1.1

NEW DRUG APPLICATION

NDA No. 86-945

NAME OF APPLICANT

Vitarine CO. Inc.

NAME OF NEW DRUG

henTermine (HCl) 30mg Caps

Receipt Date	Action Taken	Date Action Taken

1 of 1

PHENTERMINE

MEMORANDUM OF SCIENTIFIC ROUNDS

MARCH 13, 1979

The meeting was called to develop a coherent policy on the requirements to market phentermine HCl and phentermine resin complex.

DNDP presented a history of the phentermine products. Three approved NDA's exist for phentermine. One is Ionamin (15 mg. and 30 mg. phentermine resin complex capsules), NDA 11-613, DESI effective. A second is Wilpo (8 mg. t.i.d. phentermine tablets), NDA 12-737, DESI effective. The third is Fastin (30 mg. phentermine HCl capsules), NDA 17-357, approved on clinical trials. Several ANDA's are pending and the requirements for approvability are conflicting and confusing.

The Division of Biopharmaceutics presented information on the comparability of the phentermine dosage forms. Phentermine resin complex (Ionamin) has a dissolution time of approximately 6 hours, whereas phentermine HCl (Fastin) completely dissolves in 15 minutes . Although higher peak blood levels can be obtained from an immediate release tablet (30 mg.) at the initial doses, the long biologic half-life (>20 hours) assures that an equivalent steady state plasma level is achieved with either a slow or fast release dosage form. A safety problem does not exist for the immediate release forms due to phentermine's slow absorption. Equivalent steady state plasma levels are achieved with a once a day dose or a divided daily dose.

The Division of Biopharmaceutics recommended phentermine products be handled as ANDA's and an in vitro dissolution test be required to assure bioavailability. Two separate standards (salt or resin) would be required for the dissolution tests and the Therapeutic Equivalency Index. If a firm claims controlled or sustained release an in vivo study would be required.

Dr. Crout concluded that ANDA's will be accepted for 8, 15, 24, and 30 mg. dosage forms of phentermine base (or HCl equivalent) modeled on Wilpo and Ionamin.

He further judged the sustained release claim to be clinically meaningless. Those products claiming sustained release must demonstrate the claim through an in vivo bioavailability study and the clinical significance of the claim. Ionamin's claim of slow release must be qualified or subverted through appropriate labeling changes.

D. J. Ellsworth
Consumer Safety Officer

HFD-120
HFD-120/DEllsworth/3/20/79
F/T:lgp/3/21/79
NDA's 12-737, 11-613, 17-357

PHENTERMINE HCL, PHENTERMINE RESIN COMPLEX

Phentermine HCL has a long half-life (24 hours): cited by Hinsvook et al in J. Pharmacokinetics and Biopharmaceutics Vol. 1, No. 4, 1973.

Pre 1962 DESI Reviewed (effective)

DESI 11673 - NDA 12-737, Wilpo 8 mg phentermine HCL conventional tablets.

DESI 5378 - NDA 11-613, Ionamine 15 mg and 30 mg phentermine as a resin complex, controlled-release capsules. (A cation exchange resin complex of sulfonated polystyrene).

Post 1962 Approval

NDA 17-352, Fastin 30 mg (24 mg base) phentermine HCL conventional capsules (was approved on the basis of clinical trials, but without bioavailability studies to define the pharmacokinetic profile of the product). Recommended dosage (1 cap./day) is the same as the controlled-release Ionamine containing 30 mg base.

Lemmon Pharmacal Co. Submitted:

ANDA 85-128, Adipex-P - 37.5 mg (30 mg base) phentermine HCL conventional tablets. This submission was declared as not acceptable and on 7/12/77 Lemmon requested that ANDA 85-128 be filed over protest. A notice of opportunity for hearing on refusal to approve the ANDA was published in the FR on 9/6/77. A final order denying hearing has been prepared on the ground that it is not related to any of the phentermine dosage forms reviewed by DESI, and data do not support the safety and effectiveness of the 37.5 mg dosage form.

ANDA 85-933, Adipex-P 30 mg, (24 mg base) phentermine HCL conventional tablets. (Same as Fastin except table form instead of capsule.) This submission was declared as not acceptable.

NDA 18-159, (formerly ANDA 85-933) for Adipex-P 30 mg (24 mg base) phentermine HCL conventional tablets.

NDA 18-042, Adipex-P 30 mg (24 mg base) phentermine HCL conventional capsules. On 5/5/78 Lemmon submitted a protocol for a pilot bioavailability study. On 8/10/78 HFD-120 informed the firm that the submission was inadequate under section 505(b)(1) of the Act and that it fails to establish that the proposed product is identical, similar, or related to any phentermine HCL product under a DESI notice. On this basis, the product will be limited to acceptance for review as a post 1962 product under a full NDA. Adequate bioavailability data to support the labeling of the entire ingredient and dosage forms concerned are needed.

24 mg
Full NDA - need B.E. & Manf only -

Zenith Labs Submitted:

ANDA 86-329 long-acting

Phentermine HCL 30 mg (24 mg base) ~~conventional~~ capsules. This submission was declared not acceptable on 3/30/78. On 5/10/78, Zenith requested that ANDA 86-329 be filed over protest. This submission also contained a clinical study which was found not to provide substantial evidence of effectiveness. (NOH to refuse approval of ANDA is being prepared by HFD-32).

ANDA
Full Manuf.

The Lemmon section of the 1978 PDR lists: Adipex 8 mg tablets, Adipex 8 mg capsules, Adipex-P 30 mg capsules, and Adipex-P 37.5 mg tablets.

MEMORANDUM

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

TO : File 84-695

DATE: January 9, 1976

FROM : Mary Ann Jarski, HFD-530

SUBJECT: Phentermine Hydrochloride Capsules, 30 mg.
The C.M. Bundy Co.
Cincinnati, OH 45202

11-6-75: The firm was advised that the application was incomplete under section 505(b)(1)(2)(3)(4) and (6) of the Act. Particularly infonmation was requested on:

1. Studies in support of the claim of all day suppression of appetite (i.e. HOW SUPPLIED section indicates "One capsule at approximately two hours after breakfast for appetite control).
2. Rate of release of the active ingredient from "phentermine hydrochloride medicated beads".

Rationale for request was based on FEDERAL REGISTER notice of 2-12-73 which evaluated Wilpo tablets containing 8 mg. of phentermine hydrochloride per tablet (Dorsey Laboratories, Division of Sandoz-Wander Inc., NDA 12-737). The DOSAGE AND ADMINISTRATION section of the Dorsey package insert indicates "One tablet three times a day 1/2 hour before meals."

11-18-75: The firm advises:
"I would also like to point out that I believe you have assumed my application was for a time release Phenteramine Hydrochloride capsule but this is not the case. Our capsule is just an ordinary beaded capsule the action of which is based on the "Half Life" of the drug. The original NDA in this type of product is held by Beecham-Massingil in their "Fastin" capsule."

Perusal of the "Fastin" application, 17-352 (also reference , indicates:

1. Submission on 4-27-72
2. Approval on 8-22-73
3. Clinical studies, excretion studies, comparison with Ionamin, half life calculation (about 40 hrs.)
4. Formulation: see attached
5. Dissolution: see attached

Questions:

1. If the $T_{1/2}$ = 40 hrs., then why is the drug given 3 x a day?
2. Is this dosage form acceptable to the FDA without studies?
3. Is this dosage form acceptable an an abbreviated NDA?

After discussion with Dr. VV Karusaitis (HFD-530) and Dr. Harold Murdock (HFD-522) it was deemed adviasable to request a bioavailability study an dissolution profile of the 30 mg. Bundy dosage form vs. the 8 mg. Wilpo tablet (given 3 x a day)

Attachment

Formula:

Beecham Massengill

Methylcellulose, USP
Polyethylene Glycol
Alcohol, SD
Chloroform, NF*
Phentermine Hydrochloride
Non-Pareil Seeds
Isopropyl Alcohol, NF*
Purified Titanium Dioxide
FD&C Blue
Water, Deionized*
Placebo Beads, White Coated

*Used in the manufacturing process; does not appear in the final product

CM Bundy

filler beads green
filler beads yellow
phentermine HCl beads
  non-pareil beads
  phentermine HCl
  coating solution

Dissolution, Beecham Massengill
  NLT phentermine hydrochloride (based on assay) in 30 minutes

ROUTING AND TRANSMITTAL SLIP	Date 1/19/79	
TO: (Name, office symbol, room number, building, Agency/Post)	Initials	Date
1. HFD-530		
2.		
3.		
4.		
5.		

Action	File	Note and Return
Approval	For Clearance	Per Conversation
As Requested	For Correction	Prepare Reply
Circulate	For Your Information	See Me
Comment	Investigate	Signature
Coordination	Justify	

REMARKS

PLEASE NOTE:

This is an amendment to the memorandum of January 15, 1979 (Phentermine), please disregard that memorandum.

DO NOT use this form as a RECORD of approvals, concurrences, disposals, clearances, and similar actions

FROM: (Name, org. symbol, Agency/Post)	Room No.—Bldg.
	Phone No.

5041-102
* U.S. G.P.O. 1977-241-530/3090

OPTIONAL FORM 41 (Rev. 7-76)
Prescribed by GSA
FPMR (41 CFR) 101-11.206

MEMORANDUM

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

TO : Associate Director for New Drug Evaluation (HFD-100)
Director, Division Generic Drug Products (HFD-530)
Director, Division Neuropharmacological Drug Products (HFD-120)

DATE: January 19,1979

FROM : Director, Division of Biopharmaceutics (HFD-520)

SUBJECT: Bioavailability Requirement of Phentermine HCl 30 mg tablets and capsules

RECOMMENDATION:

1. The Division of Biopharmaceutics waives the in vivo bioavailability requirements for phentermine hydrochloride 30 mg tablets and capsules and substitutes an in vitro dissolution test requirement (CFR 320.22) employing the FDA paddle at 50 rpm.

2. In the event that a firm wishes to include a slow release or controlled release claim within the labelling, the firm must demonstrate such claim through an in vivo study.

3. These products should be handled as ANDA's

BASIS OF RECOMMENDATION:

1. Phentermine HCl is readily soluble and presents no known bioequivalency problem employing criteria (CFR 320.52) described in the January 7, 1977 FR entitled " Bioavailability-Bioequivalence Requirements."

2. A review of NDA files (including both Beecham's Fastin and Pennwalt's Ionamine) indicate that although higher peak blood levels can be obtained from an immediate release tablet (30 mg) at the initial doses, there does not appear to be any safety hazard associated with an immediate release 30 mg tablet (as exemplified by Fastin).

3. In light of the demonstrated dose proportionality and the long biologic half-life (in excess of 20 hours) of phentermine HCl, equivalent steady-state plasma levels would be achieved with either a slow or fast release dosage form of this drug when administered once a day or when administered in divided doses employing an 8 mg dosage form.

4. The bioavailablity of phentermine HCl can be assured through adequate dissolution which assures complete release of the drug.

Bernard E. Cabana, Ph.D.

