 5-22-75; 8:45 am]

Memorandum

February 20, 1973.

To: Deputy Director, Division of Neuropharmacological Drug Products.
From: Acting Director, Office of Scientific Evaluation.
(Through: Director, Division of Neuropharmacological Drug Products.)
Subject: Sustained Release Formulations of Anorectic Drugs—Action Memorandum.

ISSUE

Decisions are required on claims for sustained-release formulations of anorectic drugs for *Federal Register* follow-up publications. These decisions will also be applicable to amphetamine products being handled on a case-by-case basis.

FACTS

The decision memo on amphetamines and other anorectics initialed by the Commissioner took a stand to the efficacy of the various drugs marketed or proposed for marketing as anorectics. It did not go into most special claims for specific drug products, e.g., claims for individual formulations. A group of special claims requiring further decision is that of the "sustained-action" formulations.

A number of anorectic drugs are in formulations associated with claims for sustained action or something similar. Examples are:

(1) Diethylpropion in "Dospans" or "Ten-Tabs", the former being a hydrophilic matrix, carboxypolymethylene;

(2) Phentermine or amphetamine (Ionamin or Biphetamine, respectively) as a resin complex;

(3) Amphetamine or dextroamphetamine as a "Spansule";

(4) Phenmetrazine as an "Enduret", containing aluminum tristerarate and silica gel to slow dissolution; and

(5) Methamphetamine as a "Gradumet", an insoluable plastic matrix from which the drug is leached.

A brief survey of NDA's for these products yields the attached blood level curves. (Attachments—Tab A, Dexedrine;—Tab B, Tenuate). It appears that, with the possible exception of phenmetrazine the "sustained-action" formulation does not produce blood levels which differ substantially from those produced by the same dose of drug in a non-"sustained-action" formulation. Other differences exist for phenmetrazine, so that in each case examined, any practical difference or special therapeutic benefit of the "sustained-action" formulation appears unlikely, and is not supported by these studies.

Efficacy trials have by and large been done with the "sustained-action" formulations, with a demonstrated drug-placebo difference, so that general efficacy is not a question. Therapeutic (as opposed to blood-level) comparisons of the special formulations with conventional tablets or capsules have not been done; the slowness of weight loss, i.e., days to weeks, and the large inter-subject variations makes it appear impractical to do such trials. (Short-term trials of food consumption by mealtimes might be practical, however.) The SKF studies suggest less jitteriness with the "Spansule" which would be consistent with the lower, slower peak.

Administrative deadlines for decisions of two sorts exists. First, a number of New Drug Applications include claims for "sustained action" for single-entity drugs, and our conclusions on these claims should be communicated to the sponsors; our reservations may be indicated in a general way for now, and a final conclusion left until later. Second, follow-up DESI notices are due on Tenuate Dospen, Diphetamine, Ionamin, Desoxyn, and some less known amphetamines. These Notices should include our definitive conclusions.

DISCUSSION

It appears that claims for "sustained action" for current formulations of anorectics are not justified. On this basis we have incorporated the following form paragraph in letters to sponsors of NDA's.

We have serious reservations as to any labeling claims for sustained action. We request that you either delete such claims or state in more precise language any possible therapeutic difference of the sustained release formulations from an equal dose of tablets.

We hope you concur with this; if you have reservations, the language of the paragraph will permit future revision of our stand.

Assuming that "sustained-action" claims are considered inadequately supported, further questions arise, for example, what future studies and results might the firms attempt to achieve. Two pressing and visible decisions are required now however.

The first involves publishing follow-up notices for sustained-action anorectics, for which "possibly effective" notices were published over two years ago. We believe we can go ahead on these: they would require deletion of claims for sustained action, so placing the burden on the firms to support any special claim other than general efficacy.

The second involves formulation brand names. The proprietary names, "Dospan" and "Euduret" imply prolonged action, and we suggest these names be deleted or replaced by a neutral name such as "matrix formulations" or

"delayed-onset formulations". Alternatively, the name might be allowed to remain with a qualifying statement in the insert that the formulation has not been shown to produce results superior to the same dose in conventional formulations.

The question of dosage recommendations may arise. We see no objection to giving dosage regimens for each formulation—a t.i.d. regimen and a q.d. regimen, e.g., 25 mg t.i.d. standard formulation or 75 mg. q.d., matrix formulation, in the DOSAGE AND ADMINISTRATION section of the inserts.

Other issues might be raised, but these seem the main ones. Decision options are listed below. We've discussed the name question with Mary McEniry and Ted Byers, who favor deleting the names. They recalled no precedents.

RECOMMENDATION

That option 1 of each Decision group below be approved.

BARRETT SCOVILLE, M.D.

DECISIONS

A. With respect to data on "sustained-action" of anorectics:

(1) Consider the data do not support such claims, e.g., publish follow-up DESI Notices.

Approved_____ Not Approved_____.

(2) Defer decision to establishment of Committee criteria:

Approved_____ Not Approved_____.

B. With respect to drug names:

(1) Delete names which may imply special formulation claims: e.g., "Enduret", "Gradumet", "Dospan", Stedy-Tab", "Spansule" (this also would include disclaimers in insert).

Approved_____ Not Approved_____.

(2) Leave names, but label with a disclaimer.

Approved_____ Not Approved_____.

DEPARTMENT OF JUSTICE, DRUG ENFORCEMENT AGENCY

UNITED STATES GOVERNMENT

Memorandum

TO : Mr. Robert J. Rosthal
Acting Chief Counsel

FROM : Kenneth A. Durrin, Chief
Compliance Investigations Division

SUBJECT: Denial of Re-registration R. u. Strassenburgh, Lancaster, New York

Intelligence information obtained from Regions 1, 5, 6 and 11 show Bifetamina (an Amphetamine product produced by Laboratorios Strassenburgh de Mexico S.A. de C.V., Durico 21 D.F., Mexico) is readily available at drug stores throughout New Mexico, Texas, Oklahoma, Louisiana, Alabama, Tennessee, Georgia, Kentucky, Florida, and Colorado. The terms "Black Beauties," "Black Mollies," "Black Widows," and "Los Coast Two Avenues" are common among truck drivers referring to Bifetaminas throughout these states.

An intelligence survey conducted by DEA (News Since April 1, 1971, DNDD has made purchases and seizures of Bifetamina totaling over 172,000 d.u. These purchases and seizures have been made from thirteen separate cases. A summary of the cases is attached. The Louisville, Kentucky District Office of Region 6 has submitted a secondary system consisting of the illicit distribution of Bifetamina. This secondary system documents an illicit distribution of 240,000 d.u. monthly. Region 6 has proposed a secondary system concerning the illicit distribution of Bifetamina. This proposed secondary system documents a weekly diversion of 40,000 d.u.

In the above mentioned cases the sources of these Bifetamina capsules has been determined to be pharmacies across the U.S.-Mexico border. There appears to be little or no restriction of Bifetamina in Mexico. The capsules are entering the United States through El Paso, Del Rio, Eagle Pass, Laredo, McAllen and Brownsville, Texas.

The Bifetamina purchased and seized to date have for the most part been in original forty capsule bottles with the label showing production in Mexico City.

At the request of ENFA the BNDD Laboratory Division queried various State Forensic Laboratories. The results of that query are attached.

Information obtained from Strasenburgh, Rochester, New York, shows 900 kilograms of Amphetamine resin complex have been exported from the plant at Rochester, New York, to the plant in Mexico City since March 1970. This amount of resin is enough to produce 45,000,000 d.u. of Dietamine. Strasenburgh is only one of a number of firms in Mexico which is producing Amphetamine products. The amount of Amphetamine resin being shipped to Mexico City coupled with the extent of diversion of products being produced by the firm in Mexico City exposes a situation of obvious over production. This over production and subsequent diversion is creating a situation which is detrimental to the health and safety of the public.

Action should therefore be taken to deny renewal of export registration to R.J. Strasenburgh, Rochester, New York. As the renewal date for this firm is February 1972 action to deny renewal should be taken before that date.

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James B. Feelner

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TO ALL DOMESTIC REGIONAL DIRECTORS

FROM: JOHN R. ENRIGHT, CHIEF OF OPERATIONS

SUBJ: SUMMARY OF DANGEROUS DRUG TRAFFIC FROM MEXICO INTO THE UNITED STATES

THE OCCURRENCE OF AMPHETAMINES APPEARING IN THE DOMESTIC ILLICIT TRAFFIC, WHICH APPARENTLY ORIGINATED IN MEXICO HAS BEEN OCCURRING AT A CONSTANT LEVEL OVER A LONG PERIOD. IT IS REASONABLE TO ASSUME THAT THE DIVERSION AND SMUGGLING OF AMPHETAMINES FROM MEXICO WILL INCREASE DUE TO THE MOVING OF AMPHETAMINES TO SCHEDULE II. THIS CHANGE OF SCHEDULE WITH THE CORRESPONDING RESTRICTIONS ON DOMESTIC AVAILABILITY, AND THE DEMAND FOR AMPHETAMINES IN THE ILLICIT TRAFFIC WILL BE REFLECTED IN THE INCREASED ACTIVITY IN THE AMPHETAMINE DIVERSION AND SMUGGLING FROM MEXICO.

INFORMATION GATHERED TO DATE SHOWS THIS PROBLEM EMANATING FROM THREE SOURCES WHICH, THOUGH INDEPENDENT, COMPLIMENT EACH OTHER IN CREATING THE ABUSE SITUATION. BRIEFLY THESE SOURCES ARE:

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1) LABORATORIES STRASENBURGH DE MEXICO S. A. MEXICO DF MEXICO - INTELLIGENCE INFORMATION OBTAINED FROM REGIONS 5, 6, 8, 11 AND 12 SHOW BIPHETAMINA 20 (AN AMPHETAMINE PRODUCT PRODUCED BY LABORATORIES STRASENBURGH DE MEXICO FOR DISTRIBUTION IN MEXICO) IS READILY AVAILABLE AT TRUCK STOPS THROUGHOUT NEW MEXICO, TEXAS, OKLAHOMA, LOUISIANA, ALABAMA, TENNESSEE, GEORGIA, KENTUCKY, FLORIDA AND COLORADO. A PRELIMINARY INTELLIGENCE SURVEY CONDUCTED BY ENFA SHOWS THAT BETWEEN APRIL 1 - SEPTEMBER 30, 1971, ENDD HAS MADE PURCHASES AND SEIZURES OF BIPHETAMINA 20 TOTALLING OVER 177,000 DOSAGE UNITS. THESE PURCHASES AND SEIZURES HAVE BEEN MADE IN 13 SEPARATE CASES. REGION 6 HAS SUBMITTED A SECONDARY SYSTEM CONSISTING OF THE ILLICIT DISTRIBUTION OF BIPHETAMINA. THIS SECONDARY SYSTEM DOCUMENTS AN ILLICIT DISTRIBUTION OF 240,000 DOSAGE UNITS MONTHLY. ANOTHER PROPOSED SECONDARY SYSTEM SUBMITTED BY REGION 5 DOCUMENTS A MONTHLY DIVERSION OF 160,000 DOSAGE UNITS OF BIPHETAMINA. THESE TWO PROPOSED SYSTEMS, HOWEVER, REPRESENT ONLY A SMALL PORTION OF THE

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OVERALL AVAILABILITY OF THIS PRODUCT IN THE ILLICIT TRAFFIC. INFORMATION OBTAINED FROM U. S. CUSTOMS MEXICAN BORDER STATIONS INDICATES AN ADDITIONAL 157,000 BIPHETAMINA CAPSULES WERE SEIZED FROM APRIL 1, 1971 - SEPTEMBER 30, 1971. THE TOTAL PURCHASES AND SEIZURES FOR THE SIX MONTH PERIOD IS APPROXIMATELY 334,000 WITH AN ADDITIONAL 400,000 DOSAGE UNITS BEING DIVERTED PER MONTH.

IN MOST OF THE ABOVE MENTIONED CASES THE SOURCE OF THESE BIPHETAMINA CAPSULES HAS BEEN DETERMINED TO BE PHARMACIES ACROSS THE UNITED STATES - MEXICAN BORDER. THE CAPSULES ARE ENTERING THE UNITED STATES THROUGH EL PASO, DEL RIO, EAGLE PASS, BROWNSVILLE, MCALLEN AND LAREDO, TEXAS AND DOUGLAS, ARIZONA. THE BIPHETAMINA PURCHASED AND SEIZED TO DATE HAVE FOR THE MOST PART BEEN IN ORIGINAL FORTY-CAPSULE BOTTLES WITH THE LABEL SHOWING PRODUCTION IN MEXICO CITY. THE BULK RAW MATERIAL (d AND dl AMPHETAMINE RESIN COMPLEX) FOR BIPHETAMINA IS MANUFACTURED BY STRASENBURGH-ROCHESTER, N. Y. FOR PROCESSING INTO THE FINISHED CAPSULE FORM

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AT STRASENBURGH-MEXICO. INFORMATION OBTAINED FROM STRASENBURGH-ROCHESTER, N. Y. SHOWS 900 KILOGRAMS OF THE RESIN COMPLEX HAVE BEEN EXPORTED TO STRASENBURGH-MEXICO FROM THE ROCHESTER PLANT SINCE MARCH 1970. THIS AMOUNT OF RESIN IS ENOUGH TO PRODUCE 45,000,000 DOSAGE UNITS OF BIPHETAMINA. STRASENBURGH IS ONLY ONE OF A NUMBER OF FIRMS IN MEXICO WHICH ARE PRODUCING AMPHETAMINE PRODUCTS. THE POPULATION OF MEXICO IS 35 MILLION.

RECENT INTELLIGENCE INDICATES THAT BIPHETAMINA IS AVAILABLE IN ALMOST UNLIMITED QUANTITIES IN REGION 11 BORDER AREAS. A CURSORY INTELLIGENCE PROBE BY REGION 11 INDICATES THAT THERE ARE 200,000 BIPHETAMINA READY FOR IMMEDIATE DELIVERY IN THE EL PASO AREA. AT THE PRESENT TIME APPROXIMATELY 1,000,000 DOSAGE UNITS PER MONTH ARE MOVING THROUGH REGION 11.

INTELLIGENCE FROM AN INDEPENDENT SOURCE IN GEORGIA INDICATES THAT BIPHETAMINA IS AVAILABLE IN 10,000 DOSAGE UNIT QUANTITIES FROM NUMEROUS TRUCK STOPS.

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	PRECEDENCE	SECURITY CLASSIFICATION
,NDD/ENFA	ACTION: P INFO:	UUUU SEND UNDER SECURE CIRCUIT
, CLASSIFICATION	DATE PREPARED 10-8-71	TYPE OF MESSAGE
FOR INFORMATION CALL	PHONE NUMBER 4217	☐ SINGLE ☐ BOOK ☒ MULTIPLE-ADDRESS

THIS SPACE FOR USE OF COMMUNICATION UNIT

MESSAGE TO BE TRANSMITTED (Use double spacing and all capital letters)

TO:

2) SMITH, KLINE AND FRENCH S. A. MEXICO, DF MEXICO - REGION 11 REPORTS LARGE QUANTITIES OF DEXEDRINA AND BENZEDRINA PRODUCED BY THIS FIRM TO BE READILY AVAILABLE IN THE ILLICIT TRAFFIC IN THAT REGION. REGION 8 ALSO REPORTS AN AVAILABILITY OF THESE PRODUCTS.

3) "MINI-AMPHETAMINES" - TO DATE OVER FIVE MILLION "MINI-AMPHETAMINE" TABLETS HAVE BEEN PURCHASED OR SEIZED BY AUTHORITIES IN REGIONS 3, 5, 7, 8, 10, 11, 12, 13 AND 14. BNDD BALLISTICS REPORTS CONFIRM THESE "MINI-AMPHETAMINES TO BE COMING FROM TWO COMMON TABLETING MACHINES. THE LOCATION OF THE SOURCE OF THESE "MINI-AMPHETAMINES" HAS NOT YET BEEN DETERMINED. INFORMATION RECEIVED, HOWEVER, LEADS TO THE CONCLUSION THAT THESE TABLETS ARE COMING FROM A SOURCE IN BAJA, CALIFORNIA.

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STANDARD FORM 14
REVISED AUGUST 1967
GSA FPMR (41 CFR) 101-35.306

GRAPHIC MESSAGE

OF AGENCY	PRECEDENCE	SECURITY CLASSIFICATION
DOJ/BNDD/ENFA	ACTION: P INFO:	UUUU SEND UNDER SECURE CIRCUIT
ACCOUNTING CLASSIFICATION	DATE PREPARED: 10-8-71	TYPE OF MESSAGE: ☐ SINGLE ☐ BOOK ☒ MULTIPLE-ADDRESS
FOR INFORMATION CALL		
NAME	PHONE NUMBER: 4217	

THIS SPACE FOR USE OF COMMUNICATION UNIT

MESSAGE TO BE TRANSMITTED (Use double spacing and all capital letters)

TO:
THIS TWX IS BEING FURNISHED FOR INFORMATION TO ALL REGIONS AND AS A FOLLOW-UP TO MY TWX TO REPRESENTATIVES OF REGION 5, 6, 8, 11, 12 & 14 NOTIFYING THEM OF THEIR DIRECT INVOLVEMENT IN THE PLANNING AND IMPLEMENTATION OF AN AMPHETAMINE TASK FORCE.

THIS TASK FORCE WILL SERVE THE DUAL PURPOSE OF DEVELOPING ADDITIONAL INTELLIGENCE INFORMATION WITH PRIMARY EMPHASIS ON THE BIPHETAMINA SITUATION AND ALSO IDENTIFYING AND IMMOBILIZING MAJOR BIPHETAMINA DISTRIBUTORS IN THE UNITED STATES. THE TASK FORCE SHOULD REMAIN IN OPERATION UNTIL APPROXIMATELY JANUARY 15, 1972.

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STANDARD FORM 14
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GSA FPMR (41 CFR) 101-35.306

John R. Enright
Chief of Operations

OCT 8 1971

Kenneth A. Durrin, Chief
Compliance Investigations Division

Summary of Dangerous Drug Traffic from Mexico into the United States

The occurrence of amphetamines appearing in the domestic illicit traffic, which apparently originated in Mexico has been occurring at a constant level over a long period. It is reasonable to assume that the diversion and smuggling of amphetamines from Mexico will increase due to the moving of amphetamines to Schedule II. This change of schedule with the corresponding restrictions on domestic availability, and the demand for amphetamines in the illicit traffic will be reflected in the increased activity in the amphetamine diversion and smuggling from Mexico.

Information gathered to date shows this problem emanating from three sources which, though independent, compliment each other in creating the abuse situation. Briefly these sources are:

1) Laboratories Strasenburgh de Mexico S. A. Mexico DF Mexico - Intelligence information obtained from Regions 5, 6, 8, 11 and 12 show Biphetamina 20 (an amphetamine product produced by Laboratories Strasenburgh de Mexico for distribution in Mexico) is readily available at truck stops throughout New Mexico, Texas, Oklahoma, Louisiana, Alabama, Tennessee, Georgia, Kentucky, Florida and Colorado. A preliminary intelligence survey conducted by ENFA shows that between April 1 - September 30, 1971, ENFA has made purchases and seizures of Biphetamina 20 totalling over 177,000 dosage units. These purchases and seizures have been made in 13 separate cases. Region 6 has submitted a secondary system consisting of the illicit distribution of Biphetamina. This secondary system documents an illicit distribution of 240,000 dosage units monthly. Another proposed secondary system submitted by Region 5 documents a monthly diversion of 100,000 dosage units of Biphetamina. These two proposed systems, however, represent only a small portion of the overall availability of this product in the illicit traffic. Information obtained from U. S. Customs Mexican Border Stations indicates an additional 157,000 Biphetamina capsules were seized from April 1, 1971 - September 30, 1971. The

total purchases and seizures for the six month period is approximately 334,000 with an additional 400,000 dosage units being diverted per month.

In most of the above mentioned cases the source of these Biphetamina capsules has been determined to be pharmacies across the United States - Mexican border. The capsules are entering the United States through El Paso, Del Rio, Eagle Pass, Brownsville, McAllen and Laredo, Texas and Douglas, Arizona. The Biphetamina purchased and seized to date have for the most part been in original forty-capsule bottles with the label showing production in Mexico City.

The bulk raw material (d and dl amphetamine resin complex) for Biphetamina is manufactured by Strasenburgh-Rochester, N. Y. for processing into the finished capsule form at Strasenburgh-Mexico. Information obtained from Strasenburgh-Rochester, N. Y. shows 900 kilograms of the resin complex have been exported to Strasenburgh-Mexico from the Rochester Plant since March 1970. This amount of resin is enough to produce 45,000,000 dosage units of Biphetamina. Strasenburgh is only one of a number of firms in Mexico which are producing amphetamine products. The population of Mexico is 35 million.

Recent intelligence indicates that Biphetamina is available in almost unlimited quantities in Region 11 border areas. A cursory intelligence probe by Region 11 indicates that there are 200,000 Biphetamina ready for immediate delivery in the El Paso area. At the present time approximately 1,000,000 dosage units per month are moving through Region 11.

Intelligence from an independent source in Georgia indicates that Biphetamina is available in 10,000 dosage unit quantities from numerous truck stops.

2) Smith, Kline, and French S. A. Mexico, DF Mexico - Region 11 reports large quantities of Dexedrina and Benzedrina produced by this firm to be readily available in the illicit traffic in that region. Region 8 also reports an availability of these products.

3) "Mini-amphetamines" - To date over five million 'mini-amphetamine' tablets have been purchased or seized by authorities in Regions 3, 5, 7, 8, 10, 11, 12, 13 and 14. ENDD Ballistics reports confirm these 'mini-amphetamines' to be coming from two common tableting machines. The location of the source of these 'mini-amphetamines' has not yet been determined. Information received, however, leads to the conclusion that these tablets are coming from a source in Baja, California.