MEMORANDUM

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

86-329

TO : Associate Director for New Drug Evaluation (HFD-100)
Director, Division Generic Drug Products (HFD-530)
Director, Division Neuropharmacological Drug Products (HFD-120)

DATE: January 15,1979

FROM : Director, Division of Biopharmaceutics (HFD-520)

SUBJECT: Bioavailability Requirement of Phentermine HCl 30 mg tablets

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2. A review of NDA files (including both Fastin and Ionamine) indicate that although higher peak blood levels can be obtained from an immediate release tablet (30 mg) at the initial doses, there does not appear to be any safety hazard associated with an immediate release 30 mg tablet.

3. In light of the demonstrated dose proportionality and the long biologic half-life (in excess of 20 hours) of phentermine HCl, equivalent steady-state plasma levels would be achieved with either a slow or fast release dosage form of this drug when administered once a day.

4. The bioavailablity of phentermine HCl can be assured through adequate dissolution which assures complete release of the drug.

Benard E. Cabana, Ph.D.

Attachments

cc: HFD-520
HFD-525
HFD-522 (Drug)
HFD-522 (Dighe)
Chron.

BEC:KW 1/15/79

MEMORANDUM

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

TO : Director, Division of Biopharmaceutics (HFD-520) DATE: January 10, 1979
THROUGH: Chief, Pharmacokinetics and Biopharmaceutics Branch (HFD-525)

FROM : Pharmacologist, Pharmacokinetic Branch (HFD-522)

SUBJECT: Phentermine Hydrochloride

Upon review of the Phentermine Hydrochloride data it is evident that this product may meet one of the conditions for criteria for waiver of evidence of in vivo bioavailability, specifically section 320.22 (d)(5) which states:

The drug product contains the same active drug ingredient or therapeutic moiety and is in the same strength and dosage form as a drug product that is the subject of an approved full or abreviated new drug application, and both drug products meet and appropriate in vitro test that has been approved by the Food and Drug Administration.

Information as submitted in a NDA provides evidence that Fastin manufactured by Beecham (Phentermine Hydrochloride, 30 mg) dissolves 100% within 15 minutes. Fastin by Beecham is an NDA holder and was given approval based on clinical trials.

It is recommended that phentermine hydrochloride products may be subject to approval without providing evidence of the in vivo bioavailability requirement. However, such products could not be put on any type of therapeutic equivalency lists without demonstrating bioequivalency to the currently marketed NDA holders.

1/15/79

Keith S. Rotenberg, Ph.D.

KSR/kw/1-10-79

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service

TO : Bernard E. Cabana, Ph.D.(HFD-520) DATE: NOV 20 1978
Through: Associate Director for Drug Monographs 11/20/78

FROM : Associate Director for New Drug Evaluation (HFD-100)

SUBJECT: Phentermine.

Attached is a memorandum dated November 3, 1978 from Dr. Kartzinel concerning phentermine. We would like to know whether there is any evidence that phentermine resin complex is a sustained release product or whether its prolonged effect is due to the long half-life of phentermine base. Are there comparative pharmacokinetic data for the phentermine HCl salt, phentermine base and phentermine resin complex? If these products are essentially similar, in our view they could all be handled, in the future, as ANDAs.

M. J. F.
Marion J. Finkel, M.D.

Attachment

cc:
HFD-120/Dr. Kartzinel
HFD-120/Dr. Hayes

MEMORANDUM

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

TO : Associate Director, New Drug Evaluation
HFD-100

DATE: NOV - 3 1978

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

SUBJECT: Phentermine HCl and Resin Complex Dosage Forms - NDA/ANDA Policy

Lemmon Pharmacal's Adipex-P (30 mg, Phentermine HCl)
18-042, 18-159

A meeting was held today in the DNDP's conference room with R. Kartzinel, R. Hahn, J. Mansur, B. Cabana, K. Rotenberg, T. Hayes, and B. Prettyman. The subject of the meeting was a policy for pending applications for proposed phentermine products. Apparently there still exist inconsistencies in the handling of such applications and the FDA's position regarding phentermine products.

As you are aware, there are basically two approved dosage forms for phentermine, one being the resin complex (Ionamin, 15 and 30 mg - pre-1962 and reviewed by NAS/NRC) and the hydrochloride salt (Fastin, 30 mg - post-1962 and Wilpo, 8 mg, t.i.d. - pre-1962).

On July 19, 1974 a Federal Register Notice was published which upgraded to effective the claim of Ionamin in the management of exogenous obesity. However, all the other claims which included the controlled or sustained release action of the product were found as lacking evidence. However, in spite of a notice to this effect, we have been treating phentermine resin complex as a sustained or controlled release formulation, yet no one has reviewed any data substantiating this. In fact, the long half-life of phentermine may be the basis for such a claim. Neither this Division nor HFD-520 has reviewed any data which shows the resin complex to be any different from that of the hydrochloride salt.

In addition to this apparent conflict, we have been utilizing a policy regarding phentermine HCl, 30 mg, which until a meeting held on September 7, 1978, appeared to be rational and consistent. With such applications as Lemmon's Adipex-P (30 mg, Phentermine HCl) we felt that in view of the historical, clinical evidence regarding safety and efficacy of phentermine (resin complex and HCl salt), bioavailability/bioequivalency studies along with manufacturing data would be adequate.

Such a decision was made at a meeting held on March 17, 1978. In that meeting one published report for Fastin and the DESI NAS/NRC review were cited as two well controlled studies. All of our letters to Lemmon have indicated the need only for bioavailability/bioequivalency studies to substantiate the safety and effectiveness of a proposed 30 mg HCl product.

On October 20, 1978 this Division received a copy of a "Memorandum for the Record" based on a meeting held on September 7, 1978. Two conclusions are cited in this memo which cause some confusion and problems for this Division:

> #1. ANDAs will be accepted for phentermine in controlled release form based on DESI 5378 (Ionamin, NDA 11-613).

The Federal Register Notice cited, as explained earlier, refutes the claim of controlled release. Yet, this formulation has apparently been accepted as such.

> #3. NDAs will be approved for conventional forms on the basis of published literature or new studies.

This policy is in complete disagreement with that set on March 17, 1978 which cited the one published study for Fastin (NDA 17-352, 30 mg HCl, post-1962) and the DESI review for Wilpo (8 mg, t.i.d., pre-1962). One policy as decided then would be to accept adequate bioavailability/bioequivalency studies and manufacturing data for another phentermine HCl, 30 mg such as Lemmon's Adipex-P.

In view of this apparent confusion, I suggest that a complete evaluation be done by HFD-520 regarding the question of whether the resin complex of phentermine is controlled release or if there is no real difference between this formulation and that of the HCl salt. Once we have come to a conclusion, a Federal Register Notice should be published explaining our views and allowing for ANDAs.

I would also suggest that the two pending NDAs of Lemmon for Phentermine HCl, 30 mg be evaluated based upon bioavailability/bioequivalency in view of the Fastin/Wilpo literature and other historical, clinical experience with phentermine. Subsequent submissions could be handled through ANDAs.

We must consider the possibility that if Ionamin demonstrates no significant difference to Fastin, then we have the alternative of accepting ANDAs for the resin complex or HCl salt with no need for

further consideration of an NDA such as Lemmon's Adipex-P.

There also exists our option to consider pending or subsequent NDAs as "like or related" based upon Fastin (one published study), Wilpo (DESIed) and possibly Ionamin (if there is no significant difference between the behavior of the resin complex and HCl salt).

Ronald Kartzinel, M.D., Ph.D.

Enclosures

CHEMIST'S REVIEW
(If necessary, continue any item on 8" x 10½" paper. Key continuation to item by number.)

1. ORGANIZATION: HFD-530

2. NDA NUMBER: 84-695

3. NAME AND ADDRESS OF APPLICANT (City and State)
C. H. Bundy Co.
Cincinnati, OH 45202

4. DATE: 3-17-75

DATE ASSIGNED FOR EFFICACY

6. NAME OF DRUG: Phentermine HCl

7. NONPROPRIETARY NAME

8. SUPPLEMENT NUMBER / DATE

9. PURPOSE OF SUPPLEMENT

10. AMENDMENT DATE(s)

11. OTHER DATE (Report, etc.)

12. PHARMACOLOGICAL CATEGORY: anorexciant

13. AF NUMBER: 14-446

16. RELATED IND/NDA/MF(s)

14. DOSAGE FORM: capsule - long acting

15. HOW DISPENSED: XX Rx ☐ OTC

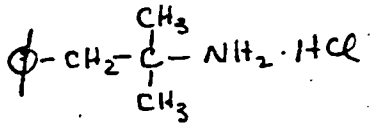
17. POTENCY(100): 30 mg.

18. NAS/NRC: ☐ UNDER REVIEW XX REVIEWED

19. CHEMICAL NAME: α,α-dimethylphenethylamine hydrochloride

20. RECORDS AND REPORTS
CURRENT: ☐ YES ☐ NO
REVIEWED: ☐ YES ☐ NO

21. CHEMICAL FORMULA



22. REMARKS

Firm indicates all day supression of appetite. Formula for a long acting preparation.

23. CONCLUSIONS

bioavailability studies are required
firm must develope rate of release specifications/tests

incomplete.

24. REVIEWER

NAME: Mary Ann Jarski

SIG

DATE COMPLETED: 10/14/75

DISTRIBUTION: ORIGINAL JACKET ✓ DUPLICATE JACKET REVIEWER

FDH FORM 2266 (10/68) PREVIOUS EDITION MAY BE USED UNTIL SUPPLY IS EXHAUSTED.

MEMO RECORD	AVOID ERRORS PUT IT IN WRITING	DATE 10-3-75
FROM: mary ann jarski (thru J.L. Meyer)		OFFICE HFD-530
TO: Mr. David H. Bryant, Office of Compliance		DIVISION HFD-322

SUBJECT: Inspection Request

SUMMARY

In connection with ANDA - 84-695

for: Phentermine HCl Capsules, 30 mg, - Long acting

Applicant: C.M. Bundy Co.
Cincinnati, OH 45202

AF - 14-446

REQUESTED:

[X] 1. Evaluation of compliance with CGMP for:

[X] a. The applicant

[] b. Others

[X] 2. Recommendation for approval/disapproval of the application/communication/supplement, based on your evaluation of compliance with CGMP

REMARKS:

Firm has submitted application for long acting dosage form but has not included bioavailability studies or rate of release testing.

SIGNATURE	DOCUMENT NUMBER

Enter explanation of comments for each item. If necessary, continue on a separate sheet. Key continuation to item by number. Enter "N.C." if no change or "N.A." if not applicable. | 84-695

25. COMPONENTS AND COMPOSITION (c, g)

composition of non-pariel beads , gelatin capsule and green, yellow/orange filler beads.

26. FACILITIES AND PERSONNEL (ca,b)

included

27. SYNTHESIS (cc)

required

28. RAW MATERIAL CONTROLS (cd,e)

a. NEW DRUG SUBSTANCE

guidelines for physical/chemical properties

b. OTHER INGREDIENTS

per issuing letter

29. OTHER FIRM(s) (cl)

~~upp~~lies active ingredient from the which is in non-compliance

30. MANUFACTURING AND PROCESSING (cc,h,j,k)

included

31. CONTAINER (ci)

needed

32. PACKAGING AND LABELING (ci,m)

included

33. LABORATORY CONTROLS (In-Process and Finished Dosage Form) (cn)

guidelines for physical/chemical parameters

34. STABILITY (cp)

needed

35. CONTROL NUMBERS (cc)

included

36. SAMPLES AND RESULTS (q)

a. VALIDATION will be necessary b. MARKET PACKAGE

37. LABELING (4)

unsatisfactory

38. ESTABLISHMENT INSPECTION

requested 10/3/75

39. RECALLS

FDH FORM 2366 (10/66)

MEMO RECORD	AVOID ERRORS PUT IT IN WRITING	DATE 10-24-74
FROM: ma jarski		OFFICE
TO: file		DIVISION

SUBJECT: Phentermine Hydrochloride

SUMMARY

Specifications for phentermine hydrochloride are essentially based on those in 12-737/S-001 approved 12-18-73. However, the following is to be noted:

loss on drying:

residue on:
ignition

assay range:

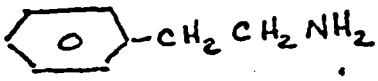
Tablets:

Content uniformit

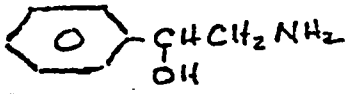
assay:

SIGNATURE	DOCUMENT NUMBER

Comparative Structures

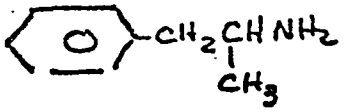


Phenylethylamine



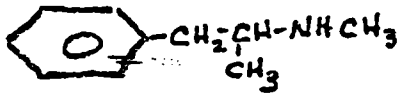
Phenylethanolamine

USP



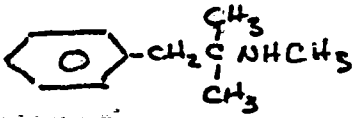
Amphetamine
Dextro-amphetamine ✓

USP

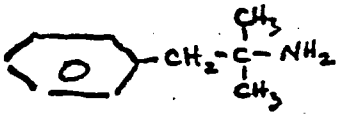


Methamphetamine ✓

USP



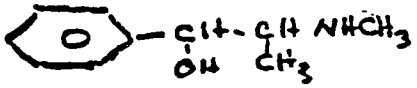
Mephentermine ✓



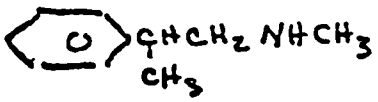
Phentermine

Phenylpropanolamine

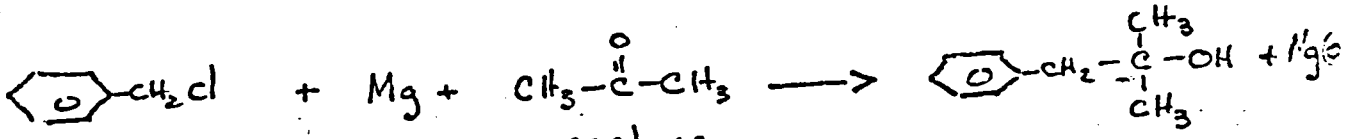
USP
NF



Ephedrine
Racephedrine



Phenylpropylmethylamine



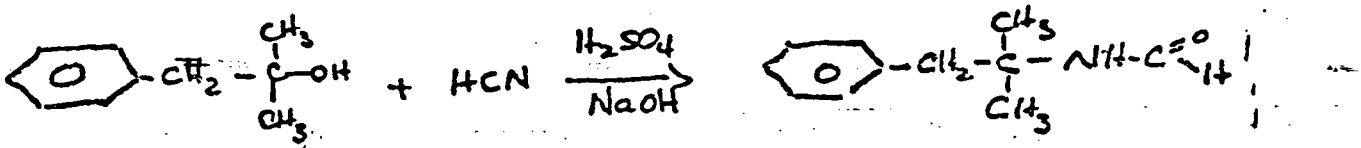
benzyl chloride

acetone

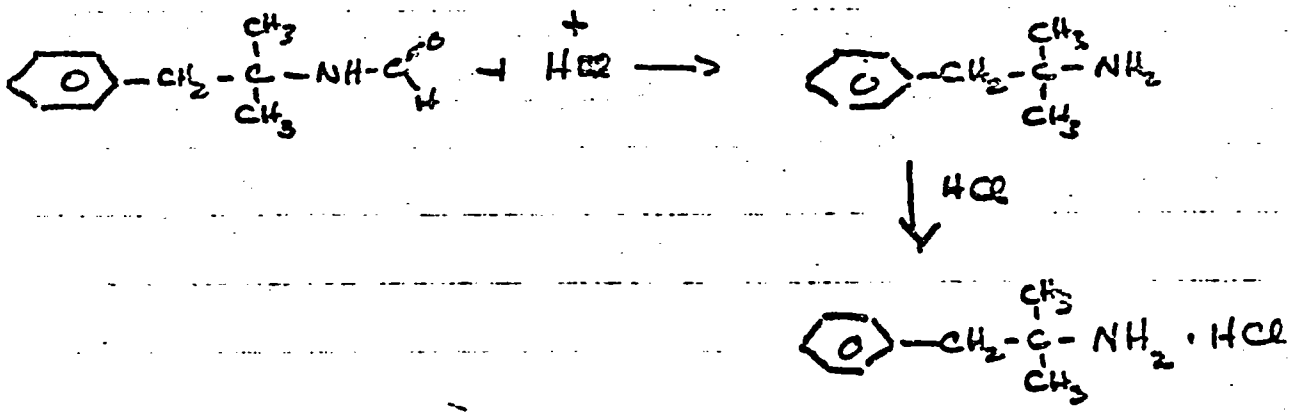
α,α-dimethylphenethyl alcohol

(benzyl dimethyl carbinol

Grignard Reaction



N-Formyl-α,α-dimethylphenethyl amine



phentermine . HCl

Standard preparation—Dissolve about 90 mg. of U. S. P. Dexamethasone Phosphate Reference Standard, accurately weighed, in water to make 250.0 ml., and mix.

Assay preparation—Dissolve about 100 mg. of Dexamethasone Sodium Phosphate, accurately weighed, in water to make 250.0 ml., and mix.

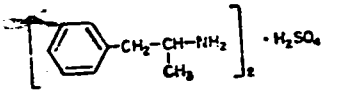
Procedure—Pipet 2 ml. each of the *Standard preparation* and the *Assay preparation*, respectively, into separate, glass-stoppered, 100-ml. graduated cylinders, add 5.0 ml. of *Alkaline phosphatase solution* to each cylinder, insert the stoppers, mix, and allow to stand at 37 ± 1° for 45 minutes. Add 50.0 ml. of methylene chloride to each cylinder, insert the stoppers, invert once each second for 30 seconds, and allow to stand until the methylene chloride layer is clear (about 20 minutes). Concomitantly and without delay, determine the absorbances of the methylene chloride solutions obtained from the *Assay preparation* and the *Standard preparation* at 236 mμ, with a suitable spectrophotometer, using methylene chloride as the blank. Calculate the quantity, in mg., of $C_{22}H_{28}FNaO_8P$ in the portion of Dexamethasone Sodium Phosphate taken by the formula $0.2730(Ar/As - 1.316D$, in which C is the concentration, in mcg. per ml., of U. S. P. Dexamethasone Phosphate Reference Standard in the *Standard preparation*, Ar and As are the absorbances of the solutions from the *Assay preparation* and the *Standard preparation*, respectively, 1.316 is the ratio of the molecular weight of dexamethasone sodium phosphate to that of dexamethasone, and D is the calculated amount, in mg., of free dexamethasone in the sample taken.

Packaging and storage—Preserve in tight containers.

CATEGORY: Adrenocortical steroid (anti-inflammatory).

USUAL DOSE: Intramuscular or intravenous, the equivalent of 2 to 4 mg. of dexamethasone phosphate six to eight times a day.

USUAL DOSE RANGE: 2 to 50 mg. daily.



Dextroamphetamine Sulfate

(+)-α-Methylphenethylamine Sulfate (2:1)
$(C_9H_{13}N)_2.H_2SO_4$ 368.50

Dextroamphetamine Sulfate, the dextrorotatory isomer of amphetamine sulfate, contains not less than 98.0 percent and not more than 101.0 percent of $(C_9H_{13}N)_2.H_2SO_4$, calculated on the dried basis.

Description: White, odorless, crystalline powder. Its 1 in 20 solution has a pH of between 5 and 6.

Solubility: Soluble in water; slightly soluble in alcohol; insoluble in ether.

Identification—

A: Dissolve about 100 mg. in 5 ml. of water, add 5 ml. of sodium hydroxide T.S., cool to 10° to 15°, add 1 ml. of a mixture of 1 volume of benzoyl chloride and 2 volumes of absolute ether, stopper, and shake well for 3 minutes. Filter the precipitate, wash it with about 10 ml. of cold water, and recrystallize it from diluted alcohol: the crystals of the benzoyl derivative of dextroamphetamine so obtained, after drying at 105° for 1 hour, melt between 155° and 160°.

B: A solution (1 in 10) responds to the tests for *Sulfate*, page 893.

Specific rotation, page 936: not less than +20° and not more than +23.5°, calculated on the dried basis, determined in a solution containing 400 mg. in each 10 ml.

Loss on drying, page 935: Dry it at 105° for 2 hours: it loses not more than 1 percent of its weight.

Residue on ignition, page 991: not more than 0.1 percent.

Assay—Dissolve about 300 mg. of Dextroamphetamine Sulfate, accurately weighed, in 25 ml. of water in a separator. Add 5 ml. of sodium hydroxide T.S., and extract with six 15-ml. portions of ether. Wash the combined ether extracts with 10 ml. of water, and extract the water with 10 ml. of ether, adding the latter to the main extract. To the ether extract add 25.0 ml. of 0.1 *N* sulfuric acid, and stir well. Heat gently until the ether is expelled, cool, add methyl red T.S., and titrate the excess acid with 0.1 *N* sodium hydroxide. Each ml. of 0.1 *N* sulfuric acid is equivalent to 18.42 mg. of $(C_9H_{13}N)_2.H_2SO_4$.

Packaging and storage—Preserve in well-closed containers.

CATEGORY: Central stimulant.
USUAL DOSE: 2.5 to 5 mg. one to three times a day.
USUAL DOSE RANGE: 5 to 50 mg. daily.

Dextroamphetamine Sulfate Elixir

Dextroamphetamine Sulfate Elixir contains, in each 100 ml., not less than 90.0 mg. and not more than 110.0 mg. of $(C_9H_{13}N)_2.H_2SO_4$.

Identification—Transfer 25 ml. of Elixir to a 250-ml. separator, add 25 ml. of water and 5 ml. of sodium hydroxide solution (1 in 10), mix, and extract with two 30-ml. portions of ether. Wash the combined ether extracts with two 5-ml. portions of sodium hydroxide solution (1 in 100). Filter the ether extracts through a pledget of cotton, previously saturated with ether, into a 100-ml. beaker, and evaporate on a steam bath in a current of air to about 1 ml. Dissolve the residue in 3 ml. of alcohol, and transfer to a glass-stoppered, 125-ml. conical flask containing 25 ml. of water. Rinse the beaker with 3 ml. of alcohol, and transfer to the flask. Cool to about 15°, add 3 ml. of sodium hydroxide T.S., then add 1 ml. of a mixture of 1 volume of benzoyl chloride and 2 volumes of absolute ether, and shake for 2 minutes. Filter the precipitate, wash with about 15 ml. of cold water, and recrystallize twice from diluted alcohol: the benzoyl derivative of dextroamphetamine so obtained, after being dried at 105° for 1 hour, melts between 154° and 160°.