Limited Official Use

It is recommended that the ARC's and/or deputies of the concerned regions be brought into headquarters and a meeting held to determine the need for additional manpower and funds to assist their operations in alleviating the problem. It is recommended that they be in Headquarters on October 19 and 20. After the meeting and a determination of required manpower and availability of funds, it is recommended that a Task Force be in the field in operation no later than November 1, 1971.

This task force will serve the dual purpose of developing additional intelligence information with primary emphasis on the Methamphetamine situation and also investigating and neutralizing major Diphetamine distributors in the United States. The task force should remain in operation until approximately January 15, 1972 at which time any cases initiated would be concluded. These cases, combined with the intelligence gathered, will be utilized as the basis for issuing a Show Cause Order to Strasenburgh Laboratories-Rochester, N. Y. denying their re-registration as 'an exporter'. The Show Cause Order must be issued prior to February 1972.

Intelligence information obtained concerning the 'mini-Benzie' and LSD situations will be utilized for future programs designed to eliminate these major situations.

ENFA Chron.
ENFA Subj.
ENFA/JMV/ml/4217/10-7-71

SENSITIVE-IN CONFIDENCE

NOV 2 2 1971

Honorable John N. Mitchell
Attorney General

John E. Ingersoll, Director
Bureau of Narcotics and Dangerous Drugs

Operation Blackjack

In anticipation that the imposition of Schedule II controls on amphetamine might generate increased smuggling activity we initiated a preliminary intelligence survey in August 1971 to determine the sources and extent of amphetamine smuggling and traffic from Mexico into the United States.

This survey disclosed patterns of diversion from the Republic of Mexico into the United States emanating from three principal sources. Two of these sources are legitimate firms in Mexico City; Laboratorios Strasenburgh de Mexico S.A. Mexico, DF Mexico and Smith, Kline and French S.A. Mexico, DF Mexico. The third source is believed to be a clandestine manufacturing operation located in the area of Baja, California, Republic of Mexico.

An overall plan was developed to immobilize these sources and R. J. Strasenburgh was selected for the first phase of this plan. Strasenburg was selected for the following reasons: 1) this is a domestic firm with direct control over their subsidiary in Mexico, 2) the firm is registered with BNDD to export controlled substances and does export to their Mexican plant the amphetamine powder used to produce their amphetamine product, Bifetamina, which has been appearing in significant quantities in the domestic illicit traffic, and 3) their product, Bifetamina, is the drug of choice among a substantial number of abusers in the southeastern and southwestern sections of the United States.

During November 1971 a Mobile Task Force was formed to operate in the Dallas, Denver, New Orleans, Miami and Detroit Regions to develop further intelligence on the

SENSITIVE-IN CONFIDENCE

patterns of smuggling and traffic involving Bifetamina. The Task Force is also operating in conjunction with the responsible Regions to develop cases against persons involved in this traffic. The resultant cases and intelligence will be used in support of an action to deny the re-registration of R. J. Strasenburg as an exporter of controlled substances. The target date for completion of this Task Force project is January 15, 1972, at which time an Order to Show Cause will be issued. The firm's present registration expires on February 29, 1972.

Investigation to date has documented approximately five hundred thousand dosage units of Strasenburg's Mexican encapsulated Bifetamina in the domestic illicit traffic. Upon completion of the domestic investigation, our Mexico City Office has been instructed to work closely with the Government of Mexico in taking action against the points of diversion in Mexico, principally drug stores along the border who are illegally selling in wholesale quantity.

Mr. Andrew C. Tartaglino
Deputy Director for Operations

Kenneth A. Durrin
Assistant Director for Compliance

Operation Blackjack

The overall objective of this operation was to document the existence of a situation which was resulting in the diversion of the amphetamine product Biphetamine (Bifetamina) produced by the Strasenburgh Prescription Products Division of the Rexmanit Corporation and to take decisive action to eliminate the source of the diversion from the illicit drug traffic in the United States.

Before action could be taken to eliminate this diversion problem, two factors had to be determined, (1) whether the diversion was occurring from domestic or foreign sources and, (2) the level or extent of diversion. An intelligence survey was conducted during the latter part of August 1971, which consisted of a review of all instances where this particular dosage form of amphetamine was known to have appeared in the illicit traffic. This included NNDD cases, significant customs seizures, and purchases and seizures reported to BNDD's Laboratory Division for analysis by state and local authorities. At this same time a request was sent to Region #2 to obtain from the Strasenburgh Prescription Products Division, Rochester, New York, information relative to organizational structure, methods of production and shipment, of bulk and finished products, locations of foreign facilities, difference in formulation of Bifetamina produced in the U. S. as compared to that produced outside the U. S., etc. Analyzation of the intelligence information collected showed the following:

(a) All bulk amphetamine resin powder for Biphetamine was produced at Strasenburgh's facility at Rochester, New York.

(b) The firm had subsidiary facilities outside the U. S. that were receiving this bulk powder for encapsulating at their respective locations, (Columbia, Canada, Argentina, Peru, and the Republic of Mexico) from this location.

(c) The firm had shipped approximately 930 kilos of amphetamine resin since January 1970, (enough to produce 45,000,000 dosage units of Diphetamine) to the subsidiary firm in Mexico City, Mexico.

(d) That there were distinct differences in filled weights, capsule markings, etc., between Diphetamine produced for domestic distribution by the plant in Rochester, New York, and Difetamina produced by the subsidiary firm Laboratorios de Strasenburgh, Mexico City, Mexico.

(e) Many dosage units which had been seized by authorities were in original containers indicating production by the firm in Mexico City.

(f) Flow patterns of illicit distribution throughout the Southern and Southeastern United States showed points of origin to be several locations along the US/Mexico border.

(g) This product had become the drug of choice in the illicit traffic for truck drivers, and related industries and was available at truck stops throughout New Mexico, Texas, Georgia, Kentucky, Florida, Colorado, Oklahoma, Louisiana, Alabama and Tennessee.

(h) The term "Black Bollies," "Black Beauties," "BBS's" and "Black Widows" were common street terms for this product, and over 173,000 dosage units of Difetamina had been purchased and seized between April 1, 1971, and October 1, 1971.

The above factors clearly pointed out a situation where a U. S. firm was exporting large quantities of a Schedule II substance without maintaining effective controls against diversion into other than legitimate medical channels. The obvious overproduction of Difetamina in Mexico was then entering the illicit traffic through numerous sources along the US/Mexico border and being distributed throughout the southern portion of the United States.

It was decided at this time to take a Task Force approach to the problem. The objectives of the Task Force were:

(a) To document as fully as possible the extent of diversion of Difetamina by a concentrated program of purchases and seizures of evidence.

-2-

(b) To determine the network of illicit distribution of the product within the United States, and

(c) To identify as many additional sources and locations where the product was being sold in the Republic of Mexico for illicit distribution in the United States.

The Task Force, which consisted of 17 agents assisted by 10 to 15 agents from Regions 5, 6, 8 and 12 on a full-time basis, became operational on November 8, 1971. The Task Force was divided so as to be able to operate in several geographical locations simultaneously. The initial areas selected for location of the Task Force were Birmingham, Alabama, Atlanta, Georgia, and El Paso, Texas, with the Task Force supervisor being located in Dallas, Texas. The Task Force was also mobile so that a concentration of manpower could be directed to any area where the activity necessitated additional resources.

During the period of November 8, 1971, to January 25, 1972, (the termination date of the Task Force phase of the operation) a total of 302,417 dosage units of Biphetamine were documented as being purchased or seized. There were twenty-five cases initiated during this period which resulted in the seizure of $160,344 (of which $7,040 were recovered CMP) and over 115,000 dosage units of other dangerous drugs. Also 38 defendants were arrested. In addition, there are outstanding warrants for 10 defendants. A total breakdown of statistics within the operation are attached to this report.

Patterns of illicit distribution were traced to additional sources at El Paso, and Mesilla, Texas, and Las Cruces, New Mexico. Also an additional two sources in the Republic of Mexico were identified.

Subsequent to the completion of the Task Force phase of the operation a meeting was held with the Deputy Attorney General Franco Rodriguez of the Republic of Mexico in which the operation was explained to him in detail. Senor Rodriguez pledged the full support of the Mexican Government in assisting BNDD in the elimination of this problem.

The Attorney General's Office has since announced that Laboratorios Strasenburgh de Mexico will no longer be allowed to produce amphetamines.

On January 18, 1972, an order to show cause why the license to export amphetamines should not be revoked and the 1972 production quota fixed under Section 306 of the Controlled

Substances Act should not be reduced by the amount previously allocated for export purposes was served on the Strasenburgh Prescription Products Division of the Pennwalt Corporation.

On January 25, 1972, the Pennwalt Corporation requested that their export license be amended to delete the exportation of amphetamines. The firm also requested that their 1972 production quota be reduced by the amount allocated for export purposes. BNDD accepted this request. This reduction will cause a reduction of 10% of the overall 1972 amphetamine production quota.

At the present time a Joint Strike Force consisting of BNDD agents from Regions 11 and 15 and Mexican Federal agents is being assembled. This Strike Force will concentrate its efforts on eliminating sources along the US/Mexico border which were identified as sources of illicit drugs during Operation Blackjack. The Strike Force will be utilizing informants developed during Operation Blackjack. The payment of informants as well as partial funding of operational costs will also be taken from funds allocated to the operation.

When this final phase of the operation is completed action will have been taken against the firms in Rochester, New York, and Mexico City, Mexico, as well as against illicit distribution in both the United States and Mexico. The results of these actions will eliminate a main source of dangerous drugs in the illicit traffic in the United States.

To date, a total of $61,000 has been expended in the operation for PE/PI. Operational costs to date amount to $40,000. The anticipated cost of the partial funding the Strike Force is $7,500. The total of these three figures amount to $108,500 which is approximately $8,500 more than was seized during the operation.

Attachment

OPERATION BLACKJACK

	April 1, 1971 to November 8, 1971	BLACKJACK November 3, 1971 to January 15, 1972	Overall
Bifetamina Seized (Dosage Units)	230,204	551,033	781,237
Bifetamina Purchased (Dosage Units)	30,840	311,354	341,194
Currently Seized	-	100,141	100,141
CAF Recovered	-	7,040	7,040
Vehicles Seized	-	25	25
Weapons Seized	-	24	24
Other Drugs			
Heroin		53 gms.	53 gms.
Cocaine		20 gms.	20 gms.
Other Amphetamines		108,662	108,662
Marihuana) Hashish)		1.5 lbs.	1.5 lbs.
Barbiturates		7,150	7,150
Arrests	25	59	85
Defendants to be Arrested		10	10

UNITED STATES DEPARTMENT OF JUSTICE

BUREAU OF NARCOTICS AND DANGEROUS DRUGS
WASHINGTON, D.C. 20537

IN THE MATTER OF

Strasenburgh Prescription Products
Division of Pennwalt Corporation
755 Jefferson Road
Rochester, New York

ORDER TO SHOW CAUSE

Pursuant to Section 1008 of the Comprehensive Drug Abuse Prevention and Control Act of 1970 (21 U.S.C. 958),

NOTICE is hereby given to afford you an opportunity to Show Cause as to why the Bureau of Narcotics and Dangerous Drugs should not deny your application, dated December 27, 1971, for a Certificate of Registration to export amphetamine, its salts, optical isomers and salts of its optical isomers and resin complexes of amphetamine and dextroamphetamine (hereafter "Schedule II, 1100") and as to why the 1972 production quota for Schedule II, 1100 fixed under Section 306 of the Comprehensive Drug Abuse Prevention and Control Act of 1970 (21 U.S.C. 826) should not be reduced by the amount now allocated by you for export purposes, for the reason that the Director of the Bureau of Narcotics and Dangerous Drugs (hereafter "Director") is unable

to determine that your application for registration to export Schedule II, 1100 is consistent with the public interest.

More particularly, the Director in applying the factors of Section 303(a) of the Comprehensive Drug Abuse Prevention and Control Act (21 U.S.C. 823(a)), notes that you have not maintained effective controls against diversion into other than legitimate medical, scientific, research, or industrial channels, of Schedule II, 1100 shipped by you into the Republic of Mexico under authority granted under your present BNDD registration (No. PS 0003183).

The Director further notes that information has been furnished to him indicating:

1. That Schedule II, 1100 is shipped by you to Laboratorios Strasenburgh de Mexico S.A. de C.V. (a subsidiary of Pennwalt Corporation) at Mexico City, Mexico, where it is used in making an amphetamine product under the trade name "Bifetamina";
2. That a substantial percentage of this Bifetamina is then smuggled into the United States and is then sold illegally in the United States. For example:

(a) On November 5, 1971, Special Agents of the Bureau of Narcotics and Dangerous Drugs arrested two individuals at Atlanta, Georgia, and seized 20,000 dosage units of Bifetamina in the original bottles;

(b) On November 13, 1971, Special Agents of the Bureau of Narcotics and Dangerous Drugs arrested two individuals at Glendale, Kentucky, and seized 40,000 dosage units of Bifetamina in the original bottles; on November 14, 1971, a third individual was arrested in connection with this case;

(c) On December 10, 1971, Special Agents of the Bureau of Narcotics and Dangerous Drugs arrested two individuals at Hattiesburg, Mississippi, and seized 72,000 dosage units of Bifetamina in the original bottles;

(d) On December 16, 1971, Special Agents of the Bureau of Narcotics and Dangerous Drugs arrested two individuals at San Antonio, Texas, and seized 30,000 dosage units of Bifetamina which were not in bottles used by Laboratorios Strasenburgh de Mexico S.A. de C.V.; on December 17, 1971, two additional individuals were arrested in connection with this case;

(e) On January 6, 1972, Special Agents of the Bureau of Narcotics and Dangerous Drugs arrested an individual at Birmingham, Alabama, and seized 24,000 dosage units of Bifetamina in the original bottles;

(f) On January 11, 1972, Special Agents of the Bureau of Narcotics and Dangerous Drugs concluded investigations into two entirely unrelated cases. In one case, two individuals were arrested at El Paso, Texas, and 60,000 dosage units of Bifetamina in the original bottles were seized. In the other case, also at El Paso, Texas, one individual was arrested and 62,000 dosage units of Bifetamina in the original bottles were seized;

(g) Beginning on November 8, 1971, and ending on January 15, 1972, a special BNDD project designated "Operation Blackjack" was in effect. Information developed by Special Agents assigned to Operation Blackjack indicates that Bifetamina enters the United States at six principal points along the Mexico-Texas border -- El Paso, Del Rio, Eagle Pass, Laredo, McAllen and Brownsville. Across the border from each of these Texas locations there exists in Mexico a "farmacia" from which the Bifetamina begins its journey into the

to the Bureau of Narcotics and Dangerous Drugs,

1405 Eye Street, N.W., Washington, D.C. 20537,

Attention: Robert J. Rosthal, Deputy Chief Counsel.

(Telephone: 202-382-3411)

John E. Ingersoll
Director, Bureau of
Narcotics and Dangerous Drugs

January 14, 1972

Department of Justice

FOR IMMEDIATE RELEASE
January 27, 1972

The country's largest amphetamine products exporter, whose Mexican stimulant drug capsules have been showing up in large quantities in the illicit United States market, has decided not to seek renewal of its export license, Attorney General John N. Mitchell announced today. Mr. Mitchell said the action will result in an additional 10% rollback in the 1972 amphetamine production quota set by the U.S. Department of Justice.

Mr. Mitchell said that the Strasenburgh Prescription Products Division of the Pennwalt Corporation has agreed to withdraw its December 27, 1971, application to the Bureau of Narcotics and Dangerous Drugs (BNDD) for a license to continue exporting amphetamines.

BNDD Director John E. Ingersoll said that the company's action came in response to an order to show cause which was served on the Strasenburgh Division on January 18, 1972.

The order, based on information developed by a special BNDD investigative task force designated "Operation Blackjack," showed that a substantial percentage of amphetamine exported to Mexico by Strasenburgh had been smuggled back into the United States for illegal sale here.

Mr. Ingersoll said that BNDD will move immediately to reduce the 1972 production quota for all U.S. manufacturers.

On December 2, 1971, the Bureau proposed 5,870 kilograms of amphetamine as the total which could be produced in this country. This figure will now be reduced by 1,190 kilograms resulting in a new, lower total of 4,680 kilograms.

The December 2 quota proposal represented a 40 per cent rollback from 1971 amphetamine production. Today's action means that the rollback will be increased to 50 per cent of 1971 production.

Mr. Ingersoll said that "since every objective sought by BNDD's order to show cause has now been achieved, the public hearing set for February 23, 1972, will be unnecessary."

The most recent report to stockholders by the Pennwalt Corporation shows approximately $8.3 million in sales of amphetamine for 1970. Of this amount, approximately $4 million resulted from amphetamine exports.

Until today the Strasenburgh bulk amphetamine powder had been shipped to customers in Canada, Argentina, Peru, Colombia and Mexico. Dosage units of amphetamine have been shipped by the firm to Alaska, Puerto Rico, Panama, Guatemala, Nicaragua, Honduras, El Salvador, Ecuador, Uruguay, Chili, Belgium, Italy, Lebanon, Switzerland, Guam, the Philippines, Dominican Republic, the Netherland Antilles and Hawaii.

Pending applications for shipments from the firm's Rochester, New York, location to Switzerland, Italy and the Philippines amounting to almost two million dosage units have been denied by the Bureau of Narcotics and Dangerous Drugs.

-30-

Form DJ-[illegible]
(Ed. [illegible])

UNITED STATES GOVERNMENT

DEPARTMENT OF JUSTICE

Memorandum

TO : Mr. Kenneth A. Durrin
Assistant Director for Compliance

DATE: NOV 2 1972

FROM : Larry Kerness, Chief
Regulatory Enforcement Division

SUBJECT: Proposal for Development of Information to Enable Denial of R.J. Strasenburgh's Domestic Registration

Reference is made to memorandum dated September 21, 1972, from Jerry N. Jenson, Associate Regional Director, New York, New York, to you requesting that a show cause order be issued to Strasenburgh Prescription Products, Rochester, New York for denial of re-registration as a Schedule II amphetamine manufacturer.

Before issuance of this show cause order we should discuss this situation in detail with Chief Counsel's Office. I think the basic approach we should take is to develop sufficient information to show that to allow Strasenburgh to continue in business would not be in the best interest of the public and deny the re-registration based on that fact as opposed to denying it on specific violation of CSA.

The facts to be considered in developing this information are as follows:

1) Operation Blackjack - All information obtained during this operation can be presented at the hearing to establish a background that the firm does not have adequate safeguards for distribution of amphetamines to foreign customers.

2) Quotas - The firm's amphetamine procurement quota for 1972 was 315 kilos. The firm interprets a procurement quota to be the amount of a substance they may purchase within a given year. The firm has already produced and sold more than its procurement quota would permit for 1972. As of June 19, 1972, the firm had sold 541 kilos. and Dr. Head stated that he anticipated production and sales of 900 kilograms during 1972. Our interpretation is that the procurement quota

is that amount needed for legitimate consumption during the year. Therefore, the firm is in effect saying that they do not care what is needed for legitimate consumption but will sell whatever the demand requires.

3) Security - Minor security violations were detected during the current audit. The firm has been advised in writing during previous audits that their security was inadequate but their security remains inadequate.

4) Statements before Rogers Committee - Shortly after Operation Blackjack Dr. Head appeared before Senator Rogers regarding the situation. He made certain statements which were false. He stated that the firm voluntarily closed their Mexican operation once the show cause order on their export registration was issued. Reports by Mexican authorities indicated that the firm was in full operation when they entered the plant after the issuance of the show cause order and that the authorities closed the plant as opposed to any voluntary action by the firm. Dr. Head also stated to the Rogers Committee that the Strasenburg in Mexico City had no intention of producing bifetamina in Mexico again. However, investigation in Mexico shows that shortly after the plant closing the firm approached the Mexican Government requesting to re-open the plant.

5) Possibility of Re-exportation of bulk amphetamine from Argentina or other countries. All foreign exports are being obtained from the firm since 1970 and follow-ups in these countries may show re-exportation.

6) Setting up Mexican Operation to Subvert CSA - This fact will be hard to prove but we do have some possibilities. A history of the firm should show that for a number of years the firm in Rochester shipped bulk to Mexico to be encapsulated there. It will also show that as of the effective date of CSA they suddenly ceased this practice since the firm in Mexico was at that time able to completely manufacture the product. It is also

possible that interviews of fired employees, namely Irwin Rahn and Mr. Fritzner could shed light on this situation.

7) Any written communications (cables, etc.) sent by the firm could be subpoenaed. This could show current transactions with foreign countries.

8) Review of Export Permits for the period immediately prior to CSA Schedule II requirements for amphetamine shows that the firm was attempting to ship large quantities of bifetamine out of the country. This was probably in anticipation of the quota system.

9) Statement by Deputy Chief of Missions (DCM), U. S. Embassy, Mexico City. During Mr. Voyles recent visit to Mexico he conferred unofficially with the DCM who stated that a Philadelphia banking official and a vice-president of Pennwalt were recently in Mexico City. The DCM had a meal with these individuals and they told the DCM that it would be good for U.S.-Mexican relations if the firm was allowed to go back in business in Mexico. We should attempt to get a written statement from the DCM regarding these conversations.

10) The records of Senator Rogers hearings should be obtained to extract any pertinent information from them.

11) An intelligence probe in accordance with N-60 should be conducted in the Regional and District Office cities to determine availability of the firm's products in the illicit market.

12) The firm's total distribution of amphetamines for the year just prior to the quota system and moving of amphetamines into Schedule II should be compared to their total distribution during the year immediately after this to see if sales have increased or remained the same. Other major firms have noted 25% - 40% decreases during the latter period. We may be able to show that Strasenburgh simply filled the void and in effect canceled the intended purpose of the quota system. These figures should be compared to the Gosselin Survey.

13) An audit of the firms Los Angeles distribution warehouse should be conducted to determine any possible diversion or security violations and also supply potential leads which could be investigated.

14) An operator of the illicit black amphetamine capsule and secobarbital laboratory in Mexico City was a former employee of Laboratorios Strasenburgh, Mexico City. We should determine the possibility of interviewing this individual relative to any knowledge he may have regarding Strasenburgh's previous activities.