Isomeric purity—Transfer 150 ml. of Elixir to a 500-ml. separator, add 15 ml. of sodium hydroxide solution (1 in 10), and extract with one 60-ml. and two 40-ml. portions of ether. Wash the combined ether extracts with two 10-ml. portions of sodium hydroxide solution (1 in 100). Wash the aqueous alkaline extracts with 20 ml. of ether, adding the ether washing to the combined ether extracts. Filter the ether extracts through a pledget of cotton, previously saturated with ether, into a 250-ml. beaker, rinse the cotton with a small amount of ether, and evaporate on a steam bath in a current of air to about 2 ml. Dissolve the residue in 20 ml. of chloroform, and transfer to a separator containing 35 ml. of 0.1 *N* sulfuric acid. Complete the transfer with two additional 20-ml. portions of chloroform. Shake the separator vigorously for 1 minute, allow the layers to separate, and discard the chloroform. Add to the liquid in the separator 2.5 g. of sodium bicarbonate, preventing it from coming in contact with the mouth of the separator, and swirl until most of the bicarbonate has dissolved. By means of a 1-ml. syringe, rapidly inject 1.0 ml. of acetic anhydride directly into the contents of the separator. Immediately stopper the separator, and shake vigorously until the evolution of carbon dioxide has ceased, releasing the pressure as necessary through the stopcock. Allow to stand for 5 minutes, and extract the solution with 50 ml. of chloroform, shaking vigorously for 1 minute. Filter the chloroform extract through a pledget of filter cotton into a 100-ml. beaker, rinse the cotton with a small amount of chloroform, and evaporate on a steam bath in a current of air or nitrogen to dryness. Heat and triturate the residue until the odor of chloroform is no longer perceptible. Allow the residue to cool, inducing it to crystallize. Reduce the crystals to a fine powder, heat at 80° for 30 minutes, and cool: the specific rotation of the acetylamphetamine so obtained, determined in a solution in chloroform containing 20 mg. per ml., a 200-mm. semi-micro polarimeter tube being used, is not less than −37.5° and not more than −44.0°.

Assay—

Chromatographic column—Pack a pledget of fine glass wool in the base of a 300- × 25-mm. chromatographic tube with the aid of a tamping rod having a disk with a diameter about 1 mm. less than that of the tube. To 2 g. of chromatographic siliceous earth in a 100-ml. beaker add 1 ml. of dilute hydrochloric acid (1 in 200). Mix with a glass rod until a fluffy mixture is obtained. Transfer the mixture to the column, and tamp moderately to compress the material into a uniform mass. Transfer the *Assay preparation* to the column, scrub the beaker with 1 g. of chromatographic siliceous earth, transferring it to the column, and tamp as before. Wipe the beaker and glass rod with a pledget of fine glass wool, place it on top of the tube, and press it down, sweeping the wall of the tube with it.

Standard preparation—Dissolve an accurately weighed quantity of U. S. P. Dextroamphetamine Sulfate Reference Standard in dilute sulfuric acid (1 in 20) that previ-

ously has been saturated with chloroform, and dilute quantitatively and stepwise with the same solvent to obtain a solution having a known concentration of about 0.5 mg. per ml.

Assay preparation—Pipet 5 ml. of Dextroamphetamine Sulfate Elixir into a 100-ml. beaker, add 1 drop of diluted hydrochloric acid, and swirl to mix. Add 6 g. of chromatographic siliceous earth, and mix with a glass rod until a fluffy mixture is obtained.

Procedure—Wash the *Chromatographic column* with 100 ml. of water-saturated chloroform, and discard the washings. Arrange to collect the eluate in a separator containing 10.0 ml. of dilute sulfuric acid (1 in 20) that previously has been saturated with chloroform. Pass through the column 60 ml. of a freshly prepared ammoniacal chloroform solution, made by shaking 50 volumes of chloroform with 1 volume of stronger ammonia water for 1 to 2 minutes and discarding the aqueous phase. Complete the elution with 60 ml. of water-saturated chloroform. Shake the separator vigorously for 1 minute, allow the layers to separate, and discard the chloroform. Concomitantly determine the absorbances of the *Standard preparation* and the *Assay preparation* in 1-cm. cells at 280 mμ and at the maximum at about 257 mμ, with a suitable spectrophotometer, using chloroform-saturated dilute sulfuric acid (1 in 20) as the blank. Calculate the quantity, in mg., of $(C_9H_{13}N)_2.H_2SO_4$ in the portion of the Elixir taken by the formula $10C(A_{257} - A_{280})_U/(A_{257} - A_{280})_S$, in which C is the concentration, in mg. per ml., of U. S. P. Dextroamphetamine Sulfate Reference Standard in the *Standard preparation*, and the parenthetic expressions are the differences in the absorbances of the two solutions at the wavelengths indicated by the subscripts, for the *Assay preparation* (U) and the *Standard preparation* (S), respectively.

Alcohol content, page 918: from 9 to 11 percent of C_2H_5OH.

Packaging and storage—Preserve in tight, light-resistant containers.

CATEGORY and DOSE: See *Dextroamphetamine Sulfate*.

Dextroamphetamine Sulfate Tablets

Dextroamphetamine Sulfate Tablets contain not less than 93.0 percent and not more than 107.0 percent of the labeled amount of $(C_9H_{13}N)_2.H_2SO_4$.

Identification—Macerate a quantity of powdered Tablets, representing about 50 mg. of dextroamphetamine sulfate, with 10 ml. of water for 30 minutes, and filter into a small flask. Cool the filtrate to about 15°, and proceed as directed in the *Identification test* under *Dextroamphetamine Sulfate Elixir*, page 178, beginning with "add 3 ml. of sodium hydroxide T.S."

Disintegration, page 932: 30 minutes, without the use of disks.

Content uniformity, page 930: meet the requirements for *Tablets*.

Isomeric purity—Pack a pledget of fine glass wool in the base of a 200- × 25-mm. chromatographic tube, with the aid of a tamping rod. Add 5 g. of chromatographic siliceous earth, and tamp firmly to compress the material to a uniform mass.

Finely powder a number of Tablets, equivalent to about 130 mg. of dextroamphetamine sulfate, mix the powder in a mortar with 5 g. of chromatographic siliceous earth, add 1 ml. of methanol and 0.5 ml. of stronger ammonia water, and triturate to a uniform mixture. Transfer the mixture without delay to the chromatographic tube, and tamp as before. Wipe the mortar and pestle with a small amount of glass wool, and insert it into the tube on top of the column. Arrange a 125-ml. separator containing 35 ml. of 0.1 *N* sulfuric acid to receive the effluent. Pass 60 ml. of chloroform through the column. Proceed as directed in the test for *Isomeric purity* under *Dextroamphetamine Sulfate Elixir*, page 178, beginning with "Shake the separator vigorously."

Assay—

Chromatographic column and *Standard preparation*—Prepare as directed in the *Assay* under *Dextroamphetamine Sulfate Elixir*, page 178.

Assay preparation—Weigh and finely powder not less than 20 Dextroamphetamine Sulfate Tablets. Weigh accurately a portion of the powder, equivalent to about 5 mg. of dextroamphetamine sulfate, and transfer to a 100-ml. beaker. Add 2 ml. of dilute hydrochloric acid (1 in 200), and swirl gently to wet the powder thoroughly. Warm on a steam bath for about 1 minute with occasional gentle swirling, and cool. Add 3 g. of chromatographic siliceous earth, and mix with a glass rod until a fluffy mixture is obtained.

Procedure—Wash the *Chromatographic column* with 100 ml. of water-saturated chloroform, and discard the washings. Place under the column as a receiver a separator containing 10.0 ml. of dilute sulfuric acid (1 in 20) that previously has been saturated with chloroform. Pass through the column 35 ml. of a freshly prepared ammoniacal chloroform solution, made by shaking 50 volumes of chloroform with 1 volume of stronger ammonia water for 1 to 2 minutes and discarding the aqueous phase. Complete the elution with 70 ml. of water-saturated chloroform. Shake the separator vigorously for 1 minute, allow the layers to separate, and discard the chloroform. Record the absorption spectra of the *Standard preparation* and the eluted *Assay preparation* in 1-cm. cells over the range of 225 mμ to 340 mμ, with a suitable recording spectrophotometer, using chloroform-saturated dilute sulfuric acid (1 in 20) as the blank. Draw the base line as a continuation of the curve between 290 mμ and 340 mμ, and determine the corrected absorbances at the wavelength of maximum absorbance at about 257 mμ. Calculate the quantity, in mg., of $(C_9H_{13}N)_2.H_2SO_4$ in the portion of the Tablets taken by the formula $10C(A_U/A_S)$, in which C is the concentration, in mg. per ml., of U. S. P. Dextroamphetamine Sulfate Reference Standard in the *Standard preparation*, and A_U and A_S are the absorbances of the eluted *Assay preparation* and the *Standard preparation*, respectively.

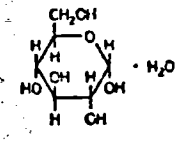
Packaging and storage—Preserve in well-closed containers.

Tablets available—Tablets usually available contain the following amounts of dextroamphetamine sulfate: 5 and 10 mg.

CATEGORY and DOSE: See *Dextroamphetamine Sulfate*.

Dextrose

D(+)-Glucose
$C_6H_{12}O_6.H_2O$ 198.17



Dextrose is a sugar usually obtained by the hydrolysis of starch. It contains one molecule of water of hydration or is anhydrous.

Description: Colorless crystals or white, crystalline or granular powder. Is odorless, and has a sweet taste.

Solubility: Freely soluble in water; very soluble in boiling water; sparingly soluble in boiling alcohol; slightly soluble in alcohol.

Identification—Add a few drops of a solution (1 in 20) to 5 ml. of hot alkaline cupric tartrate T.S.: a copious red precipitate of cuprous oxide is formed.

Specific rotation, page 936: not less than +52.5° and not more than +53.0°, calculated on the anhydrous basis, determined in a solution containing 10 g. of Dextrose and 0.2 ml. of ammonia T.S. in each 100 ml.

Color of solution—Dissolve 25 g. in sufficient water to make 50.0 ml. of solution: the solution has no more color than a solution prepared by mixing 1.0 ml. of cobaltous chloride C.S., 3.0 ml. of ferric chloride C.S., and 2.0 ml. of cupric sulfate C.S. with water to make 10 ml., and diluting 3 ml. of this solution with water to 50 ml. Make the comparison by viewing the solutions downward in matched color-comparison tubes against a white surface.

Acidity—Dissolve 5 g. in 50 ml. of carbon dioxide–free water. Add phenolphthalein T.S., and titrate with 0.02 *N* sodium hydroxide to the production of a distinct pink color: not more than 0.3 ml. is required for neutralization.