15) A complete print-out of the firms domestic distribution for a one year period should be obtained from the firm and analyzed relative to distribution patterns and leads which could be followed-up with audits and/or criminal investigations if indicated.

16) A recent Dunn and Bradstreet Statement should be obtained on the firm.

17) DIU Units in Texas and Michigan should be alerted and any intelligence obtained should be supplied to ENA.

To prepare this case for the show cause hearing an Attorney from Chief Counsel's Office should be assigned. Field personnel and ENA personnel will be available to assist the Attorney in obtaining the information necessary. If you agree with these recommendations a meeting will be arranged with Mr. Rosthal as soon as possible to implement the above and get their recommendations.

Mr. Frederick M. Garfield
Assistant Director for Scientific Support

Kenneth A. Rumin
Assistant Director for Compliance

R. J. Strasenburgh - Ionamin

ENA has recently become cognizant of the product Ionamin manufactured by R. J. Strasenburgh, Rochester, New York, appearing in the illicit traffic.

During Operation Blackjack a truck stop owner in Sylacauga, Alabama, offered unlimited quantities of the drug for sale stating that it was as good as Bifetamine, easier to get and could well take the place of Bifetamine in the illicit traffic. This drug has also been purchased by ENDD recently in Region I.

A local pharmacist has advised that a detailman of R. J. Strasenburgh advised him that Ionamin would be replacing Bifetamine as a weight reduction drug. This detailman further advised that ENDD had entered into an agreement with R. J. Strasenburgh stipulating that if Strasenburgh allowed Bifetamine to be placed in Schedule II that ENDD would not place Ionamin under control.

In view of the above it appears that Ionamin has the potential of becoming a drug of abuse. Would you please keep me advised as to any information which may come to your attention on Ionamin appearing in the illicit traffic in any dosage form.

ENAE/OHendrix/ksp/4217/3914-72

cc: ENA Chron
ENA Subject

P. 3225

federal register

Area Code 202 Phone 523-5240

DEPARTMENT OF JUSTICE

Drug Enforcement Administration

CONTROLLED SUBSTANCES IN SCHEDULES I AND II

1975 Final Aggregate Production Quotas

Section 306 of the Comprehensive Drug Abuse Prevention and Control Act of 1970 (21 U.S.C. 826) requires the Attorney General to establish aggregate production quotas for all controlled substances in Schedules I and II each year. This responsibility has been delegated to the Administrator of the Drug Enforcement Administration pursuant to § 0.100 of Title 28 of the Code of Federal Regulations.

On December 13, 1974, a notice of the proposed aggregate production quotas for these substances was published in the FEDERAL REGISTER (39 FR 2411). All interested parties were invited to comment on or object to the proposed aggregate production quotas on or before January 13, 1975. Except with reference to Methylphenidate, no requests for hearings have been received by the Administration relative to the proposed quotas. Comments and objections relative to the proposed aggregate production quotas have been received from Western Fher Laboratories relative to Phenmetrazine, from Hoffman-La Roche Inc. relative to Alphaprodine, from Eli Lilly and Company relative to Amobarbital and Secobarbital, and from Richardson-Merrell Inc. relative to that portion of the Desoxyephedrine quota allocated for the production of Levo-Desoxyephedrine for use in the manufacture of a non-controlled substance. Specific details relative to these comments will be outlined in a future FEDERAL REGISTER notice.

Due to the fact that a request for a hearing has been received by the Administration with reference to the proposed aggregate production quota for Methylphenidate, the aggregate production quota for Methylphenidate does not appear in this order.

Based upon consideration of the factors set forth in 39 FR 241, the Administrator of the Drug Enforcement Administration, under the authority vested in the Attorney General by section 306 of the Comprehensive Drug Abuse Prevention and Control Act of 1970 (21 U.S.C. 826) and delegated to the Administrator by § 0.100 of Title 28 of the Code of Federal Regulations orders that the aggregate production quotas for 1975 for controlled substances, expressed in grams in terms of their respective anhydrous bases, be established as follows:

SCHEDULE I

Basic class:	Granted (1975)
1-alpha-acetylmethadol	300,000
Tetrahydrocannabinols	500

SCHEDULE II

Basic class—Con.	Granted (1975)
Alphaprodine	34,500
Amobarbital	12,504,986
Amphetamine	3,291,300
Anileridine	88,133
Apomorphine	2,000
Cocaine	600,000
Codeine (for sale)	46,373,000
Codeine (for conversion)	1,165,000
Desoxyephedrine	1,215,374
Dihydrocodeine	731,000
Diphenoxylate	1,133,000
Ecgonine	200,000
Ethylmorphine	44,680
Fentanyl	2,000
Hydrocodone	800,000
Hydromorphone	70,200
Levorphanol	3,000
Methadone	3,245,000
Methadone Intermediate (4-cyano-2 dimethyl-amino-4, 4-diphenyl butane)	1,350,000
Methaqualone	19,608,335
Mixed Alkaloids of Opium	163,321
Morphine (for sale)	600,000
Morphine (for conversion)	42,182,000
Norpethidine	830,000
Opium (tinctures, extracts, etc. expressed in terms of opium)	1,904,666
Oxycodone (for sale)	1,769,400
Oxycodone (for conversion)	7,000
Oxymorphone	3,000
Pentobarbital	28,119,000
Pethidine	17,057,415
Phenazocine	225
Phenmetrazine	2,761,700
Secobarbital	18,430,600
Thebaine (for sale)	4,250,000
Thebaine (for conversion)	1,750,000

[1] 758,108 grams for the production of Levodesoxyephedrine for use in a non-controlled product, and 457,266 for production of Methamphetamine).

Pursuant to Title 21 Code of Federal Regulations, § 1303.23(c) the Administrator of the Drug Enforcement Administration will in early 1975 adjust individual manufacturing quotas allocated for 1975 based upon 1974 end of year inventory figures submitted by applicants and estimates of medical and scientific requirements to be provided by the Food and Drug Administration.

All persons who submitted an application for either an individual manufacturing quota or procurement quota for 1975 will be notified by mail as to their respective 1975 quota established by the Drug Enforcement Administration.

This order is effective on January 20, 1975.

Dated: January 15, 1975.

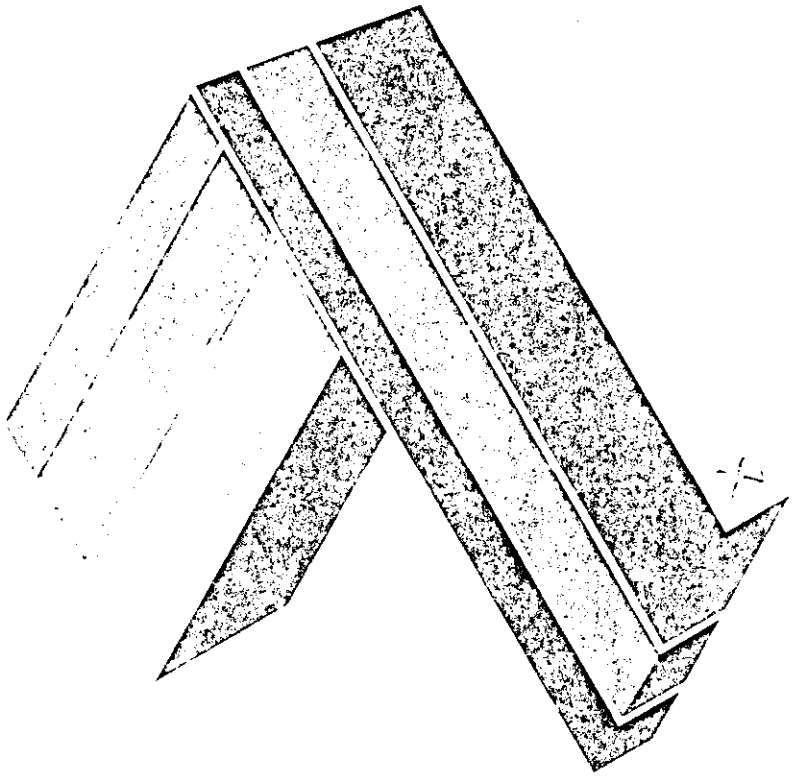
JOHN R. BARTELS, JR.,
Administrator,
Drug Enforcement Administration.

[FR Doc.75-1790 Filed 1-17-75;8:45 am]

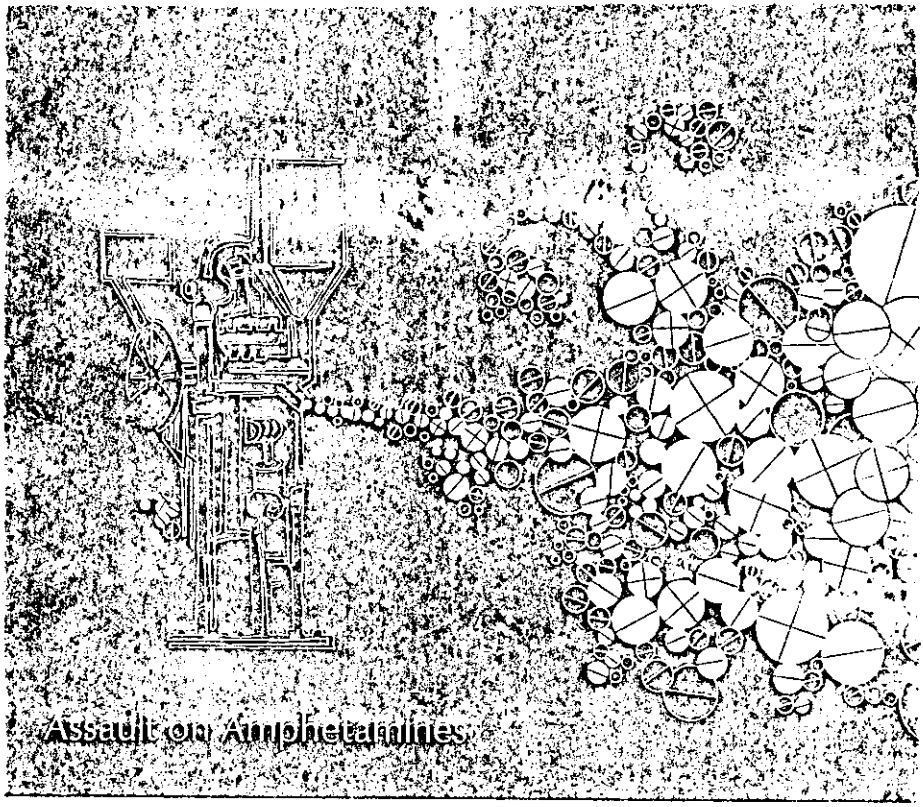
Drug Enforcement

Winter 1975

Assault on Amphetamines



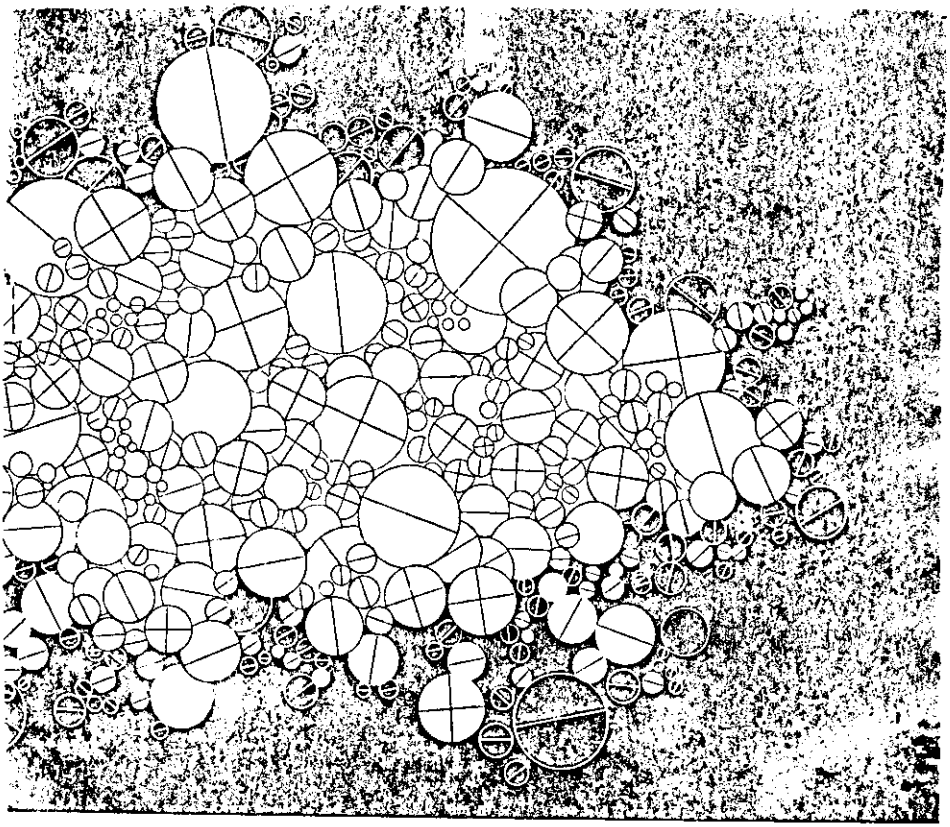
Drug Enforcement Administration
United States Department of Justice



Central Tactical Unit Four

by Douglas Chandler
Supervisor, CENTAC 4
DEA Office of Enforcement

Editor's Note: *This is the story of CENTAC 4, told from the inside by the man in charge, Special Agent Douglas Chandler. Since this conspiracy case is the first of its kind, we asked Agent Chandler to explain the particular problems assigned to DEA's Central Tactical Units. They are, he says, familiar to the held supervisor of every law enforcement agency.*



"We just don't have enough men here. Our personnel ceiling is X but we have only Y on the street. My officers are working overtime now simply to handle the problem of Z."

This is the nearly unanimous cry of first-line supervisors in every law enforcement outfit. It is up to the superior officer to recognize the genuine note of desperation among the chorus simply reporting business as usual. While this note is not rare in our profession, the chorus is most often in response to a proposal of additional assignments.

The superior officer must be prepared to hear this objection during the planning stages of an operation which will involve several subdivisions. No one welcomes a drain on manpower.

Another quote, not so often heard by superiors, goes something like this: "Here is a request from office X about their investigation of Y, which they seem to think is a big deal. They ought to see our problem of Z. As though we didn't have enough to do."

The net result is that the local problem is going to remain top priority in that squad barring radical changes of policy from above. Interoffice requests for assistance or followup will bog down with exasperating frequency. The best laid plans of the headquarters staff for the big operation will be distorted. The distortion increases as the work required of the squad becomes less mechanical and more sophisticated.

The difficulties arising from these factors grow with the distance separating offices, and they become

In the temporary office in San Diego, Contact 4 Supervisor Chandler (left) spent long planning sessions with Lee Vollmer (right), group supervisor of DEA's San Diego District Office. Vollmer's group handles all joint operations with Mexican drug authorities along that section of the border.

occasionally unmanageable in crossing jurisdictional or departmental lines. As a result the quality of investigative work suffers. It is ironic that only the bigger cases, those encompassing more than the local scene, are the ones to suffer.

The best criminal investigative work demands initiative and imagination, which means the full interest of the officer. This is especially true in handling multiple-defendant drug cases or complex conspiracies. The more complex the case, the more latitude the officer has, or should have, in his judgment of which leads to follow. The best work is done by those not so different from the detective of popular fiction, making intuitive leaps from seemingly insignificant items, pursuing leads no more concrete than a "gut feeling." Agatha Christie had the right idea, but only skimmed the surface of the serious work.

A perfunctory, mechanical treatment of investigative leads will not do the job, and it may be a mistake to think that a sharply worded command from headquarters for piecework can summon up anything else.

In planning for an important investigation, which will involve several widely scattered subdivisions, the good manager cannot ignore any factors simply because he condemns them as undesirable. Manpower is that all-important resource usually discussed in mathematical terms, but is complicated by the imponderables of human nature. The wise planner should determine in advance the answers to these questions:

How much manpower is required from that subdivision for the new operation?

How seriously will the requirement cut into its routine duties?

What are the relative priorities of the routine versus the new operation?

Does the supervisor understand the priorities?

How much of his time can be devoted to the new operation?

Who should be in charge of the overall operation? If not that particular supervisor, then what is his role, and what is his relationship to the one in charge?

I would like to commend Administrator John R. Bartels, Jr. and his fellow agents at DEA as well as the many state and local law enforcement agencies in this country, Mexico, and Canada, whose hard work and cooperation resulted in one of the most significant law enforcement endeavors in the history of our country.

Senator Birch Bayh
Chairman, Subcommittee to Investigate Juvenile Delinquency
(Congressional Record, September 12, 1974)

These considerations will apply to any outfit subdivided functionally or geographically. The negative effects grow in proportion to the size of the outfit as well. A small police department, where everyone knows everyone else, should have no problem at all. Many larger departments have a headquarters detective staff which can cross precinct lines at will to pursue a case. Travel within a city is therefore not a consideration. This may seem to be the perfect solution. State and federal agencies because of greater distances and the cost of air fare, cannot adopt that solution as standard procedure.

Moreover, something is lost. The "gut feeling" makes no sense when transmitted through formal channels and is not justification for a thousand-mile trip to check it out. Of course, there is always the informal channel, which the British call the "old boy network"—a telephone call to a friend and colleague in the other city. Many police administrators frown on this practice, and many operational manuals fairly bristle with prohibitions against it. This is probably because the results remain informal and are seldom reported properly, and the upper echelon loses control on both ends.

The Drug Enforcement Administration is a relatively small agency scattered around the world. The DEA special agent is trained to think in terms of the international traffic and distant sources of supply. That is his only business. Correspondence which crosses state lines and international borders is not only daily routine; it is the substance of the best case files and a goal to be sought in every new investigation. The experienced DEA supervisor has probably been transferred often enough and far enough to lose any provincial outlook. As a result of his travels he can often include within his formal communications a very efficient "old boy network." Thus DEA may have reduced the negative interoffice factors to the achievable minimum.

Nevertheless, intelligence turns up an occasional drug trafficking organization, which is spread across both domestic and foreign DEA Regions, of such importance that it deserves maximum effort. No single region can take command of the entire investigation, and routine correspondence, however reliable, is too cumbersome. A small, full-time group under a single supervisor with freedom to travel as indicated by the leads is the most effective approach. The police department with the central detective staff had the solution all along.

DEA calls such a group a Central Tactical Unit. "Central" connotes responsibility only to DEA Headquarters in Washington. So far, five CENTAC units have been created, each handling a different organization dealing in an identifiable dosage form of one drug. The first criterion for selection of an organization is that its contraband drug appears in such quantities as to constitute a threat to communities throughout the United States. The second criterion is that termination of the organization's activity would significantly reduce the availability of that drug within the communities. Nothing less would justify the cost of a CENTAC operation.

By the time these two criteria are met, the drug is well known on the illicit market and many purchases and seizures have already been made. Street intelligence plus forensic analysis of the evidence will indicate some common source. An examination of the files will make it possible to piece together an outline of the organization's structure.

A profit-oriented enterprise outside the law such as a drug trafficking network operates entirely by the principles of laissez-faire economics. If it is not profitable, it will disappear; if it is, it will grow at an amazing pace; there is no other kind. The original financiers thereby achieve an executive status removed by several layers from substantive violations. These men at the top will never be prosecuted for possession or sale of drugs. The only technique at our disposal is to make use of federal conspiracy statutes.

The mission of a Central Tactical Unit is to examine, select, and develop the physical and documentary evidence in such a way as to bring forth the witnesses to a conspiracy. CENTAC 4 was the first of these units to conclude its operations. Though no two units are alike, its story may serve as an example of how such tactical operations are undertaken.

The target was the minibennie, the small amphetamine tablet which was appearing in every region of the United States. The first minibennies were encountered in April 1970. They met with rapid acceptance by drug users. Production in clandestine laboratories was almost continuous after that. By mid-1974 a total of 58 million minibennies had been seized by law enforcement agencies.

DEA's Special Testing and Research Laboratory in Virginia has perfected a procedure of microscopic examination and measurement of tablets similar to ballistics. The punches and dies of a tableting machine can be positively identified from a sample of the tablets. The chemist can say that all exhibits in a list of cases came from one machine, though he has no idea where that machine might be. DEA encourages all law enforcement agencies to send samples of illicit tablets to the Special Testing Laboratory.

The submitting agency receives a reply from the lab with the results: whether the manufacturer can be identified, whether it is a previously encountered clandestine source, or whether it is a new prototype.

The more samples on file from a particular machine, the more intelligence is compiled on distribution routes, associated dealers, common wholesalers, transshipment points, and possible conspiracy evidence. All of this, by the way, is available to the submitting agency if it wishes to pursue the investigation.

In the latter part of 1973, DEA Headquarters was studying the intelligence on the minibennies with a sense of urgency. Two new machines had begun

One of the tableting machines seized in Mexico City is examined by Mexican federal agents. In the same room was a supply of raw powder ready to go into the hopper.

production, and it looked as though they were each more prolific than any predecessor. When the CENTAC concept came along, the minibennie traffic was a natural target.

More than half of all the minibennies seized had been reported by U.S. Customs at San Ysidro, California, just south of San Diego at the crossing point from Tijuana. Amounts found at any other port of entry along the border were negligible. The largest wholesalers in the country were in San Diego and Los Angeles. Obviously, the tableting machines were in Mexico, and the financiers and major traffickers in Tijuana.

During January 1974 plans were made for CENTAC 4. I served as the supervisor, and seven special agents were chosen for the special assignment from various domestic regions.

DEA Administrator John R. Bartels, Jr. sent a teletype to all regions on January 25, 1974, outlining the plan. Any case developed with over 25,000 minibennies was to be reported to CENTAC 4.

By the end of February, CENTAC 4 had moved into office space in San Diego and begun its work. The first step was to take all pertinent files and extract anything which could be used – any combination or extrapolation of facts and any names of potential informants. An organizational chart of the violators started to take shape.

The legwork began, checking motel records and all the other routine tasks. Interviewing witnesses was tricky because we wanted to maintain security and had to use indirection. If word of the investigation had hit the street, it would have been too easy for the California violators to step across the border into Tijuana or for the suspects there to move their operations.

By the middle of March we had the first witness before a federal grand jury. Meanwhile, as the special agents assigned coordinated the work of the regional offices, the organizational chart kept growing.

On April 1, a major break came along. The agents turned up an informant who could fill in the chart with names all over Mexico, going back to the beginning of the minibennie labs. He was a veteran violator from Tijuana, now living in California. And he was willing to testify.

During the first couple of months it became evident that other DEA offices around the country, in response to the Administrator's teletype, were trying to put together their own minibennie conspiracy cases. Seattle and Phoenix had good cases underway, and Milwaukee was just getting started.

This trend gave rise to the final plan, which was in outline as follows. Encourage as many offices as possible to proceed with multiple-defendant conspiracy cases. Coordinate them to go to a grand jury for indictment at about the same time. Obtain sealed indictments nationwide and wait for a simultaneous roundup. Take all the evidence against the suspects in Mexico and present it to the Mexican Attorney General. Allow time for the Mexican Federal Judicial Police to make arrests and search for the laboratories. Then, as soon as significant action occurs in Mexico, give the signal for the domestic roundup.

It worked out exactly as planned. But I was never sure that it would, and there was nothing easy about it.

During a trip to Mexico, Administrator Bartels met with the Attorney General Pedro Ojeda-Paullada and discussed the operation. We were assured of his cooperation.

On May 21, we held a meeting of Assistant U.S. Attorneys from the various cities cooperating in the investigation at the Justice Department offices in Washington. They were the ones who would handle the grand jury indictments in San Diego, San Francisco, Seattle, Phoenix, Milwaukee, Miami, and Boston. This list was to change a bit later on when some could not make the schedule, while others were added with new cases.

The CENTAC 4 agents in San Diego now had enough miscellaneous leads to keep them busy for a year. Conceivably, these local leads could have been developed into evidence to indict a couple of hundred defendants in California. But we did not have a year, and such a case would have become unmanageable. We concentrated instead on the major Mexican sources. New informants were developed and their testimony checked.

On July 17, a few of us went to Mexico City and briefed the DEA Regional Director and his staff in the

Two defendants are taken into custody—one in Tijuana (left), the other at about the same time in Los Angeles (right). The international roundup resulted in 113 arrests.

American Embassy. All the intelligence so far pointed to Guadalajara as a probable location of one of the big laboratories.

That same day the Seattle grand jury returned indictments on 15 defendants. San Diego, Phoenix, San Francisco, and the others followed. The last to go was Milwaukee on August 19.

San Francisco had a problem when their case, partially based on a Title III wiretap, went to a hearing that disclosed the case. The San Francisco agents were forced to make their roundup at once or have the defendants flee.

On August 22, we met Attorney General Ojeda-Paullada in his office in Mexico City and briefed him in detail. His reaction was positive, and his moves to handle it were enthusiastic. He assigned three of his best commandantes with their groups to travel to Guadalajara and Tijuana.

The Mexican Federal Prosecutors studied our information and extracted whatever would be evidence under their law. They suggested a procedure similar to the letters rogatory under the Napoleonic Code. Back in San Diego, we took complete statements from four of the witnesses, had them notarized, then certified before the Mexican Consul. These documents were then delivered to the Mexican prosecutors, who issued the orders for arrests.

All this took a few days. Meanwhile, on August 29, two undercover agents from Seattle flew to San Diego to negotiate with some of the local traffickers for a delivery of minibennies. CENTAC 4 agents took a break to participate in th. surveillance and arrests.

That week the DEA office in Calexico came up with some information about tableting machines in Mexico City. Two agents from Calexico went there. As a result the Mexican Federal Judicial Police raided two labs, containing two machines each, and arrested eight people.

On September 8, a group of 17 Mexican federal agents came to San Diego and spent the night. At dawn the next morning they started rounding up defendants in Tijuana.

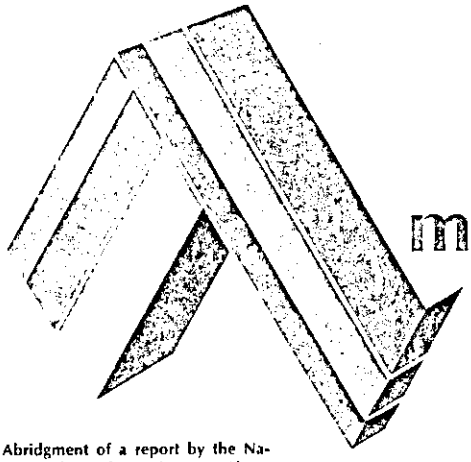
During that day 12 of the biggest violators in Tijuana went to jail. Some of them were the old legendary heroin dealers who had branched out into minibennies because they saw it as an easy and lucrative business. Most of them were multimillionaires, which gave them local stature in both political and criminal circles. The defendants were loaded into a camper in secrecy as a precaution against an attempt at a break by associates, and transported to Guadalajara. Prosecution of all Mexican defendants will be in the Guadalajara courts. Six weapons and a half-kilo of heroin were seized during these arrests.

Other defendants in Guadalajara and Mexico City were arrested, and some escaped. So far 27 have been rounded up, and the search is still going on.

On September 10, the domestic roundup began. Most of those indicted were arrested that night. During the raids other associates were found in possession of drugs and added to the list. The total number of minibennies seized incidental to the arrests came close to one million. Other seizures included weapons, cars, growing marihuana plants, a motorcycle, and an airplane. As of now 113 defendants are in custody and will be prosecuted in these cases. Eleven remain at large in fugitive status.

Going back to the fundamentals, we enforce the law by locking up criminals; not for vindictive punishment of that one offender, but rather as an example to others contemplating the same crime. It is no example if the others never know about it. Although many policemen distrust reporters and prefer to work in privacy, public communication can be an important deterrent. Almost every major newspaper in the country carried the story of CENTAC 4 and it was widely covered on television. We must now wait for the effects of the operation to be felt in the minibennie traffic. There are probably millions of dosage units sitting in caches on this side of the border, and these will be sold off in the months to come. We can expect to find minibennies on the street for a while, probably at increasing prices, even if production in Mexico should be completely shut down.

The Mexican authorities did not seize all the clandestine machines. We know, however, that the Mexican violators are susceptible to law enforcement pressures and will turn to less dangerous enterprises when threatened with vigorous enforcement.



Amphetamine

Abridgment of a report by the National Clearinghouse for Drug Abuse Information (Series 28, No. 1, 1974)

The National Clearinghouse for Drug Abuse Information *operates as a central source for the collection and dissemination of drug abuse information within the Federal Government and serves as a coordinating information agency for groups throughout the country working in drug abuse programs. Since its establishment in 1970, the Clearinghouse has developed an information dissemination service; a publications development program; computer files of resource and program information; and a national network of local drug abuse information centers. These activities are designed to provide current factual drug abuse information to the public on request. Inquiries should be directed to the National Clearinghouse for Drug Abuse Information, P.O. Box 1908, Rockville, Maryland 20850.*

Amphetamine is part of a chemical "family" which includes methamphetamine, dextroamphetamine, and other drugs. Its best known major effects include the dilation of the bronchial passages, appetite depression, the relief of fatigue, and the stimulation of the central nervous system (CNS). Some of the undesirable side effects at high dose levels include insomnia, stomach disorders, cardiac arrhythmia, and, more rarely, paranoid psychosis.

Amphetamine was first synthesized in 1887; the first significant investigation into its pharmacology, or therapeutic possibilities, was performed in 1927. At that time, Gordon Alles, a California pharmacologist, prepared a number of phenylalkylamine compounds in an effort to find a synthetic substitute for ephedrine, a drug derived from various plants and used for treating asthma. Alles' research led to his receipt of the patent for the drug in 1932. In exchange for royalties on sales, he assigned the patent to Smith, Kline, and French Laboratories which used the drug in the Benzedrine® inhaler to aid in dilating the bronchial passages.

Most of the other major effects of the drug were discovered during the 1930's. In 1937, amphetamine became available as a prescription tablet. It was used to treat narcolepsy—a disease producing an uncontrollable urge to sleep—and, paradoxically, to alleviate the hyperactive syndrome of children. As clinical use continued, amphetamine's effects as an appetite suppressant and a stimulant became known.

During World War II in Japan, amphetamine was extensively used both by Japanese civilians and the military to counteract battle fatigue, to maintain alertness, and to achieve high production quotas imposed by the war. After the war, large stocks of the drug became available without prescription, and the number of heavy users of amphetamine increased so rapidly that medical problems from its use developed. From 1948 to 1955, legal controls were steadily developed and tightened, along with expansion of treatment facilities and strengthening of penal provisions. These measures were complemented by a massive public education campaign, with the result of greatly reducing the amphetamine abuse problem in later years.

Sweden has also had a problem with amphetamine and stimulant abuse. Since the early 1940's, increased legal and medical restrictions on the distribution and use of stimulants have generally failed to halt the illegal misuse of the drugs. Legally, stimulants are restricted to very selected medical cases by special license.

In the United States the recent phase of abuse—intravenous injection of methamphetamine—spread throughout the country from its beginnings in the San Francisco Bay area in the late 1950's and early 1960's. Prescription of injectable amphetamine as an alternative to opiate addiction, and unethical distribution of the drug by a few physicians, made the drug easily available to potential abusers as a liquid in ampules. Although closer legal controls then were placed on prescriptions, a black market developed. In 1970 and 1971, the amphetamines and methamphetamine were placed under strict federal controls. Continued federal concern about the drugs was reflected in Senate hearings in 1971 and 1972, which focused on high-dose intravenous use, misuse of prescribed amphetamines, and diversion of legally produced amphetamine into illegal channels.

Current Medical Uses

Until mid-1970, amphetamines had been prescribed for a large number of conditions including depression, fatigue, and long-term weight reduction. In 1970, the Food and Drug Administration restricted the legal use of the amphetamines to three types of conditions: narcolepsy, hyperkinetic behavior, and short-term weight reduction programs.

Short-term treatment of obesity

Amphetamine, as well as a host of similar compounds, is prescribed for appetite control because it decreases hunger.

In spite of this advantage, two factors argue against the widespread, prolonged use of amphetamine for weight control. One is that tolerance develops rapidly to the appetite depressant characteristics of the drug. Even with moderate dosage increases, 4 to 6 weeks seems to be the limit before tolerance develops to the anorectic effect of amphetamine.

The second reason is that overeating seems to be controlled primarily by psychological and behavioral factors, not by the physiology of the body. Overeating is regarded by many authorities as a habit, which must be changed if the individual is to lose weight after developing tolerance to the anorectic effect of the amphetamine drugs.

Hyperkinetic syndrome of childhood

This disorder is manifested by impulsive, hyperactive behavior. The child has an unusually short attention span, and in spite of normal or superior intelligence is frequently an underachiever in school. Amphetamines have the paradoxical effect in such children of acting as a tranquilizer, increasing attention span, and decreasing hyperactive behavior. Considerable professional controversy and widespread public attention have recently been focused on drug treatment for the hyperkinetic syndrome. However, the main issue relates more to the prevalence of the syndrome and reliable diagnostic criteria than to the efficacy of amphetamine in its treatment. Caffeine has been reported in recent studies to be as effective as amphetamine in treating hyperkinesis with fewer undesirable side effects.

Narcolepsy

This is a very rare disorder in which the individual experiences frequent episodes of sudden, uncontrollable desire for sleep, sometimes as many as a hundred times a day. Amphetamine was first used to treat narcolepsy in 1955, with the discovery three years later that acute paranoid psychosis was a side effect to be guarded against.

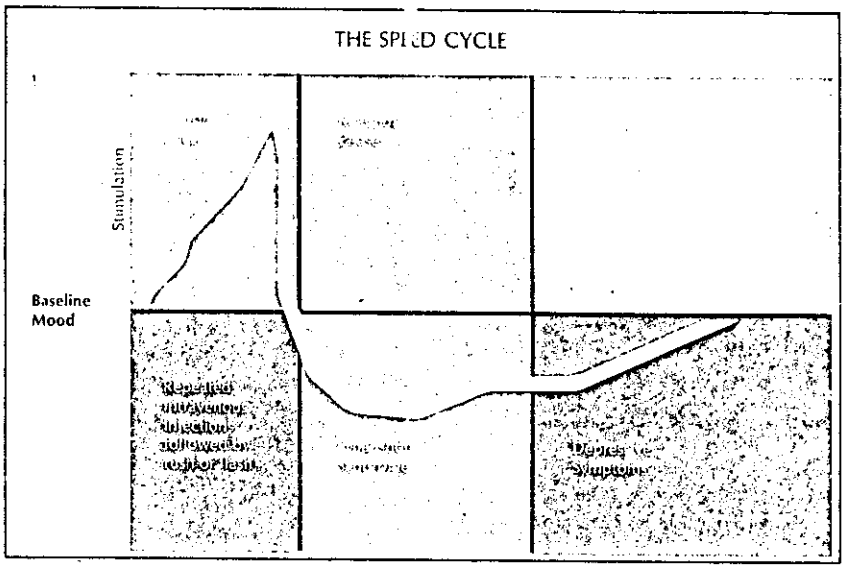
Non-Medical Use of Amphetamines

1. *Intermittent low-dose use*

Many individuals occasionally take 5 to 20 mg of amphetamines orally to allay fatigue, elevate mood while doing an unpleasant task, produce prolonged wakefulness, help recover from a hangover, or to "get high." Often the pills are obtained from friends, who more than likely obtained them by prescription for weight reduction. Only rarely are they purchased on the black market. Individuals may be any age and usually have little interest in amphetamine use as a "life style."

2. *Sustained low-dose use*

In this pattern, the individual obtains amphetamine pills from his doctor for weight control, but takes the pills 3 to 4 times a day for the stimulation and euphoria produced by the drug. He may develop a strong psychological dependence on the pills and feel that he cannot get along without them. If he stops taking daily amphetamines, withdrawal depression occurs. Since the depression can be easily and temporarily



"cured" by renewed dosage of pills, the dependence becomes difficult to break. Some individuals gradually increase their daily intake of amphetamines and begin taking sleeping pills or alcohol to relieve the insomnia which usually develops. The development of this "upper-downer" cycle is especially dangerous because it increases the probability of overdose.

3. *High-dose intravenous methamphetamine use*

This is the widely publicized pattern of "street" amphetamine abuse. Although the pattern involves fewer individuals than does oral amphetamine use, the bizarre behavior and dress of the intravenous "speed freak," the high incidence of violent behavior, and the resultant medical complications have focused disproportionate public and professional attention on this pattern. A major motivation is the "flash" or "rush," an intense feeling of pleasure immediately following the injection. During a speed binge, an individual may inject between 500 and 1,000 mg of methamphetamine every 2 or 3 hours; by contrast, the usual prescribed dose ranges between 2.5 and 15 mg per day. The substance, called "crank" or "crystal," may consist of illegally produced methamphetamine or dissolved prescription tablets.

David E. Smith (1969) described the "speed cycle" in terms of an "action-reaction" phenomenon, illustrated in the accompanying diagram. With the onset of the drug effect, one sees the "action phase" or "high." During the action phase the individual is hyperactive and may continue to shoot methamphetamine many times a day in order to perpetuate his "high" when it begins to wear off. Because of the marked stimulation the individual is unable to sleep, and because of the anorectic effect may not eat. As the individual accumulates progressively larger amounts of methamphetamine within his body, he frequently develops extreme suspiciousness which merges into an overt paranoid psychosis. The high energy level associated with paranoia results in unpredictable behavior and, sometimes, violent behavior.

For a variety of reasons—fatigue, paranoia, or simply the lack of the drug—the individual eventually stops injecting methamphetamine and the "reaction phase" begins. As the effects of the amphetamine wear off, the individual lapses into a period of exhaustion and may sleep continuously for 1 or 2 days. Following this exhaustion phase, the individual often has a prolonged and severe depression which may last days to weeks.

High-dose intravenous methamphetamine

In an analysis of 310 cases of high-dose methamphetamine abuse, David Smith (1970) divided psychological adverse reactions into five categories:

1. Anxiety reactions, in which the individual becomes fearful and tremulous with concerns about his physical well-being.

2. Amphetamine psychosis, in which the individual misinterprets the actions of others, hallucinates, and

becomes unrealistically suspicious.

3. Exhaustion syndrome, an intense feeling of fatigue and need to sleep following the stimulation phase.

4. Prolonged depression.

5. Prolonged hallucinosis, in which the individual continues to hallucinate after the drug has been metabolized.

The Amphetamine Withdrawal Syndrome

For many years the medical consensus was that amphetamines were not addicting because of the supposed absence of a withdrawal syndrome. Part of the difficulty lay in disagreement over the definition of addiction, but a greater part was the failure to recognize the withdrawal syndrome because of its qualitative difference from the narcotic or general depressant withdrawal syndrome. The amphetamine withdrawal syndrome is characterized by apathy, decreased activity, and sleep disturbances which can last for weeks or months. Another withdrawal sign was noted by Oswald and Thacore (1969). Following abrupt withdrawal of large doses of amphetamines, an increase in the percentage of rapid eye-movement sleep (REM) occurred. REM returned to normal when amphetamine was given, but increased again when amphetamine was withheld. This phenomenon provides additional evidence for the existence of physical dependence. Since suicides have occurred during amphetamine withdrawal, doctors have been advised to bring about withdrawal slowly in a controlled environment.

Legal Status

Since its emergence in an over-the-counter inhaler in the 1930's, amphetamine has been placed under closely defined controls. The Comprehensive Drug Abuse Prevention and Control Act of 1970 established five schedules, or lists, of controlled substances, ranging downward in their potential for abuse. Amphetamines were first placed in Schedule III, but on July 7, 1971, were moved to Schedule II. According to the Act, this schedule is designed for drugs which have a high potential for abuse; which have a currently accepted medical use in treatment in the United States or a currently accepted medical use with severe restrictions; or which may lead to severe psychological or physical dependence. Other drugs in Schedule II include certain opiates, methadone, methamphetamine, and cocaine.

The Act also gives the Attorney General authority to regulate "the registration and control of the manufacture, distribution, and dispensing of controlled substances." Specifically, every manufacturer, distributor, or dispenser of amphetamines must register annually with the Attorney General. "Dispensers" include scientists who are conducting research, as well as doctors and pharmacists. In addition, certain requirements for labeling and packaging amphetamines —such as securely sealing their containers—are in effect.

A third significant control is that the Attorney General determines annual production quotas for certain controlled substances. It had been estimated that before quotas, some 8 billion doses of amphetamines had been manufactured annually in the United States. During 1972, production quotas were established, reducing production approximately 80 percent below 1971 levels.

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A problem now being considered in most of the capitals of the free world is whether the benefits derived from amphetamines outweigh their toxicity. It is the consensus of the world scientific literature that the amphetamines are of very little benefit to mankind. They are, however, quite toxic.

—John D. Griffith (1972)

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The question of whether or not amphetamines are addictive or habituating is a matter of semantics. Habitual users develop a marked psychological dependence on the drug and evidence definite withdrawal symptoms, including tenseness, anxiety, tremor and nervousness, which may be of such degree as to incapacitate the user during his period of withdrawal.

—Edward R. Bloomquist (1970)

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It is generally felt that the behavior of heavy amphetamine users is consistent with the stereotype of the "dope fiend." From all evidence, amphetamines tend to set up conditions in which violent behavior is more likely to occur than would be the case had an individual not used it. Suspiciousness and hyperactivity may combine to induce precipitous and unwarranted assaultive behavior.

—John C. Kramer (1967)

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The New Chinese Connection

In the United States: The Arrest of Far Eastern Traffickers

by Ross M. Riley
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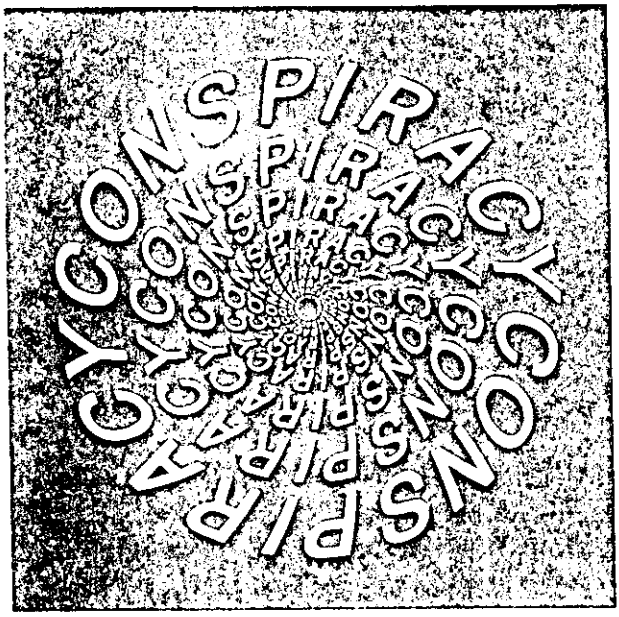


Five secret indictments were unsealed recently in the Southern and Eastern Districts of New York, charging 61 persons, most of them denationalized Chinese, with conspiring to import and distribute heroin in the United States and Canada. In a coordinated array of arrests that began on November 19, the Drug Enforcement Administration—acting together with the Immigration and Naturalization Service and the Royal Canadian Mounted Police—closed down the most thorough investigation of the Far Eastern narcotics traffic ever conducted in this country. But in doing so they opened up to public inspection a disconcerting prospect: Asian heroin on the horizon.

The cultivation of opium poppies in Asia is not a new phenomenon. Southeast Asia is, in fact, the oldest, and still by far the largest, opium-producing area in the world. According to "World Opium Survey 1972," published by the Cabinet Committee on International Narcotics Control, output of illicit opium in the remote, protected, and almost autonomous highlands of "The Golden Triangle" exceeds that of all other countries in the world combined.