Water, page 947—Dry it at 105° for 16 hours: the hydrous form loses not less than 7.5 percent and not more than 9.5 percent of its weight, and the anhydrous form loses not more than 0.5 percent of its weight.

Residue on ignition, page 901: not more than 0.1 percent.

Chloride, page 895—A 2-g. portion shows no more chloride than corresponds to 0.5 ml. of 0.02 *N* hydrochloric acid (180 parts per million).

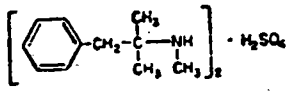
Sulfate, page 895—A 2-g. portion shows no more sulfate than corresponds to 0.5 ml. of 0.02 *N* sulfuric acid (250 parts per million).

Arsenic, page 894—Dissolve 3 g. in 35 ml. of water. The limit is 1 part per million.

Heavy metals, page 897—Dissolve 5 g. in 23 ml. of water, and add 2 ml. of diluted acetic acid: the heavy metals limit is 5 parts per million.

Packaging and storage—Preserve in well-closed, light-resistant containers.
Tablets available—Tablets usually available contain the following amounts of meperidine hydrochloride: 50 and 100 mg.

CATEGORY and DOSE—See *Meperidine Hydrochloride*.



Mephentermine Sulfate

N,α,α-Trimethylphenethylamine Sulfate (2:1)
$(C_{11}H_{17}N)_2.H_2SO_4$ (anhydrous) 424.61

Mephentermine Sulfate is anhydrous or contains two molecules of water of hydration. It contains not less than 98.0 percent and not more than 102.0 percent of $(C_{11}H_{17}N)_2.H_2SO_4$, calculated on the anhydrous basis.

Description: White, odorless crystals or crystalline powder. Its solutions are slightly acid to litmus, having a pH of about 6.
Solubility: Soluble in water; slightly soluble in alcohol; insoluble in chloroform.
Identification—
A: A 1 in 500 solution yields a dark brown precipitate when shaken with an equal volume of iodine T.S., and a white precipitate when shaken with an equal volume of mercuric-potassium iodide T.S.
B: Dissolve about 100 mg. in 5 ml. of water, and add, in small portions and with stirring, 10 ml. of trinitrophenol T.S. Allow to stand for 30 minutes, filter, and wash the precipitate with small portions of cold water until the last washing is practically colorless: the picrate so obtained, after drying at 105°, melts between 154° and 158°. [*Caution—Picrates may explode.*]
C: It responds to the tests for *Sulfate*, page 893.
Water, page 947: not more than 0.2 percent (anhydrous form) and not more than 8 percent (hydrous form), determined by the *Titrimetric Method*.
Residue on ignition, page 901: not more than 0.1 percent.
Assay—Dissolve about 300 mg. of Mephentermine Sulfate, accurately weighed, in 50 ml. of glacial acetic acid, add 4 drops of *p*-naphtholbenzein T.S., and titrate with 0.1 *N* perchloric acid to a green end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 42.46 mg. of $(C_{11}H_{17}N)_2.H_2SO_4$.
Packaging and storage—Preserve in well-closed, light-resistant containers.
Labeling—Label it to indicate whether it is anhydrous or hydrous.

CATEGORY: Adrenergic (vasopressor).
USUAL DOSE: Oral, 12.5 to 25 mg. one or two times a day.
Intramuscular or intravenous, the equivalent of 15 to 30 mg. of mephentermine; infusion, 150 mg. in 500 ml. of an isotonic solution at a rate adjusted to maintain blood pressure.
USUAL DOSE RANGE: The equivalent of 12.5 to 80 mg. of mephentermine or mephentermine sulfate, repeated as necessary.

Mephentermine Sulfate Injection

Mephentermine Sulfate Injection is a sterile solution of mephentermine sulfate in water for injection. It contains not less than 95.0 percent and not more than 105.0 percent of the labeled amount of mephentermine ($C_{11}H_{17}N$).

Identification—It responds to the *Identification tests* under *Mephentermine Sulfate*, page 399.
pH, page 938: between 4.0 and 6.5.
Other requirements—It meets the requirements under *Injections*, page 797.
Assay—Transfer to a coarse-porosity, sintered-glass filtering crucible 5 g. of purified siliceous earth and 500 mg. of chromatographic magnesium oxide, mix with the aid of a glass rod, add an accurately measured volume of Mephentermine Sulfate Injection, equivalent to about 60 mg. of mephentermine, and again mix. Add 15 ml. of hot chloroform, mix, and with gentle suction draw off the chloroform into 40 ml. of glacial acetic acid. Repeat the extraction with four 10-ml. portions of hot chloroform, successively and similarly applied, collecting each portion in the glacial acetic acid. Add 6 drops of *p*-naphtholbenzein T.S., and titrate with 0.1 *N* perchloric acid to a green end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 16.33 mg. of $C_{11}H_{17}N$.
Packaging and storage—Preserve in single-dose or in multiple-dose containers, preferably of Type I glass.
Injections available—Injection usually available contains the equivalent of the following amounts of mephentermine: 15 mg. in 1 ml.; 30 mg. in 1 and 2 ml.; 60 mg. in 2 ml.; 150 mg. in 10 ml.; 300 mg. in 10 ml.

CATEGORY and DOSE: See *Mephentermine Sulfate*.

Mephentermine Sulfate Tablets

Mephentermine Sulfate Tablets contain not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $(C_{11}H_{17}N)_2.H_2SO_4$.

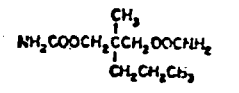
Identification—A water extract of the Tablets responds to the *Identification tests* under *Mephentermine Sulfate*, page 399.
Disintegration, page 932: 30 minutes.
Content uniformity, page 930—Finely powder 1 Tablet, and transfer the powder with the aid of four 250-mg. portions of chromatographic siliceous earth to a cylindrical, coarse-porosity, sintered-glass filtering funnel upon which previously has been placed 300 mg. of magnesium oxide (this will be used to prepare the Test solution). Transfer a portion of the powdered Tablets prepared for the *Assay*, accurately weighed and equivalent to 100.0 percent of the declared content of mephentermine, to a similar filtering funnel upon which previously has been placed 300 mg. of magnesium oxide and 1 g. of chromatographic siliceous earth (this will be used to prepare the Standard solution). Arrange to collect eluate from each funnel in suction flasks each containing 25.0 ml. of dilute sulfuric acid (1 in 350). Treat each portion as follows: Mix the mass with the aid of a glass stirring rod, while adding 1 ml. of water, accurately measured, and dropwise, continuing to stir until a uniform mixture is obtained. Add, with further stirring, four 10-ml. portions of warm chloroform, applying suction as needed to drain completely each portion before adding the next. Upon completion of the elution, shake the chloroform and acid vigorously. Clarify a portion of the aqueous supernatant liquid by centrifuging. Concomitantly determine the absorbances of the clear supernatant liquid from both the single Tablet (Test solution) and the composite powder (Standard solution) in 1-cm. cells at the wavelengths of minimum absorbance at about 251 mμ and about 261 mμ, and at the wavelength of maximum absorbance at about 257 mμ, with a suitable spectrophotometer, using dilute sulfuric acid (1 in 350) saturated with chloroform as the blank. Calculate the percentage of declared content by the formula $100A_U'/A_S'$, in which A_U' and A_S' are the differences for the Test solution and the Standard solution, respectively, given by the general formula $A' = A_{257} - 0.5(A_{254} + A_{261})$. Mephentermine Sulfate Tablets meet the requirements for *Tablets*.
Assay—Weigh and finely powder not less than 20 Mephentermine Sulfate Tablets. Transfer to a cylindrical, coarse-porosity, sintered-glass filtering funnel 1 g. of chromatographic siliceous earth and 300 mg. of chromatographic magnesium oxide, and mix with the aid of a glass rod. Add an accurately weighed portion of the powdered Tablets, equivalent to about 125 mg. of mephentermine sulfate, and mix. Wet the mixture uniformly with 1 ml. of water, added dropwise, by mixing with the glass rod. Add 10 ml. of warm chloroform, mix, and with gentle suction draw off the chloroform into 40 ml. of glacial acetic acid. Repeat the extraction with three 10-ml. portions of warm chloroform, similarly

applied, collecting each portion in the glacial acetic acid. Add 4 drops of *p*-naphtholbenzein T.S., and titrate with 0.1 *N* perchloric acid to a green end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 21.23 mg. of $(C_{11}H_{17}N)_2.H_2SO_4$.

Packaging and storage—Preserve in tight containers.

Tablets available—Tablets usually available contain the following amounts of anhydrous mephentermine sulfate: 12.5 and 25 mg.

CATEGORY and DOSE: See *Mephentermine Sulfate*.



Meprobamate*

2-Methyl-2-propyl-1,3-propanediol Dicarbamate

$C_9H_{18}N_2O_4$ 218.25

Meprobamate contains not less than 97.0 percent and not more than 101.0 percent of $C_9H_{18}N_2O_4$, calculated on the dried basis.

Description: White powder, having a characteristic odor and a bitter taste.

Solubility: Slightly soluble in water; freely soluble in acetone and in alcohol; sparingly soluble in ether.

Identification—

A: The infrared absorption spectrum of a potassium bromide dispersion of it (about 1 mg. in 200 mg.), previously dried at 60° for 3 hours, exhibits maxima only at the same wavelengths as that of a similar preparation of U. S. P. Meprobamate Reference Standard. If a difference appears, dissolve portions of both the sample and the Reference Standard in acetone at a concentration of 8 mg. per ml. Dilute 0.1-ml. portions of the acetone solutions with 1 ml. of *n*-heptane, and remove the solvents by evaporation under nitrogen at a temperature of about 30°. Dry the residues in vacuum at room temperature for 30 minutes, and repeat the test on the residues.

B: Mix 500 mg. with 1 ml. of acetic anhydride, add 1 drop of sulfuric acid, stir until solution is effected, and allow to stand at room temperature, with occasional stirring, for 30 minutes. Pour the solution into 50 ml. of water, with vigorous stirring, and allow to crystallize. Filter the crystals, wash with water until the odor of acetic acid no longer is perceptible, and dry at about 60°: the crystals melt between 123° and 128°, but the range between beginning and end of melting does not exceed 2°.

Melting range, page 935: between 103° and 107°, but the range between beginning and end of melting does not exceed 2°.

Loss on drying, page 935—Dry it in vacuum at 60° for 3 hours: it loses not more than 0.5 percent of its weight.

Assay—Transfer about 400 mg. of Meprobamate, accurately weighed, to a conical flask, add 40 ml. of hydrochloric acid and several boiling chips, and reflux for 90 minutes. Remove the condenser, and continue boiling until the volume is reduced to between 5 and 10 ml. Cool the flask to room temperature, add 50 ml. of water and 1 drop of methyl red T.S., and, while cooling the flask continuously, cautiously neutralize the acid with sodium hydroxide solution (2 in 5) until the indicator begins to change color. If necessary, add 1 *N* hydrochloric acid to restore the pink color, and carefully neutralize with sodium hydroxide solution (1 in 250). Add a mixture of 15 ml. of formaldehyde T.S. and 15 ml. of water, which previously has been neutralized with 0.1 *N* sodium hydroxide to phenolphthalein T.S., and titrate with 0.1 *N* sodium hydroxide to a yellow end-point. Add 0.2 ml. of phenolphthalein T.S., and continue the titration with 0.1 *N* sodium hydroxide to a distinct pink color. Perform a blank determination, and make any necessary correction. Each ml. of the total volume of 0.1 *N* sodium hydroxide consumed after the addition of formaldehyde T.S. is equivalent to 10.91 mg. of $C_9H_{18}N_2O_4$.