As old as the Asian opium traffic are the traditions of the master traffickers themselves. They are, with few exceptions, Chinese merchants, residing not only in Bangkok, Hong Kong, and Singapore, but in San Francisco, New York, Vancouver, and major cities around the world.

Dealing with one another in multiple illicit enterprises, they maintain close ties protected by power of immense wealth, their only loyalty to themselves, their only commitment to what they regard as venture capitalism. Penetration of this caste without a country has heretofore presented almost insurmountable difficulties.

On Christmas Eve, 1972, federal narcotics agents arrested a Danish seaman, John Thomsen, in Brooklyn, New York, in possession of 18 pounds of Asian heroin. Documented information by DEA's regional office in New York revealed that as much as a thousand pounds of Asian heroin had been smuggled into New York City by independent seamen during the period 1971-1972. In September 1973 the Special Assistant for Conspiracy Operations called for an intensive case review of Far Eastern traffickers. I was then serving as Group Supervisor of the Regional Conspiracy Group in New York. Here, in summary, is the still fragmentary situation as we reported it at that time:

- Purchase or seizure by DEA of 63.5 pounds of Asian heroin from Chinese violators—21 percent of the total amount recovered from the region in 1972.
- Seizure by the Bureau of Customs of another 40 pounds of Asian heroin bound for New York City.
- Seizures in Holland and Canada of 55 pounds of Asian heroin bound for New York City.
- Deliveries over an 18-month period of 700 pounds of Asian heroin to an Italian violator.
- DEA undercover negotiations with a Cuban of Chinese extraction for an initial shipment of 15 to 20 pounds of Asian heroin with regular shipments in 100-pound lots to follow.

The report concluded:

Southeast Asian traffickers are completely ignorant of federal conspiracy laws; they feel they cannot be arrested unless they participate directly in the sale to an enforcement officer. It should be noted, however, that to date it has been unusual to get a Far Eastern defendant to testify in court.

In January 1974, Central Tactical Unit 3 was formed under the Special Assistant for Conspiracy Operations to direct an Administration-wide search for demonstrable evidence. I was assigned to DEA Headquarters to head the unit, which included Group Supervisor Thomas O'Grady and Special Agent David Samuel, and later Special Agent Matthew Maher. We began slowly to plot the pattern of known events. It was at this point that the tenuous ties of unrelated intelligence began to acquire the strength of an inextricable web of evidence that would reach around the world. Into this net were drawn a number of the most notorious Chinese traffickers who had been operating for years beyond the reach of the law. How to get a Far Eastern trafficker to testify in court turned out to be less difficult than had been foreseen. Such is the pecking order of prison life that after a year or two they were more than willing to implicate the otherwise invulnerable violators at the top of the organizations directing both supply in Southeast Asia and distribution in North America.

The indictments drawn up under the direction of Paul J. Curran, U.S. Attorney for the Southern District of New York, and David G. Trager, U.S. Attorney of the Eastern District of New York, allege that about 250 pounds of heroin and a hundred pounds of opium were smuggled into North America and distributed in New York, Chicago, San Francisco, Toronto, Montreal, and Vancouver from 1970 to 1972.

About one-third of the defendants are foreign nationals, most of them Chinese traffickers who are responsible for directing the movement of hundreds of pounds of heroin into the United States in recent years. These suppliers and financiers have previously been insulated from police action and prosecution in the sanctuaries they operate in Southeast Asia. The primary purpose of CENTAC 3 was to find a way to bring them to justice. The indictments obtained in New York are the first in a series of carefully planned steps to achieve this end. Extradition or prosecution in their own countries of nationality is the next necessary step. Public exposure attending the outcome of CENTAC 3 should help to achieve this.

In Europe: An Incursion of Asian Heroin

by Michael A. Antonelli
Chief, European Section
DEA Office of Enforcement

A noteworthy trend is rapidly developing on the European drug scene. The previously drug-free capital cities are quickly becoming hubs of activity for groups of "ethnic" Chinese engaged in the traffic of heroin smuggled from Hong Kong and other principal cities in the Far East. Chinese criminal elements of Amsterdam, Brussels, and London, once content to reap profits from their prostitution and gambling interests, have now shifted their efforts to the marketing and distribution of Asian heroin throughout Western Europe.

In March 1972 U.S. and Netherlands narcotics officials made the first successful penetration of this traffic, culminating in the seizure of more than five pounds of white Asian heroin in Amsterdam. Included in the list of defendants was the owner of a Chinese restaurant in Breda.

One of the earliest cases involving this traffic occurred in London during June 1972 when H.M. Customs Service searched the bedrolls of two Chinese residents of Hong Kong upon their arrival at Heathrow Airport. The search uncovered 16 pounds of No. 3 heroin.

In early 1973 U.S. and European narcotics officials identified Amsterdam as the main distribution point for Asian heroin in Western Europe. As a result of a case initiated in New York, DEA identified an extremely active group of Chinese traffickers who were operating in The Hague, Rotterdam, and Amsterdam. In March two DEA agents traveled to Netherlands and conducted an investigation of eight members of the organization. It was learned that the leader was planning to sell 30 pounds of brown No. 3 heroin. Upon delivery three defendants were arrested in Amsterdam by Dutch authorities. Since Netherlands law does not recognize the act of conspiracy, the remaining defendants could not be charged. During their investigations the agents learned that the group was seeking to establish a link for Asian heroin distributors connecting Hong Kong, Europe, and the United States.

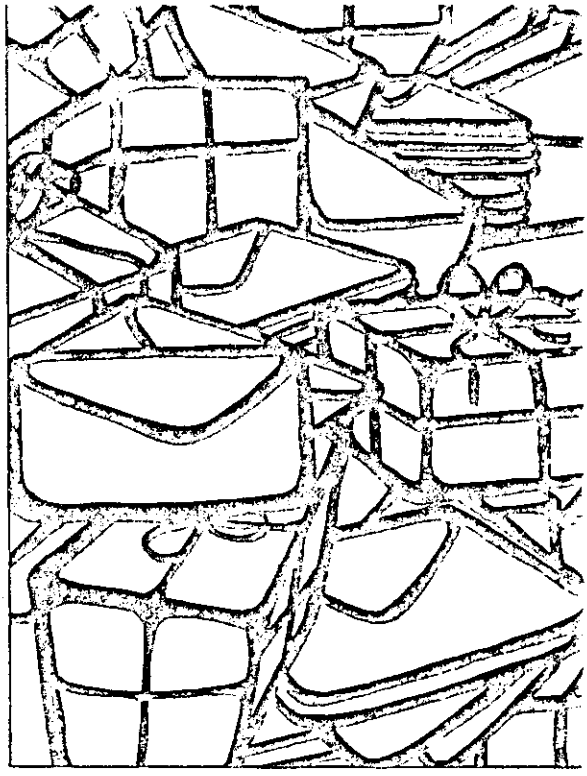
After the successful penetration of the Amsterdam group, DEA and foreign authorities recognized that the traffic pattern had been shifting from Paris to Brussels, then back to Amsterdam like a fast-moving shadow. In mid-1973 Chinese groups were dispatching the majority of their couriers from the Far East via commercial aircraft. At a time when a fairly certain pattern and trend was identified, the shadow shifted to Hamburg where, on August 19, 1973, German customs officials and the Hamburg police seized 11 pounds of No. 3 heroin from a Chinese seaman who had concealed a part of the load on his person and the rest of it in his cabin.

During the fall of 1973 DEA, in concert with police and customs officials in France, Germany, Belgium, and Netherlands, continued to put forth concentrated efforts to break the links which were then connecting the Chinese traffic between The Orient and Europe. On August 30, 1973, a routine check of a Chinese resident of Singapore on his arrival at Kastrup Airport in Copenhagen resulted in the seizure of seven pounds of No. 3 heroin. In an effort to avoid suspicion during his travels, he had flown from Singapore via Moscow to Copenhagen. After a second seizure in Copenhagen in December 1973, the groups sent their couriers on their previous travel pattern from Hong Kong via Paris to Amsterdam.

On January 21, 1974, a seizure of heroin of Asian origin in Europe was made at Orly Airport, Paris. During a routine inspection of a Chinese traveler's suitcase, a large number of camphor balls were uncovered, evidently to inhibit a detector dog's ability to locate the seven pounds of No. 3 heroin which had been secreted in the suitcase's lining. Two couriers were arrested. One of them had previously visited Norway, Denmark, and Amsterdam, the pivotal point of this traffic.

Since July 1972 European police and customs officials have arrested 62 Chinese traffickers and seized a total of 178 pounds of Asian heroin.

In a few years heroin addiction has increased in the principal cities of Netherlands, France, Germany, and Italy. As New York has historically been the primary distribution center for heroin here, Amsterdam has become the focal point for this traffic which thus far has been adequately contained within Europe. In the coming months DEA and foreign counterpart officials will continue to apply resources to strike at this traffic or contain it at a level where it hopefully will not be able to spread towards North America.



Narcotics in the Mail Stream

by William J. Cotter
Chief Postal Inspector
U. S. Postal Service

"The Inspection Service has investigative jurisdiction whenever the mails are used in furtherance of an illegal scheme, but our efforts would be sorely limited without the cooperative quid pro quo which exists today among all law enforcement agencies."

When the Drug Enforcement Administration was established on July 1, 1973, its creation underlined the President's determination to win the battle against illicit narcotics traffic in the United States. Here, for the first time, was a consolidation of various agencies into a single comprehensive organization, "empowered to investigate and prepare for prosecution all suspects for violation under the federal drug trafficking laws."

As with other segments of the law enforcement community, we in the Postal Inspection Service applauded the creation of DEA since our participation in narcotics investigations has always been a cooperative effort with the other agencies which prosecute under statutes within their own investigative jurisdiction. Although the yearly number of narcotics and drug cases which the Inspection Service opens is but a small portion of our total criminal investigations, the fact remains that today one out of every five mail thieves is a narcotics user. Over 27 percent of all persons arrested for postal holdups are narcotics users. This dependence on drugs has become a major cause of postal crime since the unguarded letter box, especially in large urban areas, represents an attractive target to the criminal who must support his addiction by theft of checks and money from the mail.

In the span of just a few short years, our investigative involvement in narcotics and dangerous drug cases has increased tremendously. Since use of the mails in any unlawful activity is always a matter of investigative

William J. Colter

concern to the Postal Inspection Service, we have for many years cooperated with other federal and local authorities in their efforts to combat the pernicious problem of traffic in drugs. In the past, with the exception of the routine referrals of intelligence to other agencies having more explicit statutory responsibility in this area, our direct participation was confined to an occasional case where the mails were used to transport the drugs. But during the last few years, when the flow of narcotics into this country reached floodtide proportions, our efforts increased proportionately. Witness the fact that in 1967 we investigated 142 drug cases in collaboration with other agencies and made only 68 arrests in postal-related cases. By contrast, in the last fiscal year, our narcotics investigations totaled 3,291, resulting in 912 arrests and 845 convictions. This comparison represents a tremendous increase in the man-hours which our inspectors have devoted to this type of crime. Unhappily, it is also indicative of how serious the problem has become in our society today.

I would like briefly to outline how the inspection service with a complement of some 1,700 inspectors meets not only its unique postal-related responsibilities but also cooperates with other federal law enforcement agencies in a broad exchange of information and assistance.

Our activities fall into three principal categories:

1. The enforcement of postal laws and federal statutes through the investigation and apprehension of persons committing crimes against the Postal Service. This activity occupies over 60 percent of our time.
2. The protection of mail, postal funds, and property through a wide variety of physical security programs and the presence of a uniformed Security Force.
3. The internal audit of all Postal Service financial and non-financial operations.

Some time ago we calculated there were roughly 880 million *government* checks alone mailed each year and that the value of just Federal Reserve mailings in one year approximated $25 billion! Obviously, this volume offers an attractive target to those who find stealing from the mails easier than robbing a bank. Add to this the 38,536 postal facilities throughout the United States and the magnitude of our responsibilities comes into sharper focus. To not only halt but also reduce some of the spiraling losses which the Postal Service was experiencing from criminal attacks just a few years ago, we had to take a new and hard look at our traditional approach to problems. Historically, ours was a role which concentrated primarily on the investigation and apprehension of criminals. Now we had to broaden this approach to include a greater emphasis on the *protection* of the mail, our employees and facilities, through the prevention of postal crimes. This decision resulted in the implementation of various new programs designed to strengthen the overall security given the more than 90 billion letters and parcels which move through the mail stream each year.

Perhaps the greatest innovation in terms of numbers was the creation of a uniformed and what has become today a highly efficient Security Force, comprising some 2,600 men and women. The presence of this guard force at crime-prone locations throughout the country has not only helped to deter would-be criminals; it has also had an incalculable effect on employee safety and morale.

In addition to a stepped-up effort to provide additional security through the installation of improved security containers and intrusion alarms, an intensified investigative effort led to the apprehension of several organized groups responsible for the rash of postal burglaries which plagued us in the late 1960's and early 1970's. As a consequence, we were able to reduce losses due to postal burglaries from a 1970 high of $3.2 million to just $197,000 last fiscal year. Additionally, losses of registered mail at airports alone totaled over $70 million during the period 1967-1970. Through a coordinated program of segregating such mail and conveying it under the aegis of the Security Force, these losses were reduced to just over 400,000 by the end of fiscal year 1973. This decrease has continued to a point where today such losses of registered mail are negligible.

It is in the area of what we call "prohibited mailings" or the criminal misuse of the mails, through such illegal means as fraud, extortion, obscenity and bombs, that our involvement in illegal narcotics traffic lies. As with the narcotics problem, the ever-present threat of letter and parcel bombs passing through the mail stream offers a good example of how we cooperate, not only with federal, state, and local law enforcement officials but with the international community as well, in the sharing and exchange of intelligence and investigative techniques.

The Inspection Service has investigative jurisdiction whenever the mails are used in furtherance of an illegal scheme, but our efforts would be sorely limited without the cooperative quid pro quo which exists today among all law enforcement agencies. For example, utilization of the Federal Bureau of Investigation's National Crime Information Center provides our inspectors with invaluable and instantaneous data in their criminal investigations. Our role in the overall enforcement of the Comprehensive Drug Abuse Prevention and Control Act of 1970 is one of cooperation with DEA, which has primary responsibility for its implementation. The U.S. Customs Service cooperates in the enforcement of those provisions relating to the importation of substances controlled by the Act, and we are called upon from time to time to assist in arranging for controlled deliveries of mail suspected of containing contraband other than drugs. It is a system where we, together with Customs, assist DEA, the investigative agency having primary jurisdiction over drug law violations.

I am both gratified and proud that the spirit of cooperation among so many agencies of government, each with its own administrative peculiarities and sometimes unique personalities, continues to work so well. And I believe it is a tribute to the many people involved in solving the dangerous and pressing problems of narcotics control that individual issues can be reconciled to the general good which is attainable only through the ultimate apprehension and conviction of those responsible for this evil.

Unquestionably, the spreading addiction to drugs throughout our country, in many cases involving the very young, is of serious concern to us all. Any effort to reach and obstruct the supplies of illegal drugs demands the fullest cooperation of all law enforcement organizations working with the problem. You have my pledge that the Inspection Service will continue to support and work closely with the Drug Enforcement Administration in its efforts to carry forward the programs designed to curb the flow of narcotics in our country.

Trafficking Behind Bars...

Tijuana, Mexico—Mexican Federal Police supported by army troops put an end to an unusual narcotics conspiracy in the predawn hours of October 17 when they stormed the La Mesa State Penitentiary.

Inside the bars, they arrested three prisoners now well known to the press—Helen Calderon Hernandez, her husband Roberto, and his brother Juan.

In the quarters of Mrs. Hernandez, the authorities seized $80,000 in U.S. currency and about $100,000 worth of jewelry. They also found records revealing that the ring, operating for almost four years within prison, had been grossing about $3 million a month on the movement of heroin, cocaine, marihuana, amphetamines and other drugs into the United States.

Roberto and Helen Hernandez

The records documented the existence of a network of drug traffickers extending from cocaine producers in South America to narcotics dealers in Canada. They further confirmed connections with the French Corsican group in South America, headed by the now imprisoned Auguste Ricord, which moved tons of French heroin into the United States in the 1960's.

About a month after the raid on the La Mesa State Penitentiary, Mexican authorities arrested Patricia Evelyn Torres de Hernandez, wife of Juan, in a Tijuana motel as she was delivering a kilo of heroin to a U.S. customer. In her possession were found other family records documenting extensive real estate holdings and a balance in Hernandez accounts of about $20 million in cash.

The Hernandez ring is no stranger to the Drug Enforcement Administration or Mexican authorities. For more than a decade it has been the target of state and local, as well as federal, agencies in Southern California. In 1968, Mrs. Hernandez, her husband Roberto, his brother Juan, and 48 others were indicted in San Diego after the seizure by San Ysidro Customs officials of a million-dollar shipment of heroin and cocaine. A number of those charged pleaded guilty. But the Hernandezes fled to Mexico. They never stood trial in the United States.

In 1970, the Hernandez trio and seven others were arrested after investigators traced a 10-pound shipment of heroin to their hillside estate in Tijuana. Mexican police said they found in it an arsenal of illegal weapons, $25,000 in cash, 31 uncashed money orders, and a heroin laboratory stocked with $2.4 million worth of pure heroin. Convicted on narcotics charges in a Mexican Court they have been serving 11-year sentences ever since.

The latest and, it is hoped, the last chapter of the long Hernandez case history has been in preparation for months at the DEA Regional Office in Los Angeles. On the basis of far-reaching intelligence as well as local undercover buys, DEA agents pieced together a detailed picture of transborder trafficking directed by the Hernandezes within the snug sanctuary of their prison cells. The evidence was turned over to Ramon Herrera Esponda, special assistant to Mexican Attorney General Pedro Ojeda-Paullada. Acting on orders from the top, Esponda permanently sealed off the penitentiary from other traffickers at large. But the case is not over yet. Reverberations from it will be heard for months to come.

—Joe Flanders

and While Awaiting Trial

Chicago, Ill. - Television viewers in living rooms across the country recently witnessed sale after sale of heroin recorded by cameras hidden in an apartment overlooking a backyard in the city's North Side.

While a team of DEA agents with a television crew from the local CBS station filmed the macabre scene, one addict after another entered the backyard by way of an alley and passed money through a chain-link fence in exchange for a balloon of brown heroin.

Among them was a young girl, apparently still in her teens. After a few words with the dealer, she too passed her money, and was handed a brightly colored balloon. Like many of the others, she put it in her mouth for safekeeping. At that moment she was grabbed by the throat and forced to the ground by a male addict twice her size. After choking her for several seconds to force open her mouth, he scooped out the heroin-laden balloon and fled down the alley.

Shortly after this incident, DEA agents and Chicago police moved in and rounded up the dealer and a number of associates who had been a primary source of supply for addicts in the area. One of them was Israel Gonzales, 30, owner of the El 7 DeCopas Club on North Sheffield Street.

On arraignment Gonzalez was able to post $10,000—10 percent of the $100,000 bond set by the court—and was freed to await trial. In November he went to trial and was found guilty on charges of distribution of heroin.

Before Gonzalez was given his day in court, however, while still out on bail, he had another encounter with DEA agents. On September 24 he met with undercover agents outside his club to make a deal for a multi-kilo quantity of heroin. They showed him a $50,000 flashroll. He told them that the heroin had recently arrived from Mexico and that he would sell it for $16,000 a kilo.

The agents then accompanied Gonzalez to an apartment building that he owned on West Berry Street where Julio Santana, 33, and Ramon Castill, 49, awaited their cut on the deal. Santana was later identified as the source of the supply. After arresting the trio, the agents seized more than three pounds of heroin.

This was the final step in a three-month investigation which established that Gonzalez had graduated in his drug dealings from street-level supplier to wholesaler. It is estimated that this organization was selling as much as seven pounds of heroin a week in the Chicago area.

Gonzalez is now being held on $500,000 cash bond while awaiting sentence on the first conviction, which carries a maximum penalty of 15 years and $25,000. Conviction on a second offense doubles the penalties.

"The heroin dealer is after profits and he will take the risk even though he has been trapped once," commented Jerry N. Jenson, DEA's former Chicago Regional Director. "We have found that if he is out on bond, it is only a matter of time before he is back in the traffic to cover his legal expenses and make as much as he can."

To underscore the problem Jenson cited another recent example in the Chicago area. On November 26, 1974, Willie Rogers was convicted on narcotics charges in Federal Court and sentenced to two years. He was given the first week in December to put his affairs in order before beginning to serve his sentence. That very evening, in a roundup of a ring that had a major share of the wholesale heroin and cocaine market in the Chicago area, DEA arrested 27 suspects, among them Willie Rogers. While awaiting his initial sentence, he had sold heroin to an undercover DEA agent.

Hank Price

Editor's Note: *Israel Gonzales on January 6 was sentenced to 10 years in prison. In imposing the sentence, Judge Frank J. McGarr of the Federal District Court expressed regret for the three-to five-year sentences set earlier for six accomplices who had pleaded guilty without going to trial. After viewing five hours of videotapes showing Gonzales and other defendants selling balloons of heroin in the backyard of his home, Judge McGarr said, "The sentences were light—much too light in view of what I now know of the operation."*

Legal Corner

Possession with Intent to Distribute

A number of federal cases have recently been decided regarding an important drug offense in the United States Code: possession with intent to distribute a controlled substance as contained in 21 U.S.C. 841(a)(1).

Recent cases interpreting this statute have reached constitutional dimensions. In *United States* v. *King*, 485 F. 2d 353 (C.A. N.M. 1973), the court held that 21 U.S.C. 841(a)(1) was a valid exercise by Congress of a power vested in it by the Constitution. The decision goes on to hold that "possession with intent to distribute" in 841(a)(1) is not unconstitutionally vague, and that the question as to the quantity which would permit the inference that the possessor had an intent to distribute is evidentiary in nature and necessarily depends upon all the facts and circumstances of the case on hand. See also *United States* v. *Dupart*, 483 F. 2d 1393 (C.A. La. 1973).

Possession with intent to distribute means the actual constructive or attempted transfer of a controlled substance, whether or not there exists an agency relationship. *United States* v. *Marsullo*, 489 F. 2d 217 (C.A. N.Y. 1973). To violate this section of the Controlled Substances Act one must knowingly and intentionally possess a controlled substance and intend to distribute it. Both the *possession* of the contraband and the *intent to distribute* it are elements of the offense. *United States* v. *Hutchinson*, 488 F. 2d 484 (C.A. Minn. 1973).

Possession

Possession may be actual or constructive, and either sole or joint. In *United States* v. *Hutchinson*, *supra*, "constructive possession" has been defined as knowingly having both the power and intent at a given time to exercise dominion or control over the property. *Rodella* v. *United States*, 286 F. 2d 306 (C.A. Calif.). The following cases illustrate the fine line of constructive possession:

United States v. *Horton, 488 F. 2d 374 (C.A. Tex. 1973)*

Although demonstrating the defendant's proximity to an illegal substance and to a person who did have control over heroin, the evidence was insufficient to sustain a conviction of possessing with intent to distribute since it did not establish any type of working relationship between parties regarding heroin but merely an association.

United States v. *Epperson, 485 F. 2d 514, (C.A. Ariz. 1973)*

Evidence of mere presence at the scene was insufficient without further evidence to establish guilt of marihuana possession with intent to distribute.

United States v. *Martin, 483 F. 2d 974 (C.A. Tex. 1973)*

Evidence of mere presence in a room with a roommate, who was later convicted of possessing mescaline with intent to distribute it, together with indications that the defendant may have had knowledge of the sale of the drug, did not demonstrate that the defendant took an active part in the sale and was insufficient to show constructive possession, dominion, or control over the drug by the defendant.

United States v. *Nunez, 483 F. 2d 453, (C.A. Ariz. 1973) cert. denied 94 S. Ct. 594*

Evidence of ownership of the vehicle that stored marihuana, consent given for its use, the raising of bail for a co-conspirator, and a phone call made during negotiations was sufficient to sustain a conviction for possession with intent to distribute.

United States v. *Doran, 483 F. 2d 369 (C.A. Mass. 1973)*

Evidence of an attempted phone call to a co-conspirator, annoyance at the lateness of the co-conspirator during a sale of heroin, use of the defendant's residence for three heroin transactions, together with the co-conspirator's statement was sufficient to sustain a conviction for possession with intent to distribute.

United States v. *Irion, 482 F. 2d 1240 (C.A. Calif. 1973)*

Evidence in a prosecution of the defendant on charges of illegal importation and possession with intent to distribute marihuana was sufficient to sustain a

conviction of the defendant, who was aboard a sailboat which traveled from Mexico to California without clearing customs and which carried a large amount of marihuana. See *United States v. DeBerry*, 487 F. 2d 448 (C.A. N.Y. 1973) for a similar case involving an airplane.

United States v. Suarez, 487 F. 2d 236 (C.A. Fla. 1973)

Evidence that the defendant was seen entering and leaving the house of a known narcotics dealer carrying a small paper bag was insufficient to sustain a conviction for possession with intent to distribute.

United States v. Ogden, 484 F. 2d 1274 (C.A. Calif. 1973)

Evidence that the defendant had been aware of the activities of her husband in growing and harvesting marihuana, had been seen traveling with him at the time of their arrest, and had in her possession claim checks for baggage containing either contraband or paraphernalia for making marihuana bricks was sufficient to sustain a conviction for possession with intent to distribute.

McDowell v. United States, 472 F. 2d 1157 (C.A. Pa. 1973)

Evidence demonstrated that control of the drug need not be exclusive to show constructive possession but must be more than a mere proximity.

United States v. Davis, 480 F. 2d 725 (C.A. Ind. 1973)

Evidence that the defendant lived in an apartment where heroin and marked money were found in plain view, together with testimony of an informer, was sufficient to sustain a conviction for possession with intent to distribute.

Walker v. United States, 489 F. 2d 714 (C.A. Mo. 1974)

Evidence that the defendant had stayed at an apartment where heroin was found in plain view, together with a statement from the resident of the apartment proclaiming innocence, was sufficient to show that the defendant had dominion and control of the heroin.

Intent to Distribute

The other crucial element in 21 USC 841(a)(1) is the intent to distribute a controlled substance. The validity of establishing intent to distribute depends upon whether the amount and value of a controlled substance will support an inference of an intent to distribute as distinguished from mere possession for personal use. *United States v. Blake*, 484 F. 2d 50 (C.A. Mo. 1973). Other factors disclosing an intent to distribute are the purity of the substance, the packaging of the product, the presence of cutting or manufacturing materials, and the physical signs of the defendant's drug use. The following cases illustrate these points:

United States v. Hutchinson, supra

Evidence of large quantities of cocaine found in the defendant's residence could tend to show an intention to distribute cocaine.

United States v. Polite, 489 F. 2d 679 (C.A. Fla. 1974)

Evidence that the confiscated heroin was 94.5 percent pure was relevant to whether possession was with intent to distribute or for personal use of the defendant.

United States v. Martinez, 434 F. 2d 199 (9th Cir. 1970)

Evidence that the defendant possessed 120,000 barbiturate tablets and 30,000 amphetamine tablets was by itself sufficient to sustain a conviction of possession with intent to distribute. See also *United States v. Ortiz*, 445 F. 2d 1100 (10th Cir. 1971), 8.5 pounds of methamphetamine.

United States v. Moses, 360 F. Supp. 301 (D.C. Pa. 1973)

Evidence that the defendant had 51 glassine packets containing 22 grams of heroin, that he was not a user of heroin, that the heroin was packaged in the manner commonly used in the illegal street distribution of drugs, and that he was armed was sufficient to establish beyond a reasonable doubt that the defendant intended to distribute the heroin in his possession.

What Makes Kenneth Run?

Surveillance photograph of Kenneth Garrett (left) and Glen Cheaves, also known as "Bird Dog" (right).

When Kenneth Garrett was 14 years old he came to Detroit with wild ideas on ways to make a fast buck and a yen for fancy cars.

In his school years he managed a string of prostitutes along the bars that line "Cass Corridor," a typical inner-city area inhabited by those on low fixed incomes and frequented at night by loan sharks, gamblers, and narcotics dealers.

The Corridor was Garrett's type of place and over the years he kept it as a base of operations. But it was not long before he moved to a luxury apartment in an upper-middle class neighborhood. Reportedly, he parlayed his earnings into a bankroll of $150,000 by backing a pool hustler.

Within ten years of his arrival Garrett is alleged to have had his own heroin distribution ring that was grossing $6 million a year.

The Drug Enforcement Administration's investigation into Garrett's activities, which began in December 1973, extended through 11 months of 1974. All things considered it was a lucky year for Garrett, who is now safely in custody in spite of a Western-style shootout with fellow traffickers at his apartment on Providence Drive in Southfield.

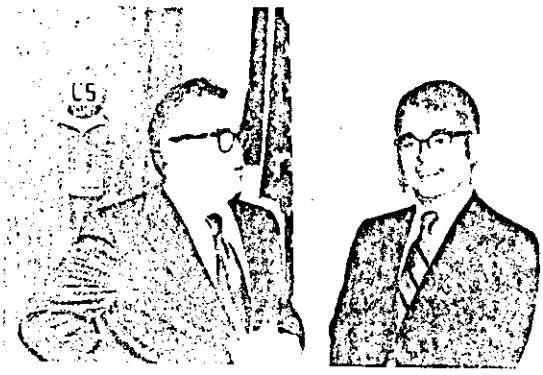
Returning to pick up some clothes before a trip to the West Coast to buy brown heroin, according to intelligence reports, he was carrying $60,000 in cash. A trio of gunmen were waiting for him to emerge from the elevator. But he decided to walk up the stairs. By the time they spotted him he had pulled out a 9 mm 13-shot Browning automatic. When DEA agents arrived on the scene, they counted 14 bullet holes in the walls and ceiling of the hallway.

Meanwhile, a search warrant had already been executed by DEA agents who found lactose, mixers to cut heroin, and traces of heroin in plastic bags on the premises. But more evidence was needed. Garrett continued to operate out of a bar in the Cass Corridor, but he was now extremely cautious. He sold to his customers, mainly street wholesalers, only one-ounce quantities of heroin—approximately 12 percent pure—for $1,300 to $1,400 an ounce. He made deliveries only through his lieutenants. The heroin was contained in heat-sealed bags, and he refused to guarantee the drugs if a seal was broken.

In the early hours of November 27 the final roundup took place. In the Red Dog Bar, Garrett, now 25, his brother Ronald, 24, his top lieutenant Glen Cheaves, 34, also known as "Bird Dog," and eight other ring members were arrested. DEA agents seized a half-pound of heroin, two ounces of cocaine, six guns, $8,000 dollars in cash, and three of Garrett's prized possessions—two 1973 Cadillacs and a 1974 Mercedes-Benz.

The roundup, according to DEA Regional Director Theodore L. Vernier, required the teamwork of federal, state, and local agencies: U.S. Department of Justice Strike Force Attorney Laurence J. Leif; the U.S. Treasury's Bureau of Alcohol, Tobacco and Firearms; the Intelligence Division of the Michigan Department of Internal Revenue; and the Detroit Police Department.

—Hank Price



James P. Hunt (left) with DEA Administrator John R. Bartels, Jr.

For Distinguished Service

James P. Hunt, Assistant Director of the New York Regional Office of the Drug Enforcement Administration, was recently awarded one of the highest honors of the U.S. Department of Justice—the Attorney General's Award for Distinguished Service.

The veteran criminal investigator, who has more than 23 years of experience in federal drug law enforcement, was nominated for the award as a result of "leadership which has inspired his division to initiate an extraordinary number of high-level cases."

In an award ceremony on December 12, Administrator Bartels cited his units as responsible for the arrest of more major violators than any other division in the entire Drug Enforcement Administration.

On the same day a number of others received the DEA Award of Honor. Among them was Rogelio L. Guevara, Special Agent from the Los Angeles Regional Office, who was ambushed by 20 Mexican traffickers and seriously wounded while on duty with "Operation SEAM," a joint U.S.-Mexican task force to control the transborder drug traffic. (Shortly after Christmas, Guevara entered a Los Angeles hospital for surgery on his right eye, which suffered impaired vision as a result of a bullet wound in the head.)

John Moseley, Director of the Miami Regional Office, accepted an Award of Honor on behalf of his entire staff, whose actions in the wake of the disastrous collapse of their office building on August 5, 1974, "exemplified the highest tradition of professionalism and exhibited countless acts of valor." (The accident resulted in the death of eight DEA employees and injury to 14 others.)

For his superior leadership at the scene of the disaster in safeguarding the lives of fellow employees and maintaining the security of the area, the Award of Honor was given to Special Agent Inspector Luke P. Benson.

DEA's highest awards also went to five members of the New York Joint Task Force. New York City Detectives John Copeland and Kevin Daly were honored together with DEA Special Agents John E. Gartland, Peter C. Nies, and Harold A. Rudell.

"On November 8, 1974," said Mr. Bartels, "while conducting a narcotics surveillance, these men observed an armed robbery in progress in New York. One defendant was firing a revolver into the front window of a restaurant. His two accomplices had commandeered an automobile parked at the curb and were holding the driver at gunpoint. The three robbery defendants, after a struggle, were disarmed and placed under arrest—without any of these officers discharging their revolvers."

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CONTROLLED SUBSTANCES

Final 1975 Revised Aggregate Production Quotas in Schedules I and II

Section 306 of the Comprehensive Drug Abuse Prevention and Control Act of 1970 (21 U.S.C. 826) requires the Attorney General to establish aggregate production quotas for all controlled substances in Schedules I and II each year. This responsibility has been delegated to the Administrator of the Drug Enforcement Administration pursuant to § 0.100 of Title 28 of the Code of Federal Regulations.

On May 27, 1975, a notice of the proposed revised aggregate production quotas for 1975 was published in the FEDERAL REGISTER (40 FR 102). All interested parties were invited to comment or object to the proposed aggregate production quotas on or before June 30, 1975. No comments or objections were received.

Therefore, under the authority vested in the Attorney General by Section 306 of the Comprehensive Drug Abuse Prevention and Control Act of 1970 (21 U.S.C. 826), and delegated to the Administrator of the Drug Enforcement Administration by § 0.100 of Title 28 of the Code of Federal Regulations and further, having been duly designated as Acting Administrator by Order No. 607-75 of the Attorney General, dated May 30, 1975, in accordance with the authority stated therein, and pursuant to the authority delegated to the Acting Administrator by § 0.132(d) of Title 28 of the Code of Federal Regulations, and based upon consideration of the factors set forth in 40 F.R. 102, the Acting Administrator of the Drug Enforcement Administration hereby orders that the aggregate production quotas for the controlled substances listed below, expressed in grams in terms of their respective anhydrous bases, be established as follows:

Basic class	Previously published 1975 aggregate production quotas [1]	Newly revised 1975 aggregate production quotas [1]	Net change [1]
Alphaprodine	34,500	47,000	+12,500
Cocaine	600,000	749,000	+149,000
Desoxyephedrine	1,215,374	[2] 1,566,833	+351,459
Dihydrocodeine	771,000	500,000	−271,000
Methaqualone	19,668,335	10,751,000	−8,917,335
Oxycodone	1,765,460	1,540,000	−225,460
Secobarbital	18,450,000	21,918,800	+3,468,800

[1] Expressed in terms of grams of anhydrous base.
[2] Of this, 1,195,000 g are to be used for the production of l-desoxyephedrine for use in the manufacture of a noncontrolled substance ([illegible] g more than the previously published quota) and 371,833 g are to be used for the production of methamphetamine ([illegible] g less than the previously published quota).

This order is effective August 19, 1975.

Dated: August 5, 1975.

JERRY N. JENSON,
Acting Administrator,
Drug Enforcement Administration.

[FR Doc.75-21830 Filed 8-18-75;8:45 am]

METHYLPHENIDATE

Final 1975 Aggregate Production Quota

Section 306 of the Comprehensive Drug Abuse Prevention and Control Act of 1970 (21 U.S.C. 826) requires the Attorney General to establish aggregate production quotas for all controlled substances in Schedules I and II each year. This responsibility has been delegated to the Administrator of the Drug Enforcement Administration pursuant to § 0.100 of Title 28 of the Code of Federal Regulations.

On August 19, 1975, a notice of the proposed aggregate production quota for 1975 for Methylphenidate was published in the FEDERAL REGISTER (40 FR 161). All interested parties were invited to comment or object to the proposed aggregate production quota on or before September 26, 1975. No comments or objections were received.

Therefore, under the authority vested in the Attorney General by Section 306 of the Comprehensive Drug Abuse Prevention and Control Act of 1970 (21 U.S.C. 826), and delegated to the Administrator of the Drug Enforcement Administration by § 0.100 of Title 28 of the Code of Federal Regulations and further, having been duly designated as Acting Administrator by Order No. 607-75 of the Attorney General, dated May 30, 1975, in accordance with the authority stated therein, and pursuant to the authority delegated to the Acting Administrator by § 0.132(d) of Title 28 of the Code of Federal Regulations, and based upon consideration of the factors set forth in 40 F.R. 102, the Acting Administrator of the Drug Enforcement Administration hereby orders that the aggregate production quota for the controlled substance listed below, expressed in grams in terms of anhydrous base, be established as follows:

NOTICES

SCHEDULE II

Basic class:	*Granted—1975*
Methylphenidate	1,240,000

This order is effective October 14, 1975.

Dated: October 7, 1975.

HENRY S. DOGIN,
Acting Administrator,
Drug Enforcement Administration.

[FR Doc.27566 Filed 10-10-75;8:45 am]

notices

CONTROLLED SUBSTANCES IN SCHEDULES I AND II

Final 1976 Aggregate Production Quotas

Section 306 of the Comprehensive Drug Abuse Prevention and Control Act of 1970 (21 U.S.C. 826) requires the Attorney General to establish aggregate production quotas for all controlled substances in Schedules I and II each year. This responsibility has been delegated to the Administrator of the Drug Enforcement Administration pursuant to § 0.100 of Title 28 of the Code of Federal Regulations and has been further delegated to the Acting Administrator by virtue of his designation as such by Order Number 607-75 of the Attorney General, dated May 30, 1975 and pursuant to the authority delegated to him by § 0.132(d) of Title 28 of the Code of Federal Regulations.

On August 26, 1975, a notice of the proposed aggregate production quotas for 1976 was published in the FEDERAL REGISTER (40 FR 37240). All interested parties were invited to comment or object to the proposed aggregate production quotas with these comments or objections to be received by September 30, 1975.

Mallinckrodt, Inc. of St. Louis, Missouri submitted comments relative to the proposed aggregate production quota for Thebaine (for sale). Mallinckrodt commented that the proposed quota does not permit the conversion of all Thebaine derived from the processing of raw opium to a stable form. As a result of this valuable quantities of Thebaine would be lost which could be converted to medicinal Hydrocodone or Oxycodone, if the Thebaine were processed to a stable form.

Endo Laboratories, Inc. of Garden City, New York also commented that the proposed aggregate production quota for Thebaine (for sale) will not permit the full recovery of Thebaine from gum opium and poppy straw which is processed in the United States.

Western Fher Laboratories of Ponce, Puerto Rico through their counsel Kleinfeld, Kaplan, and Becker of Washington, D.C. have commented that the proposed aggregate production quota for Phenmetrazine is inadequate to provide for the estimated medical needs of the United States for 1976.

Winthrop Laboratories, Division of Sterling Drug Inc. of Rensselaer, New York has advised that it is their opinion that the proposed aggregate production quota for Pethidine is insufficient for 1976. The firm further advised that the underlying reason for their opinion may be related to the fact that their 1975 and 1976 production cycles have been recently changed.

Pennwalt Corporation of Rochester, New York has commented that the Drug

Enforcement Administration should consider building into the aggregate production quotas an amount to be available to manufacturers later in the quota year, which would allow the Drug Enforcement Administration more flexibility than it currently has and would obviate the administrative time delay which would be encountered by both the Drug Enforcement Administration and individual companies by having to republish in the FEDERAL REGISTER revised aggregate production quotas, when increases of the aggregate production quota are warranted.

Ciba-Geigy Corporation (Ciba) through their Attorney William Ragolia, Jr. filed a comment relative to the proposed aggregate production quota for Methylphenidate for 1976. Ciba requested that the Acting Administrator defer establishing the 1976 aggregate quota for Methylphenidate pending the outcome of Administrative Hearings with reference to the registration of Importers of basic class Methylphenidate (see 40 FR 37060–61, August 25, 1975). It is Ciba's opinion that as a result of these hearings the aggregate production quota as proposed for 1976 may prove to be inadequate.

None of the above mentioned comments specifically requests a formal hearing on the aggregate quotas as proposed for 1976. Pursuant to § 1303.11(c), the Acting Administrator of the Drug Enforcement Administration has deemed, in his sole discretion, that hearings relative to any of the above mentioned comments are not necessary. Representatives of the Drug Enforcement Administration will meet with representatives of the above mentioned firms to review the comments submitted.

Therefore, under the authority vested in the Attorney General by section 306 of the Comprehensive Drug Abuse Prevention and Control Act of 1970 (21 U.S.C. 820), and delegated to the Administrator of the Drug Enforcement Administration by § 0.100 of Title 28 of the Code of Federal Regulations and further, having been duly designated as Acting Administrator by Order No. 607–75 of the Attorney General, dated May 30, 1975, in accordance with the authority stated therein, and pursuant to the authority delegated to the Acting Administrator by § 0.132(d) of Title 28 of the Code of Federal Regulation, the Acting Administrator of the Drug Enforcement Administration hereby orders that the aggregate production quotas for the controlled substances listed below, expressed in grams in terms of their respective anhydrous bases, be established as follows:

SCHEDULE II

	Quota Established—1976
Basic class:	
Alphaprodine	47,000
Amobarbital	21,975,000
Amphetamine	3,586,000
Anileridine	345,000
Apomorphine	1,700
Cocaine	1,213,000
Codeine (for sale)	51,426,000
Codeine (for conversion)	806,000
Desoxyephedrine	[1] 1,598,000
Dihydrocodeine	395,000
Diphenoxylate	1,141,000
Ethylmorphine	33,100
Fentanyl	2,000
Hydrocodone	718,000
Hydromorphone	96,000
Levorphanol	6,700
Methadone	2,407,000
Methadone Intermediate (4-cyano-2 dimethyl-amino-4,4-diphenyl butane)	759,000
Methaqualone	24,096,000
Methylphenidate	2,007,000
Mixed Alkaloids of Opium	44,000
Morphine (for sale)	592,000
Morphine (for conversion)	46,778,000
Norpethidine	795,000
Opium (tinctures, extracts, et ceters, expressed in terms of opium)	1,692,000
Oxycodone (for sale)	1,475,000
Oxycodone (for conversion)	7,000
Oxymorphone	4,000
Pentobarbital	23,697,000
Pethidine	9,474,000
Phenmetrazine	2,312,000
Secobarbital	30,106,000
Thebaine (for sale)	1,231,000
Thebaine (for conversion)	1,010,000

[1] 1,265,000 g for the production of levo-desoxyephedrine for use in a noncontrolled, nonprescription product, and 331,000 g for the production of methamphetamine.

Pursuant to Title 21 of the Code of Federal Regulations, § 1303.23(c), the Acting Administrator of the Drug Enforcement Administration will in early 1976 adjust individual manufacturing quotas allocated for 1976 for the above listed controlled substances based upon 1975 end of year inventories and a review of 1975 disposition data as submitted by quota applicants.

All persons who submitted an application for either an individual manufacturing quota or a procurement quota for 1976 will be notified by mail as to their respective 1976 quotas established by the Drug Enforcement Administration.

This order is effective upon the date of its issuance.

Dated: October 23, 1975.