Packaging and storage—Preserve in tight containers.

USP XXIII

CATEGORY: Minor tranquilizer.

USUAL DOSE: Oral or intramuscular, 400 mg. three or four times a day.

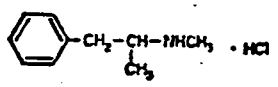
USUAL DOSE RANGE: 1 to 2.4 grams daily.

* Patented. See notice, page iv.

sodium hydroxide T.S., mix, and proceed as directed in the *Assay* under *Methadone Hydrochloride Injection*, page 411, beginning with "and extract with six 20-ml. portions."
Packaging and storage—Preserve in well-closed containers.
Tablets available—Tablets usually available contain the following amount of methadone hydrochloride: 5 mg.

CATEGORY and DOSE: See *Methadone Hydrochloride*.

Methamphetamine Hydrochloride



(+)-*N*,α-Dimethylphenethylamine Hydrochloride
$C_{10}H_{15}N.HCl$ 185.70

Methamphetamine Hydrochloride contains not less than 98.5 percent and not more than 100.5 percent of $C_{10}H_{15}N.HCl$, calculated on the dried basis.

Description: White crystals or white, crystalline powder. Is odorless or practically so. Its solutions have a pH of about 6.
Solubility: Freely soluble in water, in alcohol, and in chloroform; very slightly soluble in absolute ether.
Identification—
A: The ultraviolet absorption spectrum of a 1 in 2000 solution exhibits maxima and minima at the same wavelengths as that of a similar solution of U. S. P. Methamphetamine Hydrochloride Reference Standard, concomitantly measured.
B: To a solution (1 in 100) add mercuric chloride T.S.: a crystalline precipitate is formed (*epinephrine, ephedrine, and phenylephrine give no precipitate with this reagent*).
C: To a solution (1 in 100) add trinitrophenol T.S.: a crystalline precipitate is formed.
D: It responds to the tests for *Chloride*, page 892.
Melting range, page 935: between 171° and 175°.
Specific rotation, page 936: not less than +16° and not more than +19°, calculated on the dried basis, determined in a solution containing 200 mg. in each 10 ml.
Loss on drying, page 935—Dry it at 105° for 2 hours: it loses not more than 0.5 percent of its weight.
Residue on ignition, page 901: not more than 0.1 percent.
Assay—Dissolve about 400 mg. of Methamphetamine Hydrochloride, accurately weighed, in a mixture of 40 ml. of glacial acetic acid and 10 ml. of mercuric acetate T.S., warming slightly to effect solution. Cool the solution to room temperature, add 5 drops of crystal violet T.S., and titrate with 0.1 *N* perchloric acid. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 18.57 mg. of $C_{10}H_{15}N.HCl$.
Packaging and storage—Preserve in tight, light-resistant containers.

CATEGORY: Central stimulant.
USUAL DOSE: 2.5 to 5 mg. one to three times a day.
USUAL DOSE RANGE: 2.5 to 50 mg. daily.

Methamphetamine Hydrochloride Tablets

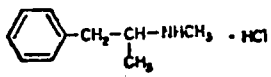
Methamphetamine Hydrochloride Tablets contain not less than 93.0 percent and not more than 107.0 percent of the labeled amount of $C_{10}H_{15}N.HCl$.

Identification—
A: The ultraviolet absorption spectrum of the solution employed for measurement of absorbance in the *Assay* exhibits maxima and minima at the same wavelengths as that

sodium hydroxide T.S., mix, and proceed as directed in the *Assay* under *Methadone Hydrochloride Injection*, page 411, beginning with "and extract with six 20-ml. portions."
Packaging and storage—Preserve in well-closed containers.
Tablets available—Tablets usually available contain the following amount of methadone hydrochloride: 5 mg.

CATEGORY and DOSE: See *Methadone Hydrochloride*.

Methamphetamine Hydrochloride



(+)-*N*,α-Dimethylphenethylamine Hydrochloride
$C_{10}H_{15}N.HCl$ 185.70

Methamphetamine Hydrochloride contains not less than 98.5 percent and not more than 100.5 percent of $C_{10}H_{15}N.HCl$, calculated on the dried basis.

Description: White crystals or white, crystalline powder. Is odorless or practically so. Its solutions have a pH of about 6.
Solubility: Freely soluble in water, in alcohol, and in chloroform; very slightly soluble in absolute ether.
Identification—
A: The ultraviolet absorption spectrum of a 1 in 2000 solution exhibits maxima and minima at the same wavelengths as that of a similar solution of U. S. P. Methamphetamine Hydrochloride Reference Standard, concomitantly measured.
B: To a solution (1 in 100) add mercuric chloride T.S.: a crystalline precipitate is formed (*ephedrine, epinephrine, and phenylephrine give no precipitate with this reagent*).
C: To a solution (1 in 100) add trinitrophenol T.S.: a crystalline precipitate is formed.
D: It responds to the tests for *Chloride*, page 892.
Melting range, page 935: between 171° and 175°.
Specific rotation, page 936: not less than +16° and not more than +19°, calculated on the dried basis, determined in a solution containing 200 mg. in each 10 ml.
Loss on drying, page 935—Dry it at 105° for 2 hours: it loses not more than 0.5 percent of its weight.
Residue on ignition, page 901: not more than 0.1 percent.
Assay—Dissolve about 400 mg. of Methamphetamine Hydrochloride, accurately weighed, in a mixture of 40 ml. of glacial acetic acid and 10 ml. of mercuric acetate T.S., warming slightly to effect solution. Cool the solution to room temperature, add 5 drops of crystal violet T.S., and titrate with 0.1 *N* perchloric acid. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 18.57 mg. of $C_{10}H_{15}N.HCl$.
Packaging and storage—Preserve in tight, light-resistant containers.

CATEGORY: Central stimulant.
USUAL DOSE: 2.5 to 5 mg. one to three times a day.
USUAL DOSE RANGE: 2.5 to 50 mg. daily.

Methamphetamine Hydrochloride Tablets

Methamphetamine Hydrochloride Tablets contain not less than 93.0 percent and not more than 107.0 percent of the labeled amount of $C_{10}H_{15}N.HCl$.

Identification—
A: The ultraviolet absorption spectrum of the solution employed for measurement of absorbance in the *Assay* exhibits maxima and minima at the same wavelengths as that

of a similar solution of U. S. P. Methamphetamine Hydrochloride Reference Standard, concomitantly measured.

B: Finely powder a number of Tablets, equivalent to about 50 mg. of methamphetamine hydrochloride, and digest with 20 ml. of water for 30 minutes. Filter, and wash with 5 to 10 ml. of water. To the filtrate add 0.1 ml. of dilute hydrochloric acid (1 in 10), and evaporate on a steam bath to about 5 ml. To 2 ml. of the resulting solution add a few drops of mercuric chloride T.S.: a crystalline precipitate is formed.

C: To the remaining 3 ml. of the solution from *Identification test B* add 5 ml. of trinitrophenol T.S., stir, and allow to stand in a refrigerator for 3 hours: a crystalline precipitate is formed. Filter the precipitate with suction, wash it with about 0.5 ml. of ice-cold water, and dry it at 105° for 30 minutes: the methamphetamine picrate so obtained melts between 145° and 147°. [*Caution—Picrates may explode.*]

Ammonia—Heat a quantity of powdered Tablets, equivalent to about 50 mg. of methamphetamine hydrochloride, with 5 ml. of sodium hydroxide T.S. on a steam bath for 1 minute: no odor of ammonia is evolved.

Disintegration, page 932: 30 minutes.

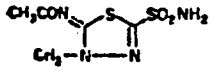
Content uniformity, page 930: meet the requirements for *Tablets*.

Assay—Weigh and finely powder not less than 20 Methamphetamine Hydrochloride Tablets. Weigh accurately a portion of the powder, equivalent to about 25 mg. of methamphetamine hydrochloride, and transfer to a separator with 20 ml. of water. Add sufficient sodium hydroxide T.S. to make the mixture neutral, then add 2 ml. in excess. Extract the liberated methamphetamine with four 25-ml. portions of chloroform, collecting the chloroform extracts in a second separator. Pipet 50 ml. of chloroform-saturated 0.1 *N* sulfuric acid into this separator, and shake for 10 minutes. Allow the layers to separate, discard the chloroform layer, and collect the aqueous layer in a glass-stoppered flask. Dissolve an accurately weighed quantity of U. S. P. Methamphetamine Hydrochloride Reference Standard in chloroform-saturated 0.1 *N* sulfuric acid to obtain a Standard solution having a concentration of about 500 mcg. per ml. Concomitantly determine the absorbances of both solutions in 1-cm. cells at the wavelength of maximum absorbance at about 257 mμ, with a suitable spectrophotometer, using chloroform-saturated 0.1 *N* sulfuric acid as the blank. Calculate the quantity, in mg., of $C_{10}H_{15}N.HCl$ in the portion of the Tablets taken by the formula $0.05C(A_U/A_S)$, in which *C* is the concentration, in mcg. per ml., of U. S. P. Methamphetamine Hydrochloride Reference Standard in the Standard solution, and A_U and A_S are the absorbances of the solution from the Tablets and the Standard solution, respectively.

Packaging and storage—Preserve in well-closed containers.

Tablets available—Tablets usually available contain the following amounts of methamphetamine hydrochloride: 2.5, 5, 7.5, 8, and 10 mg.

CATEGORY and DOSE: See *Methamphetamine Hydrochloride*.



Methazolamide*

N-(4-Methyl-2-sulfamoyl-Δ^3-1,3,4-thiadiazolin-5-ylidene)acetamide

$C_5H_8N_4O_3S_2$ 236.27

Methazolamide contains not less than 96.0 percent and not more than 100.5 percent of $C_5H_8N_4O_3S_2$, calculated on the dried basis.

Description: White or faintly yellow, crystalline powder having a slight odor. Melts at about 213°.

Solubility: Very slightly soluble in water and in alcohol; soluble in dimethylformamide; slightly soluble in acetone.

Identification—

A: The infrared absorption spectrum of a potassium bromide dispersion of it exhibits maxima only at the same wavelengths as that of a similar preparation of U. S. P. Methazolamide Reference Standard.

B: The ultraviolet absorption spectrum of a 1 in 100,000 solution in 0.1 *N* sodium

* Patented. See notice, page iv.