HENRY S. DOGIN,
Acting Administrator
Drug Enforcement Administration.

[FR Doc.75-29117 Filed 10-29-75;8:45 am]

DEPARTMENT OF JUSTICE

Drug Enforcement Administration

CONTROLLED SUBSTANCES IN SCHEDULES I AND II

Final 1976 Revised Aggregate Production Quotas

Section 306 of the Comprehensive Drug Abuse Prevention and Control Act of 1970 (21 U.S.C. 826) requires the Attorney General to establish aggregate production quotas for all controlled substances in Schedules I and II each year. This responsibility has been delegated to the Administrator of the Drug Enforcement Administration pursuant to § 0.100 of Title 28 of the Code of Federal Regulations.

On May 14, 1976, a notice of the proposed revised aggregate production quota for 1976 for various Schedule II controlled substances was published in the FEDERAL REGISTER (41 FR 19991-2). All interested parties were invited to comment or object to the proposed aggregate production quotas on or before June 21, 1976. No comments or objections were received.

Therefore, under the authority vested in the Attorney General by section 306 of the Comprehensive Drug Abuse Prevention and Control Act of 1970 (21 U.S.C. 826), and delegated to the Administrator of the Drug Enforcement Administration by § 0.100 of Title 28 of the Code of Federal Regulations, the Administrator of the Drug Enforcement Administration hereby orders that the 1976 aggregate production quotas for the controlled substances listed below, expressed in grams of anhydrous base, be established as follows:

Basic class:	*1976 aggregate production quota*
Amobarbital	13,330,000
Dihydrocodeine	400,000
Methadone intermediate	2,548,000
Methaqualone	20,028,000
Morphine for conversion	51,000,000
Norpethidine	
Pentobarbital	21,862,000
Pethidine	11,095,000
Phenmetrazine	3,098,000
Secobarbital	25,000,000
Thebaine for conversion	1,311,000

This order is effective upon date of its issuance.

Dated: July 1, 1976.

PETER B. BENSINGER,
Administrator.

[FR Doc.76-19754 Filed 7-7-76;8:45 am]

Form P

ANNUAL STATISTICS OF PSYCHOTROPIC SUBSTANCES

A SINGLE COPY of these statistics should be sent to the INTERNATIONAL NARCOTICS CONTROL BOARD, Palais des Nations, Geneva (Switzerland), as soon as possible, but not later than 30 June, after the end of the year to which they relate.

COUNTRY OR REGION: UNITED STATES OF AMERICA DATE: JUL 14 1976

COMPETENT DEPARTMENT: DRUG ENFORCEMENT ADMINISTRATION

(Signed) Peter B. Bensinger TITLE OR FUNCTIONS: Administrator

These statistics relate to the calendar year 1975.

REMARKS

This report includes American Samoa, Guam, Panama Canal Zone, and the Virgin Island Territories of the United States.

Please note:

The drug schedules listed in this report filed with the International Narcotics Control Board do not correspond with the drug schedules utilized by DEA in controlling substances in the United States.

SUBSTANCES LISTED IN SCHEDULE II

See *Instructions*	1 Amphetamine	2 Dexamphetamine	3 Methamphetamine	4 Methylphenidate	5 Phencyclidine	6 * Phenmetrazine
	Kilogrammes	*Kilogrammes*	*Kilogrammes*	*Kilogrammes*	*Kilogrammes*	*Kilogrammes*
I. Quantity manufactured [a]	209	3109	369	1219	Nil	2741
II. Quantity utilized for the manufacture of preparations exempted under art. 3, paras. 2 and 3 [b]	Nil	Nil	Nil	Nil	Nil	Nil
III. Quantity utilized for the manufacture of non-psychotropic substances or products [c]	Nil	Nil	Nil	Nil	Nil	Nil
IV. Manufacturers stocks at 31 December [d]	70	943	175	949	Nil	2117
V. Imports [e] Total	Nil	Nil	Nil	Nil	*	Nil
In detail Imported from: *Specify* *Quantities →* *Country or region ↓*						
Australia					*	

P. 42965

Federal Register

Area Code 202 Phone 523-5240

Drug Enforcement Administration

CONTROLLED SUBSTANCES

Proposed Aggregate Production Quotas for 1977

Section 306 of the Controlled Substances Act (21 U.S.C. 826) requires that the Attorney General establish aggregate production quotas for all controlled substances listed in Schedules I and II. This responsibility has been delegated to the Administrator of the Drug Enforcement Administration by § 0.100 of Title 28 of the Code of Federal Regulations.

The quotas are to provide adequate supplies of each such substance for (1) The estimated medical, scientific, research, and industrial needs of the United States, (2) lawful export requirements, and (3) the establishment and maintenance of reserve stocks.

In establishing the below listed proposed 1977 aggregate production quotas, the Administrator considered pursuant to Section 302 subsection (a) of the Public Health Services Act (42 U.S.C. 242 (a)) the "Results of studies and investigations of the quantities of narcotic drugs or other drugs subject to control under such Acts, together with reserves of such drugs, that are necessary to supply the normal and emergency medicinal and scientific requirements of the United States" which were supplied by the Department of Health, Education, and Welfare. In addition, the proposed aggregate quotas were established considering the following factors:

(1) Total actual 1975 and estimated 1976 and 1977 net disposals of each substance by all manufacturers.

(2) Projected trends in the national rate of net disposals of each substance.

(3) Estimates of inventories of each substance and of any substance manufactured from it, and trends in accumulation of such inventories.

(4) Projected demand as indicated by procurement quota applications which were filed pursuant to § 1303.12 of Title 21 of the Code of Federal Regulations.

Pursuant to Title 21 Code of Federal Regulations, § 1303.23(c), the Administrator of the Drug Enforcement Administration will in early 1977 adjust individual manufacturing quotas allocated for 1977 based upon 1976 end of year inventory figures and actual 1976 disposition figures of each basic class of Schedule I and II controlled substances which will be provided by quota applicants.

Based upon consideration of the above factors, the Administrator of the Drug Enforcement Administration hereby proposes that aggregate production quotas for 1977 for the following controlled substances, expressed in grams in terms of their respective anhydrous base, be established as follows:

Basic class:	Proposed 1977 quota
Schedule I	
2-5 dimethoxyamphetamine	42,000,000
Lysergic acid diethylamide	1
Mescaline	200
Schedule II	
Alphaprodine	45,000
Amobarbital	18,142,000
Amphetamine	Reserved
Anileridine	270,000
Cocaine	1,249,000
Codeine (for sale)	43,918,000
Codeine (for conversion)	1,343,000
Desoxyephedrine (1,490,000 g for the production of levo-desoxyephedrine for use in a noncontrolled, nonprescription product, and 393,000 g for the production of methamphetamine)	1,883,000
Dihydrocodeine	602,000
Diphenoxylate	1,272,000
Ethylmorphine	21,000
Fentanyl	2,000
Hydrocodone	721,000
Hydromorphone	78,000
Levorphanol	6,000
Methadone	2,432,000
Methadone intermediate (4-cyano-2 dimethyl-amino-4,4-diphenyl butane)	2,153,000
Methaqualone	17,914,000
Methylphenidate	1,729,000
Mixed alkaloids of opium	49,000
Morphine (for sale)	489,000
Morphine (for conversion)	46,597,000
Opium (tinctures, extracts, etc.) (expressed in terms of powdered opium)	2,855,000
Oxycodone (for sale)	1,667,000
Oxycodone (for conversion)	5,400
Oxymorphone	3,500
Pentobarbital	19,144,000
Pethidine	12,428,000
Phenmetrazine	2,125,000
Secobarbital	17,346,000
Thebaine (for sale)	2,880,000
Thebaine (for conversion)	720,000

The proposed aggregate production quota for Amphetamine is being reserved pending the completion of a review of data on hand relative to this substance. It is anticipated that DEA will publish a proposed aggregate production quota for 1977 for this substance in the near future.

All interested persons are invited to submit their comments and objections in writing regarding this proposal. Those comments or objections should state with particularity the issues concerning which the person desires to be heard. A person may object or comment on the proposals relating to any one or more of the above mentioned substances without filing comments or objections regarding the others. Comments and objections should be submitted in quintuplicate to the Administrator, Drug Enforcement Administration, United States Department of Justice, Washington, D.C. 20537, Attention: DEA Federal Register Representative, and must be received by October 29, 1976. If a person believes that one or more issues raised by him warrant a full adversary-type hearing, he should so state and summarize the reasons for his belief.

In the event that comments or objections to this proposal raise one or more issues which the Administrator finds, in his sole discretion, warrants a full adversary-type hearing, the Administrator shall order a public hearing in the FEDERAL REGISTER summarizing the issues to be heard and setting the time for the hearing (which shall not be less than 30 days after September 29, 1976).

Dated: September 23, 1976.

PETER B. BENSINGER,
Administrator,
Drug Enforcement Administration.

[FR Doc.76-28533 Filed 9-28-76;8:45 am]

DEPARTMENT OF JUSTICE

Drug Enforcement Administration

AMPHETAMINE

Aggregate Production Quota for 1974

Section 306 of the Controlled Substances Act (21 U.S.C. 826) requires that the Attorney General establish aggregate production quotas for all controlled substances listed in Schedule I and II by July 1 of each year. This responsibility has been delegated to the Administrator of the Drug Enforcement Administration by § 0.100 of Title 28 of the Code of Federal Regulations. The quotas are to provide adequate supplies of each such substance for (1) the estimated medical, scientific, research, and industrial needs of the United States, (2) lawful export requirements, and (3) the establishment and maintenance of reserve stocks.

On July 3, 1973, the Drug Enforcement Administration published in the FEDERAL REGISTER a notice of proposed 1974 Aggregate Production Quota for Amphetamine (38 FR 17741).

In order to meet the statutory requirement that 1974 [illegible] quota be established on or before July 1, 1973, the Administration utilized the same data used for setting the 1973 quota on May 8, 1973 (38 FR 11473).

On [illegible] the Drug Enforcement Administration published in the FEDERAL REGISTER a Notice of Proposed 1974 Amphetamine Aggregate Production Quota revising the July 3, 1973 proposed aggregate production quota.

All interested parties were invited to comment on or object to the proposed aggregate production quota on or before April 19, 1974. No comments or objections have been received by the Administration.

Therefore, the Administrator of the Drug Enforcement Administration under the authority vested in the Attorney General by section 306 of the Comprehensive Drug Abuse Prevention and Control Act of 1970 (21 U.S.C. 826) and delegated to the Administrator, Drug Enforcement Administration by Section 0.100 of Title 28 of the Code of Federal Regulations, orders that the 1974 aggregate production quota for amphetamine expressed in grams in terms of its anhydrous base, be established as follows:

Basic class. Amphetamine.

Grantee. 3,057,150.

All persons who submitted an application for either an individual manufacturing quota or procurement quota for 1974 will be notified by mail as to their respective 1974 quota established by the Administration.

This order is effective on June 17, 1974.

Dated: June 11, 1974.

JOHN R. BARTELS, JR.,
Administrator,
Drug Enforcement Administration.

[FR Doc.74-13769 Filed 6-14-74;8:45 am]

MATERIAL ON PENWALT CORP. FROM FILES OF DRUG ENFORCEMENT AGENCY, DEPARTMENT OF JUSTICE

[redacted] CORPORATION

PRESCRIPTION PRODUCTS

755 JEFFERSON ROAD, ROCHESTER, N. Y. 14623, P.O. BOX 1750, ROCHESTER, N. Y. 14603 · (716) 271-1700

August 13, 1970

ALL FIELD SALES PERSONNEL

You undoubtedly have read in your newspapers that the Food and Drug Administration has officially published a general policy statement for anoretic drugs. As we have experienced in the past, lay press reporting of such information is not always an accurate interpretation of the Food and Drug Administration's publications. In this bulletin we will attempt to pass along to you, (1), the facts concerning our particular products - Biphetamine, Ionamin and Biphetamine-T, and (2), information concerning all other amphetamines.

1. Biphetamine, Ionamin and Biphetamine-T

The drug amendments of 1962 require that any marketed drug with an NDA approved during the period 1938-1962 had to submit data regarding efficacy. The reason for this was that prior to the drug regulations of 1962, the Food and Drug Administration was only concerned with the safety of the drug and not the efficacy of the drug. Since Biphetamine, Ionamin and Biphetamine-T were "NDA'd drugs", we submitted efficacy data in September of 1964. The Food and Drug Administration did not have sufficient personnel to review this data and contracted with the National Academy of Sciences and the National Research Council to review the efficacy data. The Food and Drug Administration has just made public the evaluation of the academies with regard to Biphetamine, Ionamin and Biphetamine-T. All three products were ruled "possibly effective" for the treatment of obesity. The regulations state that any drug ruled as "possibly effective" may continue on the market and the manufacturer is required to submit new data to establish the efficacy of the product within a six month period from the time of the announcement (August 8, 1970).

For your information, of the volume of data submitted to the Food and Drug Administration to establish efficacy of Biphetamine, Ionamin and Biphetamine-T only a few specific points were questioned. We are confident that we will be able to supply the Food and Drug Administration with the data requested and establish the efficacy of these products to their satisfaction.

2. Amphetamines

The National Academy of Sciences and the National Research Council evaluated amphetamines as generally effective for short-term anoretic action. The Food and Drug Administration is thus requiring all manufacturers of amphetamine preparations to change their labeling to conform with the findings of the academy. As soon as the new labeling is available, it will be forwarded to you. As far as we are concerned, there is nothing objectionable in the labeling suggested by the Food and Drug Administration for these products.

The above information is not the best news we could have received nor is it the worst. For the past three years many of the so-called experts have declared amphetamines worthless for the treatment of obesity. We now have recognition from the National Academy of Sciences and the National Research Council that amphetamines are generally effective in the treatment of obesity for a limited period of time. We certainly can not disagree with these findings. In fact, the National Academy of Sciences and the National Research Council endorse our "four essentials" for treating obesity with the following statement which appears in their report -

"Anoretic agents supress appetite. They are not a treatment of obesity in themselves and should be used as an adjunct to a total program of weight reduction for obese patients that includes patient education, motivation, caloric restrictions and exercise. The anoretic effect of anoretic agents often plateaus or diminishes after four to six weeks. The dosage of the drug must be individually titrated.....".

Thus, our complete program of "Are You Really Serious" and Biphetamine, Ionamin and Biphetamine-T fulfills the overall treatment design of the National Academy of Sciences and the National Research Council for the treatment of obesity.

DO YOU HAVE SOMETHING TO SELL?

Cordially yours,

Isaac R. McGraw, II
Vice President

IRM/sw

WHAT YOU CAN SAY ABOUT BIPHETAMINE®, BIPHETAMINE®-T

Biphetamine® is a sympathomimetic amine with CNS stimulant activity. The anoretic effect diminishes after a few weeks. Biphetamine® is indicated in exogenous obesity as a short term (a few weeks) adjunct in a regimen of weight reduction based on caloric restriction. Dosage of Biphetamine® is one capsule daily, 10 - 14 hours before retiring which may be adjusted to individual requirements. Biphetamine® is available in three strengths: Biphetamine® '7½', Biphetamine® '12½' and Biphetamine® '20'.

Biphetamine®-T is a sympathomimetic amine with CNS stimulant activity. The anoretic effect diminishes after a few weeks. Patients on Biphetamine®-T may experience less irritability than those on amphetamine alone. Biphetamine®-T is indicated in exogenous obesity as a short term (a few weeks) adjunct in a regimen of weight reduction based on caloric restriction. Dosage of Biphetamine®-T is one capsule daily upon arising. Biphetamine®-T is available in two strengths: Biphetamine®-T '12½' and Biphetamine®-T '20'.

SUBJECT August 8, 1970 Federal Register Notices - Action & Responsibility Guidelines

DATE August 20, 1970

TO Dr. Wallace P. Mead
Dr. Aldo P. Truant

FROM Elwood A. Gerner

IN REPLY TO

COPIES TO Isaac R. McCrew, Erwin P. G. Kahn, Giovanni Costa, Zarch Hadidian, L-9

The following is a summary of the action and responsibility guidelines hammered out during our conference on the subject in Rochester Wednesday, August 19, 1970. Also present and participating were Vincent Kleinfeld, our counsel on F & DA legal and regulatory matters, and Dr. Jean Mayer from Harvard, well known authority in the field of nutrition and most recently Special Assistant to the President of the United States for Nutritional Affairs and the continuing special consultant to us in matters of obesity and nutrition.

I. Required Action #1: --

By October 6, 1970 the Pharmaceutical Division must revise the labeling of its orally administered amphetamine and dextroamphetamine containing products to conform with the requirements set forth on pages 12692 and 12693 of the Procedural and Interpretive Regulations published in the Federal Register, Vol. 35, No. 154 -- Saturday, August 8, 1970.

Responsibility for carrying out this required action is assigned to Dr. William F. Mead.

1. Specific products to be re-labeled are:

   a. Biphetamine '7½', '12½', and '20'.

   b. Biphetamine-T '12½', Biphetamine-T '20'

2. Indication and dosage information contained in the revised labeling shall be restricted to exogenous obesity and shall exclude narcolepsy and hyperkinetic behaviour disorders.

3. Our presently used dosage statement in labels and labeling shall be retained.

4. Re-labeling requires "slavish adherence" to the F & DA order that labeling of orally administered amphetamine and dextroamphetamine and their salts should be substantially as published in the August 8, 1970 Federal Register.

5. Disposition of other items: --

a. The word "amphetamine" is to replace the dl-amphetamine designation in new labels and labeling in line with the nomenclature used in the Federal Register notices.

b. 'Biphetacel' containing amphetamine and dextroamphetamine as phosphates is to be deleted as of October 8, 1970 or as much before that date as stocks may be exhausted. Sales and sales potential of the product are too insignificant to warrant retention in the line.

c. Injectible 'Raphetamine' Phosphate 1% is not an orally administered amphetamine product and therefore not subject to the August 8, 1970 order.

d. Mr. McGraw and Dr. Head are to make an immediate determination and recommendation with respect to the disposition of methamphetamine-containing products in the line, i.e., 'Elfran', 'Efroxine'. If retained on the market, the labels and labeling for these products must be brought into conformity with the provision of A.1. found on Page 12679 of the Federal Register notice of August 8, 1970. The only question to be resolved by the determination and recommendation of Mr. McGraw and Dr. Head is whether to delete these products as of October 8, 1970 or as of February 8, 1971.

II. Required Action #2: --

By February 8, 1971 the Pharmaceutical Division must submit in response to the implementation notice of August 8 new, previously unsubmitted data including that "from adequate and well controlled clinical investigations". In support of effectiveness claims for 'Biphetamine', 'Biphetamine-T', and 'Ionamin' now ruled as "Possibly Effective" by the F & DA.

Responsibility for Action #2 -- Dr. Aldo P. Truant and staff.

1. Specific products for Action #2 are:

   a. Biphetamine '7½', Biphetamine '12½', Biphetamine '20'.

   b. Biphetamine-T '12½' and Biphetamine-T '20'.

   c. Ionamin '15' and Ionamin '30'.

2. Pending determinations that can be achieved only in conference with F & DA officials, objectives of protocols shall include the following:

   a. 'Biphetamine' --

      (1) Short term anorectic effectiveness in "exogenous obesity", as a short term (a few weeks) adjunct in a regimen of weight reduction based on caloric restriction.

      (2) Contribution of resination in terms of

         (a) Blood levels.

         (b) Longer duration of effect.

         (c) Fewer adverse reactions and less "peaking" effect.

   b. 'Biphetamine-T' --

      (1) Short term anorectic effectiveness in "exogenous obesity", as a short term (a few weeks) adjunct in a regimen of weight reduction based on caloric restriction.

      (2) Contribution of resination in terms of

         (a) Blood levels.

         (b) Longer duration of effect.

         (c) Fewer adverse reactions and less "peaking" effect.

         (d) Contribution of Tuarole to 'Biphetamine-T'.

c. 'Ionamin'

(1) Short term anorectic effectiveness.

(2) Contribution of resination in terms of:

(a) Blood levels and bioavailability.

(b) Longer duration of effect.

(c) Advantages.

III. Some Pertinent Observations

1. Vincent Kleinfeld accurately confirmed the distinction between the "possibly effective" ruling for our drugs as contained in the implementation notice of August 8 from the "effective, but ...." observation contained in the NAS/NRC reports. As Vincent pointed out, the NAS/NRC "effective, but...." observation as opposed to the "possibly effective" ruling by the F & DA could be of value in a court but was otherwise meaningless to us since we have no choice but to comply with the "possibly effective" F & DA ruling.

2. In the new label copy for 'Biphetamine-T' under "Actions" Jean Mayer laid the foundations for a statement with respect to the contribution of Tuazole to 'Biphetamine-T' expressed along these lines --- "Biphetamine-T produces an anorectic effect which diminishes after a few weeks. Patients may experience less irritability than with amphetamine alone".

3. The wisdom of caution and the critical importance of "slavish adherence" to the August 8, 1970 implementation order published by the F & DA were heavily underscored by Vincent Kleinfeld.

4. It was concluded that each strength of our products be included in studies.

5. It was unanimously agreed that every effort should be made in line with Aldo Tavant's thinking to get the thinking of the appropriate F & DA officials with respect to satisfactory objectives and the protocols themselves. The suggestion that the PMA be asked to help bring to the attention of the F & DA the importance of giving manufacturers such as ourselves the benefit of their attention with respect to our protocols will be pursued. But we shall have to rely primarily upon Aldo Tavant, Giovanni Costa, to glean some guidelines from F & DA officials.

The first step is a conference that Jean Mayer and Aldo Truant will have with James Grant, the Deputy Commissioner. It is hoped that Mr Grant will be able to help with F & DA policy and procedural matters and that he can be of help in lining up a conference with those F & DA officials who have specific responsibility for handling the matters in question.