Physical/Chemical Parameters for

Phentermine Hydrochloride

Descriptive Section:

Name, generic (USAN)	Phentermine Hydrochloride
Name, chemical (USAN)	α,α-Dimethylphenethylamine hydrochloride
Empirical formula	$C_{10}H_{15}N.HCl$
Molecular weight	185.70
Structural formula	To be added
Description	To be added: physical properties
Solubility	To be added: solubility; partial solubility; insolubility
Extraction	To be added
Storage	To be added: N.B., procedures/precautions

Specifications:

Identification for chloride	Compendium methodology
Melting (range)	As per reference standard. U.S.P. Class 1A (on a sample dried in a desiccator over silica gel for 16 hours)
Melting (range) of picrate derivative	As per reference standard (re: USP XVIII, Nephentermine Sulfate, Identification B.)
Loss on drying	Compendium methodology. 105° to constant weight
Heavy metals	Compendium methology
Residue on ignition	Compendium methodology
pH (range)	(of a 2% solution) As per reference standard, specify test conditions.

Ultraviolet absorption	(in 0.1N H_2SO_4) Exhibits maxima and minima at the same absorbances as the reference standard (indicating these).
Infrared absorption	Exhibits maxima only at the same wavelengths as the reference standard (indicating major peaks)
Assay	by re: USP, BP. If alternate methodology is used, comparative data is requested

Reference standard: To be established, minimum purity,

Phentermine Hydrochloride Finished Dosage - Long Acting

Phentermine Hydrochloride Dosage Forms contain not less than and not more than of the labeled amount of $C_{10}H_{15}N.HCl$.

Description	To be added: physical properties
Storage	To be added: N.B. procedures/precautions
Identification	To be added. Methodology is requested for validation
Rate of release of active ingredient	To be added. Specifications to be developed in conjunction with studies.
Content uniformity	To be added; compendium standards
Weight variation	To be added: compendium standards
Assay	(as above). Methodology is requested for validation.

VINCENT A. KLEINFELD
ALAN H. KAPLAN
ROBERT H. BECKER
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LAW OFFICES
KLEINFELD, KAPLAN AND BECKER
1200 SEVENTEENTH STREET, N. W.
WASHINGTON, D. C. 20036

TELEPHONE
(202) 659-2155

March 22, 1979

Dr. Ronald Kartzinel
Director,
Division of Neuropharmacological
Drug Products
Bureau of Drugs
Food and Drug Administration
Rockville, Maryland 20857

Re: NDA - 17-960

Dear Dr. Kartzinel:

This letter requests reactivation of the above-referenced new drug application for phentermine HCl 30 mg. capsules submitted by the Vitarine Co., Inc., Springfield Gardens, New York.

This NDA was originally submitted to the FDA on June 10, 1975, and was assigned ANDA No. 84842. Subsequently, by letter dated August 25, 1976, from the Division of Generic Drug Monographs, Vitarine was advised that the 1975 submission was "not in accordance with any Federal Register notice relating to phentermine HCl products". As a result, NDA-84842 was tranferred to the Division of Neuropharmacological Drug Products from the Division of Generic Drug Monographs. It was renumbered NDA 17-960. On two subsequent occasions, the FDA's files pertaining to this NDA were lost and, on November 9, 1976, additional copies were provided by Vitarine to your division. Subsequently, on May 25, 1978, Vitarine was informed by letter that the new drug application could not be approved in the absence of in vivo bioavailability data.

Vitarine has now been advised that the FDA has recently changed its policy concerning products of this type and they are now eligible for review by the Division of Generic Drug Monographs and the requirement for in vivo bioavailability data has been waived. Accordingly, it is respectfully requested that the copies constituting NDA 17-960 (84842) be reactivated and reviewed.

Several years have elapsed since this application was submitted to the Agency and I have been advised that the only substantial question to be resolved as of May 1978 concerned the need for in vivo bioavailability studies. Since the requirement for such studies is now waived, it would be appreciated if the application will be given an expedited review.

Sincerely,

Alan H. Kaplan

AHK/prs

NEW DRUG APPLICATION

17-960

LAW OFFICES

KLEINFELD, KAPLAN AND BECKER

1200 SEVENTEENTH STREET, N. W.

WASHINGTON, D. C. 20036

TELEPHONE (202) 659-2155

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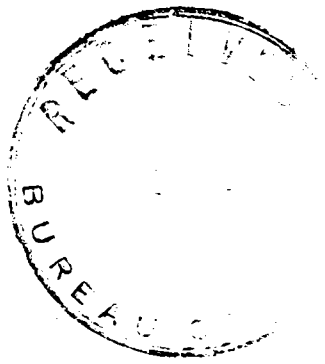
November 8, 1976



Mr. Bruce E. Byer
Products Management Staff
Division of Neuropharmacological
Drug Products (HFD-120)
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20852

Re: NDA 84-842

Dear Mr. Byer:

In our telephone conversation of November 1, you advised me that the FDA's copies of the above-referenced NDA had been lost. In our conversation of November 8, you further advised me that they had not yet been located. In order to avoid any further delay in the evaluation of this application, I have obtained from The Vitarine Co. Inc., the applicant, copies of relevant materials in its possession. These are enclosed in triplicate and include copies of:

1. The original NDA submission, dated June 10, 1975;

2. The FDA acknowledgement, dated June 27, 1975;

3. FDA letters of December 11, 1975, January 6, 1976, and August 25, 1976;

4. Vitarine submissions of November 24, 1975, and June 15, 1976.

The most recent communication from the FDA pertaining to this new drug application, the letter dated August 25, 1976, states that the initial submission was "not in accordance with any Federal Register notice relating to phentermine hydrochloride products." As a consequence of that letter, the new drug application was transferred to your office. While it is our opinion that the submission, as initially made, qualified for handling as an abbreviated new drug application under the terms of DESI 5378 (as updated in the Federal

Register of July 19, 1974) the additional data submitted on June 15, 1976, contained a published report of studies which independently support the safety and effectiveness of a preparation of this formulation and dosage strength.

In view of the fact that a substantial period of time has passed since the original submission of this new drug application, it is respectfully requested that it now be processed expeditiously.

Sincerely,

Alan H. Kaplan

AHK/vel

Purpose. Reviews and evaluates all available data concerning the safety, effectiveness, and reliability of gastroenterology and urological devices currently in use.

Agenda. Open session: Comments and presentations by interested persons. General discussion of Good Manufacturing Practices (GMPs) and gastroenterological-urological medical devices. Closed session: Continuing review and classification of various classes of gastroenterological and urological devices.

Committee name	Date, time, and place	Type of meeting and contact person
8. Dental Drug Products Advisory Committee.	June 21, 9 a.m., conference room I, Parklawn Bldg., 5600 Fishers Lane, Rockville, Md.	Open 9 a.m. to 10 a.m., closed after 10 a.m. Clarence C. Gilkes, D.D.S., room 18B-19, 5600 Fishers Lane, Rockville, Md. 20852, 301-443-3564.

Purpose. Reviews and evaluates all available data concerning the safety and effectiveness of presently marketed and new prescription drug products proposed for marketing for use in the practice of dentistry.

Agenda. Open session: Comments and presentations by interested persons. Closed session: Fluoride tablets; fluoride home treatment kits (discussion of confidential data submitted by manufacturers as a result of Federal Register statement).

Agenda items are subject to change as priorities dictate.

During the open sessions shown above, interested persons may present relevant information or views orally to any committee for its consideration. Information or views submitted to any committee in writing before or during a meeting shall also be considered by the committee.

A list of committee members and summaries of meetings may be obtained from the Executive Secretariat for the committee both for meetings open to the public and those meetings closed to the public in accordance with section 10(d) of the Federal Advisory Committee Act.

Most Food and Drug Administration advisory committees are created to advise the Commissioner of Food and Drugs on pending regulatory matters. Recommendations made by the committees on these matters are intended to result in action under the Federal Food, Drug, and Cosmetic Act, and these committees thus necessarily participate with the Commissioner in executing his law enforcement responsibilities.

The Freedom of Information Act recognized that the premature disclosure of regulatory plans, or premature internal discussions of alternative regulatory approaches to a specific problem, could have adverse effects upon both public and private interests. Congress recognized that such plans, even when finalized, may not be made fully available in advance of the effective date without damage to such interests, and therefore provided for this type of discussion to remain confidential. Thus, law enforcement activities have long been recognized as a legitimate subject for confidential consideration.

These committees often must consider trade secrets and other confidential information submitted by particular manufacturers which the Food and Drug Administration by law may not disclose and which Congress has included within the exemptions from the Freedom of Information Act. Such information includes safety and effectiveness information, product formulation, and manufacturing methods and procedures, all of which are of substantial competitive importance.

In addition, to operate most effectively, the evaluation of specific drug or device products requires that members of committees considering such regulatory matters be free to engage in full and frank discussion. Members of committees have frequently agreed to serve and to provide their most candid advice on the understanding that the discussion would be private in nature. Many experts would be unwilling to engage in candid public discussion advocating regulatory action against a specific product. If the committees were forced to engage in the deliberative portions of their work on a nonconfidential basis, the consequent loss of frank and full discussion among committee members would severely hamper the value of these committees.

The Food and Drug Administration is relying heavily on the use of outside experts to assist in regulatory decisions. The Agency's regulatory actions uniquely affect the health and welfare of every citizen, and it is imperative that the best advice be made available to it on a continuing basis in order that it may most effectively carry out its mission.

A determination to close part of an advisory committee meeting does not mean that the public should not have any participation in these advisory committees considering regulatory issues. A determination to close the meeting is subject to the following conditions: First, any interested person may submit written data or information to any committee, for its consideration. This information will be accepted and will be considered by the committee. Second, a portion of every committee meeting will be open to the public, so that interested persons may present any relevant information or views orally to the committee. The period for open discussion will be designated in any announcement of a committee meeting. Third, only the deliberative portions of a committee meeting, and the portion dealing with trade secret and confidential information, will be closed to the public. The portion of any meeting during which nonconfidential information is made available to the committee will be open for public participation. Fourth, after the committee makes its recommendations and the Commissioner either accepts or rejects them, the public and the individuals affected by the regulatory decision involved will have an opportunity to express their views on the decision. If the decision results in promulgation of a regulation, for example, the proposed regulation will be published for public comment. Closing a committee meeting for deliberations on regulatory matters will therefore in no way preclude public access to the committee itself or full public comment with respect to the decisions made based upon the committee's recommendation.

The Commissioner has been delegated the authority under section 10(d) of the Federal Advisory Committee Act to issue a determination in writing, containing the reasons therefor, that any advisory committee meeting is concerned with matters listed in 5 U.S.C. 552(b), which contains the exemptions from the public disclosure requirements of the Freedom of Information Act. Pursuant to this authority, the Commissioner hereby determines, for the reasons set out above, that the portions of the advisory committee meetings designated in this notice as closed to the public involve discussion of existing documents falling within one of the exemptions set forth in 5 U.S.C. 552(b) or matters that, if in writing, would fall within 5 U.S.C. 552(b), and that it is essential to close such portions of such meetings to protect the free exchange of internal views and to avoid undue interference with Agency and committee operations. This determination shall apply only to the designated portions of such meetings which relate to trade secrets and confidential information or to committee deliberations.

Dated: July 12, 1974.

A. M. SCHMIDT,
Commissioner of Food and Drugs

[FR Doc.74-16410 Filed 7-18-74;8:45 am]

[DESI 6378; Docket No. FDC-D-887; 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; Sorensenburgh Laboratories, Division of Wallace and Tiernan Inc., Post Office Box 7710, Rochester, NY 14603 (NDA 10-093).