6. The suggestion was made that it might be well to write to the Food & Drug Administration with copies to the local press, to our Congressmen and Senators, expressing our sympathy with their objectives and citing the fact that we have deleted certain of our amphetamine and methamphetamine drugs. While this idea may deserve some consideration, the general feeling of the group was to the effect that this would be an ill-advised move, that we should proceed in a business-like way; that any announcement of our decision to withdraw from the market such products as 'Biphetacel', 'Efroxine', 'Elfren', would be the occasion for an immediate order from the F & DA pressing for our voluntary withdrawal from trade channels all inventories of these items. The expense of carrying out such an order alone negates the idea.

7. In the opinion of Vincent Kleinfeld it will take the F & DA some months after February 8 to evaluate the February 8, 1971 submissions. It is our judgment that we, on this count alone, will be able to continue marketing these products without interruption through the greater part of 1971.

8. Although Vincent Kleinfeld emphasized the fact that the F & DA is definitely hostile toward amphetamine and amphetamine-containing combinations, and that officials react strongly to political pressures, led by the opinion of Jean Mayer there is plenty of room for optimism that expert compliance and presentation of data will win approval.

9. Vincent Kleinfeld had the following to say in answering the question "What recourse do we have if the F & DA rejects approval of our supplemental submission?"
"You have the right to ask for a public hearing within thirty days of the rejection notice. If the request is granted, it must be recognized that the chances of winning are very slight. At the same time that the request for a public hearing is made, attorneys should get on the job of preparing to challenge the F & DA in an appeal to the courts. A request for a public hearing and possible subsequent

court tests automatically stays withdrawal of the product from the market until the matter can be resolved. It is impossible to cite the number of months or years such proceedings might take". The real point of the question here was to determine by what means, if any, we could prolong the life of the products in question on the market despite rejection of approval of a supplement -- the worst that could happen. It appears that the life could be prolonged by these methods for at least several months, which would buy more time. If the worst should happen, rejection of approval, wisdom of requesting a hearing and a possible subsequent court test would have to be carefully weighed in terms of the costs of so doing against the desirability of prolonging the sales of the products.

10. Unquestionably, submissions by firms which failed to supply adequate supporting evidence of safety and effectiveness for claims will be rejected and subject to withdrawal proceedings. It is conceivible that this could result in some firms securing approval and others not. And some suppliers could fall by the wayside. In our judgment, we feel it very likely that all good submissions will either be approved or rejected. Rejection in the case of good submissions would have to be made on technicalities. Submissions which are outright deficient we believe will be rejected in any case.

11. Sharing the feeling particularly of Jean Mayer we have every reason to proceed with hard-headed optimism in successfully discharging the horrendous burden laid on our shoulders.

E.A.G.

Elwood A. Garner

/bl

STRASENBURGH
PRESCRIPTION PRODUCTS
755 JEFFERSON ROAD, ROCHESTER, N. Y. 14623, P.O. BOX 1788, ROCHESTER, N. Y. 14603 · (716) 271-1000

November 2, 1970

TO: All Division and District Managers

FROM: J. Marion Meason

SUBJECT: *ACTION NEEDED NOW!*

I have just completed a spot check of your salesmen's daily reports. Excluding those districts on our new Call Planning System, your salesmen are averaging about six M. D. calls per day including those seen at hospital displays.

Is it merely coincidence that names like Gobar, Gallop, Bridges, Brannon, Farrar and Gayley popped out on the list with 40 or more calls for the week?

Too many men are making as few as 25 to 30 calls per week. Is it merely coincidence that these same men are making little, if any, sales progress?

Ethical anti-obesity preparations, according to DK&K, climbed to 14.5% in August. Strasenburgh claimed only a 12.7% Share of Market for the lowest share of market we have held in a very long time. Any way you slice it, we are being outsold by our competitors! Merrell is up; Abbott is up; Semed is up; National is up; Lederle is up with a new entry.

Too few physician calls, I am sure, are only partly responsible for this state of our business. Very closely tied to this must be the fact that our men are less than effective on the calls which are made. Why?

Let me pose a few questions to you. Is it possible that, having been blasted by some physician who said in effect, "Amphetamines are no damn good and should be taken off the market", your salesman is afraid to bring an anorectic out of his bag in front of the next physician? Is this same fear of being "put down" the reason for making fewer calls? Is it possible that this same fear stampedes your salesman when a normal question or objection arises in an interview? Is this responsible for the actions of a salesman who is swinging strongly to IONAMIN because it is non-amphetamine? Are you teaching salesmen to ask *why* when a physician says, "I have quit prescribing anorectics"? Are you teaching him to pursue this with the physician in terms of giving the doctor adequate justification

to prescribe BIPHETAMINE, BIPHETAMINE-T or IONAMIN and *Are You Really Serious About Losing Weight?* rather than refer them to "Weight Watchers" or "TOPS"? What do your salesmen do when the doctor says, "I don't prescribe amphetamines anymore"? Have you taught them to ask *why*? Remember that amphetamines, both plain and combos, still held 69.1% of the $7,696,000 market for August. Are our competitors better equipped to sell their products? Are they really better salesmen and managers?

Enclosed is a "structured" presentation for BIPHETAMINE, BIPHETAMINE-T and IONAMIN that suggests a way to utilize the strongest support we have had for our *4 Essentials System*. Not a single one of our competitors has as much to sell!

This presentation will be forwarded to all salesmen and should be implemented to your satisfaction immediately.

Selling today requires guts! Timorous "detailing" won't quite get the job done.

CAN WE MEASURE UP?

Cordially,

J. Marion Meason
National Sales Manager

JMM/mr

Enclosure

BIPHETAMINE - BIPHETAMINE-T - IONAMIN "STRUCTURED" PRESENTATION

"Doctor _____,

"We, at Strasenburgh, have for sometime advocated a program or system of successful weight loss and control that incorporates certain essentials: (1) patient education and motivation; (2) caloric restriction; (3) exercise; and (4) medication, when indicated, as an adjunct to a weight reduction program.

"It is quite gratifying for Strasenburgh, and especially for me, Doctor _____, to learn that our ideas are in line with the National Academy of Sciences and the National Research Council.

"The National Academy of Sciences and the National Research Council, in their review of anorectic agents, stated that 'they are not a treatment of obesity in themselves and should be used as an adjunct to a total program of weight reduction that includes patient education, motivation, caloric restriction and exercise.'

"In theory, how does this approach sound?" (Let him answer - listen.) "This approach is feasible in actual practice with *Are You Really Serious About Losing Weight?*

"*Are You Really Serious About Losing Weight?* provides you with the educational material and helps you communicate quickly with the overweight patient (1st Part - show) 'About Their Problem' and (2nd Part) 'What to Do About the Problem'. For example -- True - False Quiz -- you don't have to correct.

"The three alternatives to rigid dieting (Substitution Diet section, 100 Calorie Portion section and the Portion Control section) help you provide your patient with a diet that isn't dull and give you a way to tailor-make a diet to the ethnic background and economic status of the patient. (Show how.)

"Your patient will better understand the role of exercise after studying pages 19 and 20. Many physicians are now prescribing a daily activity schedule for their overweight patients.

"Doctor _____, do you think that you could use *Are You Really Serious About Losing Weight?* with your overweight patients?" (Let him answer - listen.)

"The National Academy of Sciences and the National Research Council states further that 'dosage of anorectic drugs should be individually titrated.'

"Doctor _____, when you prescribe an appetite suppressant, have you found that one certain medication fulfills the requirements of most of your overweight patients or do you vary the formulation and dosage strength to the individual patient?

"Strasenburgh is the only company offering you the flexibility of dosage strength and formulation in the three types of medication to curb appetite.

(Show BIPHETAMINE starter.)

"BIPHETAMINE is amphetamine resin. BIPHETAMINE provides appetite control on one capsule daily. BIPHETAMINE is available in three dosage strengths: BIPHETAMINE '7 1/2', BIPHETAMINE '12 1/2' and BIPHETAMINE '20'.

(Show BIPHETAMINE-T starter.)

"BIPHETAMINE-T is amphetamine resin with Tuazole (methaqualone resin). BIPHETAMINE-T provides appetite control on one capsule daily. Patients taking BIPHETAMINE-T may experience less irritability on BIPHETAMINE-T than on plain amphetamine. BIPHETAMINE-T is available in two strengths: BIPHETAMINE-T '12 1/2' and BIPHETAMINE-T '20'.

(Show IONAMIN starter.)

"Should you prefer to prescribe medication which has less of an energizing effect, IONAMIN (phentermine resin), a non-amphetamine, will provide appetite control on a single daily capsule dose -- IONAMIN 15 or IONAMIN 30 mg.

"Doctor _____, how many overweight patients would you see in six weeks that would benefit from *Are You Really Serious About Losing Weight?*

"Would you like starters of BIPHETAMINE, BIPHETAMINE-T or IONAMIN to give to your patients with each book? What strengths?

CLOSE: "So that we can continue to provide this service and expand it, we ask that when you use *Are You Really Serious About Losing Weight?* and in your judgment the patient needs an appetite suppressant, would you prescribe (doctor's choice of BIPHETAMINE-BIPHETAMINE-T - IONAMIN)?" (Get his commitment.)

"BIPHETAMINE, BIPHETAMINE-T and IONAMIN are available at every drug-store and I will be happy to supply you with additional copies of *Are You Really Serious About Losing Weight?* when I call on you in six weeks."

SUBJECT Drug Abuse Act

DATE November 5, 1970

TO W. F. Head, A. P. Tracht, I. R. McGraw, E. Kuhn

FROM E. A. Garner

IN REPLY TO

COPIES TO

Attached you will find a copy of Vincent Kleinfeld's letter to me regarding the "Comprehensive Drug Abuse Prevention and Control Act of 1970".

Dr. William F. Head, V. P. Technical Operations, shall be our chief compliance officer with respect to the provisions of this Act that are pertinent to our operations.

Will 'Biphetamine' and 'Biphetamine-T', falling into Schedule III under the Act, be transferred to Schedule II? The Attorney General has the power to initiate proceedings affecting such a transfer, but according to Vincent Kleinfeld and Alan Kaplan only with the advice and concurrence of the F & DA. After talking with people at the Justice Department, if the Attorney General wished to move a drug or substance out of a controlled category, he could not do so without the concurrence of the F & DA. Although the language of the law is not too explicit and there is still some confusion about the point, it is presently felt that the same restriction would apply to moving a substance from one schedule to another. The whole point is that if 'Biphetamine' and 'Biphetamine-T' were moved into Schedule II, these drugs would become subject to production quotas. Production quotas in turn would be established by the Attorney General who, according to the law, "shall determine the total quantity and establish production quotas for each basic class of controlled substance in Schedules I and II to be manufactured each calendar year to provide for the estimated medical, scientific, research, and industrial needs of the United States, for lawful export requirements, and for the establishment and maintenance of reserve stocks. Production quotas shall be established in terms of quantities of each basic class of controlled substance and not in terms of individual pharmaceutical dosage forms prepared from or containing such a controlled substance".

Thus it becomes doubly imperative that our February 8, 1971 submission to the Food & Drug Administration definitely re-prove and re-establish the true medical need for 'Biphetamine' and 'Biphetamine-T' as anorectics to avoid production quotas being established merely on the basis of narcolepsy and the hyperkinetic syndrome.

Elwood A. Garner

/bd

[illegible]
[illegible]

[illegible]
[illegible]

KLEINFELD AND KAPLAN
[illegible]
[illegible]
WASHINGTON, D. C. 20036

[illegible]
[illegible]

Mr. Elwood A. Garner
Executive Vice President
Pennwalt Corporation
P. O. Box 1710
Rochester, New York 14603

Dear Elwood:

We are enclosing, for your information, a copy of the "Comprehensive Drug Abuse and Prevention and Control Act of 1970." The Act which consolidates, modifies and expands upon nineteen separate pieces of legislation, provides a comprehensive and complex scheme to deal with the problems of drug abuse. The principal provisions of the Act will become effective six months following its enactment date of October 27, 1970.

The Act establishes five schedules of controlled substances and lists those substances which are initially included in each of the five schedules (§202). A procedure is provided whereby the Attorney General, upon making appropriate findings, may promulgate regulations adding a drug or other substance to one of the five schedules, removing a drug or other substance entirely from the schedules, or transferring a drug or other substance between schedules. Before initiating these procedures, the Attorney General is required to request from the Secretary of HEW "a scientific and medical evaluation, and his recommendations, as to whether such drug or other substance should be controlled or removed as a controlled substance." A recommendation by the Secretary that a drug or other substance should not be controlled is binding on the Attorney General, and he cannot subject such drug or other substance to control under the Act. Exceptions to these procedures are provided where 1) control is required under the treaty obligations of the United States, 2) the Attorney General decides to control an immediate precursor of a controlled substance, and 3) a final determination to control a drug is made pursuant to administrative procedure initiated prior to the enactment date of the Act.

Under the listings provided for in the Act, the amphetamines and barbiturates, with the exception of the liquid injectable methamphetamines, are subject to Schedule III classification.

The liquid injectable methamphetamines are classified as Schedule II controlled drugs. However, it is important to note that John Ingersoll, who is Director of BNDD, in a letter addressed to Congressman Pepper, indicated that the Bureau will initiate procedures pursuant to Section 201 of the Act to transfer certain of the amphetamines from Schedule III to Schedule II classification. The effect that such a transfer would have on the manufacturing and distribution of the transferred amphetamines will be discussed later in this letter.

Except as otherwise provided in regulations promulgated by the Attorney General, every person who manufactures, distributes or dispenses any controlled substance (§302), or who imports into the United States any controlled substance, or exports from the United States any controlled substance in Schedules I, II, III, or IV (§1007), is required to obtain annually a registration issued by the Attorney General. A separate registration is required for each principal place of business. Unlike Section 510 of the FFDCA, registration under the Act is not automatic, rather, Section 303 and Section 1008 set forth the requirements or criteria for the issuance or denial of a registration. Provisions are made for provisional registration pending registration or denial under the Act. Finally, a procedure, including the right to an administrative hearing and judicial review, is provided for the denial, revocation or suspension of registration (§304).

Registrants, with certain exceptions, are required by Section 307 to keep and make available for inspection the following records or reports: 1) On the effective date of Section 307 and every second year thereafter, a complete and accurate record of all stocks of controlled substances on hand, 2) a current, complete and accurate record of each controlled substance manufactured, received, sold, delivered, or otherwise disposed of by him. In addition, registered manufacturers are required, upon request of the Attorney General, to "make periodic reports to the Attorney General of every sale, delivery or other disposal" of any controlled substance and distributors are required to make such reports with respect to narcotic controlled substances.

The label and labeling of controlled substances must contain an identifying symbol in accordance with regulations of the Attorney General. The label of drugs listed in Schedules II, III or IV must bear warnings as to the consequences of illegal distribution which are prescribed by the Secretary of HEW pursuant to Section 503(b) of the FFDCA. Also, controlled

substances in Schedules I or II and narcotic drugs in Schedules III or IV must be distributed in containers securely sealed as required by regulations of the Attorney General.

In addition to the requirements specified above, which are generally applicable to all persons who manufacture, distribute or dispense controlled substances, the manufacturer of Schedules I or II controlled substances are subject to manufacturing quotas based on medical and scientific needs (§306), and these substances cannot be distributed "except in pursuance of a written order (which must be preserved for a period of two years) of the person to whom such substance is distributed, made on a form to be issued by the Attorney General" (§308). Further, prescriptions for controlled drugs in Schedule II may not be refilled (§309).

The limitations and restrictions on the importation and exportation of controlled substances which are set forth in Title III of the Act are even more restrictive than those previously discussed. Except under specified circumstances and pursuant to regulations promulgated by the Attorney General, Section 1002(a) provides for an outright prohibition on the importation of any controlled substance in Schedules I or II and any narcotic drug in Schedules III, IV or V. The importation of any nonnarcotic controlled substances in Schedules III, IV or V is prohibited unless it is "imported for medical, scientific or other legitimate uses" and "pursuant to such notification or declaration requirements as the Attorney General may by regulation prescribe."

Unless otherwise authorized, the exportation of any Schedules I or II controlled substances and any narcotic drug in Schedules III or IV is prohibited unless certain specified requirements are met and "a permit to export the controlled substance in each instance has been issued by the Attorney General." The exportation of any nonnarcotic controlled substance in Schedules III or IV or any controlled substance in Schedule V is prohibited unless: 1) "there is furnished (before export) to the Attorney General documentary proof that importation is not contrary to the laws or regulations of the country of destination;" 2) "a special controlled substance invoice, in triplicate, accompanies the shipment setting forth such information as the Attorney General may prescribe ...;" and 3) "two additional copies of the invoice are forwarded to the Attorney General before the controlled substance is exported from the United States."

In this letter, we have summarized those provisions of the Act which we felt would be of particular concern. Embodied in the Act are other provisions, such as those dealing with administrative inspections and warrants, penalties, forfeitures (seizures), and injunctions which we have not discussed but which are pertinent to the manufacture, distribution, importation, and exportation of controlled substances.

If you have any questions, please let us know.

Sincerely,

Vincent A. Kleinfeld

VAK/mbc
cc: Dr. W. F. Head, Jr.

PRESCRIPTION PRODUCTS

[illegible] JEFFERSON ROAD, ROCHESTER, N. Y. [illegible] • (716) 271-1627

February 5, 1971

ALL FIELD SALES PERSONNEL

You are aware of the August 5th ruling by the Food and Drug Administration in which Biphetamine®, Isoamin®, and Biphetamine-T® were ruled as "possibly effective". As a result of this ruling we had to submit, within six months, efficacy and certain other data. Our program to successfully achieve these objectives was:

1. to search out the best clinicians in the United States to conduct the clinical studies

2. to prepare protocols and laboratory criteria which far exceed FDA demands

3. to consult with the FDA for the purpose of keeping them continually apprised of our progress and when possible their recognition of the quality of the work that was being done

The program is progressing satisfactorily and due to the excellence of the work that is being done, the FDA has today granted us a six month extension of the time period in which to submit the data. This represents the recognition of high quality of the work which is being done by our laboratories and clinicians by the FDA and also establishes that the FDA's intent is to accurately establish the therapeutic value of these agents. The extension of time given by the FDA was not an extension of the deadline to all manufacturers concerned but specifically to Stresenburgh.

This information is supplied to you so you will know the status of Biphetamine, Isoamin®, and Biphetamine-T® as of February 8, 1971 and should not be used in any way in the promotion of these products.

Cordially yours,

Isaac R. [illegible], II
Vice President

IRH/sw

[redacted]
CORPORATION

[redacted]
PRESCRIPTION PRODUCTS
755 JEFFERSON ROAD, ROCHESTER, N. Y. 14625, P.O. BOX 1756, ROCHESTER, N. Y. 14603 · (716) 271-1600

March 11, 1971

TO: All Division & District Managers

FROM: J. Marion Meason

SUBJECT: STATUS OF ANORECTICS

It is apparent that many of our wholesale customers have grave doubts and varying degrees of apprehension about the status of amphetamine products today. This explains why the inventories of our products, Biphetamine®, Biphetamine®-T and Ionamin, as well as our competitors' are being allowed to dwindle to nothing. Reports of *out of stock* and *back orders* are more frequent than ever.

These wholesalers need your reassurance *NOW*!

The retailer is a victim of the same thinking in too many instances.

Your salesmen are affected in direct proportion to the number of exposures to such negative thoughts.

Therefore, consider the following actions mandatory on your part every day you are in the field.

1. Take your salesman to his wholesaler. Reassure the wholesale buyer, sales manager, etc., that:

   A. Biphetamine, Biphetamine-T and Ionamin are still *going* products. Use Isaac McGraw's letter of February 5, 1971, regarding the status of Biphetamine, Biphetamine-T and Ionamin.

   B. Show them what our promotion schedule is.

   C. Show them "Are You Really Serious About Losing Weight?" and what we are doing in the physician's office.

   D. Get that inventory back up to adequate levels for doing business.

2. Every wholesaler must be called on by your salesmen at least once a month to reassure and motivate the buyer and sales manager.

3. At least five retail calls should be made by every salesman each day. Show the salesman how to reassure the pharmacist in the same way you will with the wholesaler.

4. Your visit with each salesman should include bolstering his own belief in what he is doing. Probe and listen. You may prevent disaster before it can occur and negative customer reaction can destroy a salesman's morale and effectiveness.

He, you or we cannot afford to let this happen.

Let's do the job right!

Cordially,

J. Marion Meason
National Sales Manager

JMM/mr

Enclosures (2)

cc: I. R. McGraw, II

STRASENBURGH
CORPORATION INTERNATIONAL

JEFFERSON ROAD, ROCHESTER, NEW YORK, 14623 • POST OFFICE BOX 1710, ROCHESTER, NEW YORK, 14603 • (716) 271-1020

May 20, 1971

Dr. Barrett Scoville
Office of Scientific Evaluation
Bureau of Drugs
Food and Drug Administration
Rockville, Maryland 20852

Re: NDA 11-538/S-004

Dear Dr. Scoville:

We have carefully reviewed your letter of April 29, 1971, regarding proposed changes in the labeling for our product Biphetamine-T. We are in general agreement with the basic theme of your revision to incorporate full disclosure information for the methaqualone component as it relates specifically to Biphetamine-T. Prior to adopting this copy for final revision in printing we have several comments which you may wish to consider.

On page two of your letter, paragraphs 3 and 9 represent a clear departure from recent FDA policy suggesting the elimination of results and data obtained from studies on laboratory animals.

On page three, paragraph 7 regarding methaqualone metabolism in the liver, we suggest the following sentence. "Since Biphetamine-T contains methaqualone which is metabolized in the liver, it should be used with caution in those with impaired hepatic function." The physician is not administering methaqualone as a single entity, and it is not possible for him, the pharmacist or the patient to reduce the methaqualone dosage in a unit dose of Biphetamine-T. The unit dose of Biphetamine-T already contains a substantially reduced dose of methaqualone, 40 mg. as compared to a 300 mg. sedative dose.

On page three, paragraph 8, we disagree that the adverse reactions listed have positively occurred with the combination. It is suggested that a more accurate phrasing would be, " ... have occurred with the individual drug components and which may possibly occur with the combination."