2. Ionamin "15" Capsules and Ionamin "30" 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 5-004).

4. Amphedroxyn Hydrochloride Tablets containing 5 milligrams methamphetamine hydrochloride per tablet; Eli Lilly and Co., Post Office Box 618, Indianapolis, Ind. 46206 (NDA 6-390).

5. Delatramine Steadytabs containing 30 milligrams dl-methamphetamine hydrochloride per controlled release tablet; Eastern Research Laboratories, Inc., 202 South Central Ave., Baltimore, MD 21202 (NDA 13-416).

6. Desoxyn Tablets containing 2.5 milligrams methamphetamine hydrochloride per tablet, Desoxyn Gradumet Tablets containing 5, 10, or 15 milligrams methamphetamine hydrochloride per tablet, and Desoxyn Filib containing 20 milligrams methamphetamine hydrochloride per 30 milligrams; Abbott Laboratories, 14th and Sheridan Road, North Chicago, Ill. 60064 (NDA 5-878).

7. Drinalfa Tablets containing 5 milligrams methamphetamine hydrochloride per tablet; E. R. Squibb, P.O. Box 400, Princeton, NJ 08540, (NDA 5-756).

8. Tenuate Dospan Tablets containing 75 milligrams diethylpropion hydrochloride per controlled release tablet; Merrell-National Laboratories, Division of Richardson-Merrell Inc., 110 East Amity Road, Cincinnati, OH 45215 (NDA [illegible]).

9. Racemic Desoxyephedrine Hydrochloride Tablets containing 5 milligrams dl-methamphetamine hydrochloride per tablet; Hive Chemical Co., 1760 North Howard Street, Philadelphia, PA 19122 (NDA 5-909).

10. Miller-Drine Tablets containing 10 milligrams dl-methamphetamine hydrochloride per tablet; Smith, Miller and Patch, Inc., 301 Hoyt Kilmer Avenue, New Brunswick, NJ 08902 (NDA [illegible]).

11. Nasodin Tablets containing 5 milligrams methamphetamine hydrochloride per tablet; Endo Laboratories, 1000 Stewart Avenue, Garden City, Long Island, NY 11530 (NDA 5-873).

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, Nasodin Tablets (methamphetamine hydrochloride); Endo Laboratories.

NDA 6-390, Amphedroxyn Hydrochloride Tablets (methamphetamine hydrochloride); Eli Lilly and Company.

Other drugs (combination anoretic 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 anoretic effects, for the claims for prolonged, continuous or sustained release, and for certain other claims.

Based on information submitted by the manufacturers of anoretic 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 pending 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) has ensued to general management.

3. All of the above 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 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 Preventing and Diminishing Hypothalamic

INDICATIONS

(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; Serious or 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 intoxication is psychosis, often clinically indistinguishable from schizophrenia.

FOR AMPHETAMINE, DEXTROAMPHETAMINE, METHAMPHETAMINE HYDROCHLORIDE AND DL-METHAMPHETAMINE HYDROCHLORIDE

INDICATION

Exogenous obesity as a short-term (a few weeks) adjunct in a regimen of weight reduction based on caloric restriction, for patients [illegible] whose obesity is refractory to alternative [illegible], e.g., repeated diets, group programs, and other drugs. The limited usefulness of (name of drug) [illegible] 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—Minimal Brain Dysfunction in Children as adjunctive therapy to other remedial measures (psychological, educational, social).

Special Diagnostic Considerations:

Specific etiology of Minimal Brain Dysfunction (MBD) is unknown, and there is no single diagnostic test. Adequate diagnosis requires [illegible] not only of medical but of special psychological, [illegible] educational, and social resources.

The characteristic signs most [illegible] observed are chronic history of short attention span, distractibility, emotional lability, 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 [illegible] placement is essential and psychological [illegible] social intervention [illegible] necessary. When remedial measures [illegible] insufficient, the decision to prescribe [illegible] medication will depend upon the [illegible] assessment of the chronicity and severity of the child's symptoms.

Drug treatment is not intended for use in the child who [illegible] due to environmental factors and/or primary psychiatric disorders.

ACTIONS

(Name of drug) [illegible]

[illegible]

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 [illegible]. For [illegible] when comparing a [illegible] mg. controlled release form normally given every [illegible] conventional form [illegible] should involve [illegible] controlled release form given once and one unit of the [illegible] form given every 4 hours.

[illegible] who does not hold [illegible]

tion 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 applicant(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 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.

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 [illegible], 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 DESI number): Hearing Clerk, Food and Drug Administration (HFC-20), Room [illegible], Parklawn Building.

Requests for the Academy report: Drug Efficacy Information Activity (HFD-[illegible]), 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.74-16523 Filed 7-18-74;8:45 am]

[DESI 12179; Docket No. FDC-D-780; NDA 12-179 etc.]

OTIC PREPARATIONS CONTAINING ACETIC ACID WITH OR WITHOUT HYDROCORTISONE IN A PROPYLENE GLYCOL VEHICLE CONTAINING PROPYLENE GLYCOL DIACETATE AND BENZETHONIUM CHLORIDE

Follow-up Notice and Notice of Opportunity for Hearing

In a notice (DESI 12179), published in the FEDERAL REGISTER of September 18, 1970 (35 FR 14630), the Commissioner of Food and Drugs announced his conclusions pursuant to the evaluation of reports received from the National Academy of Sciences–National Research Council, Drug Efficacy Study Group, on the following drugs:

NDA 12-179, VoSol Otic Solution containing acetic acid in a propylene glycol vehicle containing propylene glycol diacetate and benzethonium chloride; and

NDA 12-770, VoSol-HC Otic Solution containing hydrocortisone, and acetic acid, in a propylene glycol vehicle containing propylene glycol diacetate and benzethonium chloride, both marketed by Wampole Laboratories, 35 Commerce Road, Stamford CT 06902.

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 notice stated that VoSol-HC Otic Solution was regarded as probably effective and VoSol Otic Solution as probably effective and possibly effective for their labeled indications. Pursuant to the notice, Wampole Laboratories submitted data. The data have been evaluated and have been determined to provide substantial evidence of effectiveness for the indications described below.

The two studies submitted to establish effectiveness of VoSol Otic Solution for the possibly effective indication (prophylaxis of otitis externa in swimmers and susceptible subjects), failed to demonstrate substantial evidence of effectiveness. When each of these studies was separately analyzed, the results showed no significant difference between the treatment and control groups.

Accordingly, the previous announcement is amended to read as follows.

A. *Effectiveness classification.* The Food and Drug Administration has considered the Academy's reports, as well as other available evidence, and concludes that:

1. Acetic acid is effective for the treatment of superficial infections of the external auditory canal caused by organisms susceptible to the action of the antimicrobial.

2. Acetic acid with hydrocortisone is effective for the treatment of superficial infections of the external auditory canal caused by organisms susceptible to the action of the antimicrobial, complicated by inflammation.

3. Acetic acid lacks substantial evidence of effectiveness for the use in the prophylaxis of otitis externa in swimmers and susceptible subjects.

B. *Conditions for approval and marketing.* The Food and Drug Administration is prepared to approve abbreviated new drug applications and abbreviated

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
ROCKVILLE, MARYLAND 20852

NDA 84-842

AUG 25 1976

The Vitarine Co., Inc.
Attention: Norman Porter
227-15 North Conduit Avenue
Springfield Gardens, NY 11413

Gentlemen:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for Phentermine Hydrochloride Capsules, 30 mg.

Reference is also made to your communication dated June 15, 1976, relating to this application.

We have re-evaluated this application and your product is not in accord with any FEDERAL REGISTER notice relating to phentermine hydrochloride products.

If you elect to file for this product, a full new drug application should be appropriately submitted.

Your material is not being evaluated but will be retained in the file.

Sincerely yours,

Marvin Seife, M.D.
Director
Division of Generic Drug Monographs
Office of Drug Monographs
Bureau of Drugs

Enclosure: FR 7-19-74

8. 26. 76

NP ⟶ Dr. SIMOST

MR SHAW

MR SMEDSTAD

RECEIVED
AUG 26 1976
THE VITARINE CO., INC.

Duplicate Set

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
ROCKVILLE, MARYLAND 20852

NDA 84-842

The Vitarine Company, Inc.
Attention: Norman Porter
227-15 Conduit Avenue
Springfield Gardens, NY 11413

Gentlemen:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for Phentermine Hydrochloride Capsules, 30 mg.

Reference is also made to (1) your amendment dated November 24, 1975, providing for an alternately colored dosage form, and (2) our letter of December 11, 1975, describing the application as incomplete.

We have reviewed the material submitted and note that the comments in our referenced letter are applicable to the alternate dosage form.

Therefore, since the application is incomplete under section 505(b)(1), (2),(3),(4) ~~and (6)~~ of the Act, it may not be filed as an application provided for in section 505(b).

Sincerely yours,

Marvin Seife, M.D.
Director
Division of Generic Drug Monographs
Office of Drug Monographs
Bureau of Drugs

1-8-76 N. Porter → Dr. Most
I.F. Shaw
M. Smedresman

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
WASHINGTON, D.C. 20204

NDA 84-842

DEC 11 1975

The Vitarine Company, Inc.
Attention: Norman Porter
227-15 Conduit Avenue
Springfield Gardens, NY 11413

Gentlemen:

Reference is made to your abbreviated new drug application dated June 10, 1975, submitted pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for Phentermine Hydrochloride Capsules, 30 mg.

The application is incomplete under Section 505(b)(1)(2)(3) and (4) of the Act in that it fails to contain the following information required in an application:

Reports on any studies in support of your claim of all day suppression of appetite.

A full list of the articles used as components of the drug. This list should include all substances used in the preparation of the finished dosage form, regardless of whether they undergo chemical change or are removed in the process. If any proprietary preparation (gelatin capsules; non-pariel beads) is used as a component, the proprietary item should be followed by a quantitative statement of composition. Also include a copy of your master formula record for this product.

A full description of the methods, facilities and controls used in the manufacture, processing, packaging and holding of this specific drug dosage form. In this regard:

I. Provide adequate assurance of the identity, strength, quality and purity of components and final dosage form:

A. For the active ingredient, recommended modifications to your procedures are attached.

B. For the following components, procedures should include:

(1) gelatin capsules: solubility/disintegration testing.

(2) for non-pariel beads: microbial limit testing; mesh size.

12-15-75 N. Porter → Dr. Most
I.F.Shaw → M. Smedresman → R.Mazon
R. Goldman (Pg. 1-2)
N. Scott (Pg. 1-3)
Laszlo Ek (Pg. 1-3)
G. Guise (Pg. 1-10)

(1)

(3) for "phentermine hydrochloride seeds": assay and rate of release of active ingredient (comment is invited on in-process rate of release testing).

C. For the final dosage form, guidelines for comprehensive parameters are attached.

II. Include operating procedures/precautions due to the hygroscopic nature of phentermine HCl and its controlled drug status. Also, approximate the number of times the beads are dusted with active ingredient and coated.

III. Include full information on containers and closures.

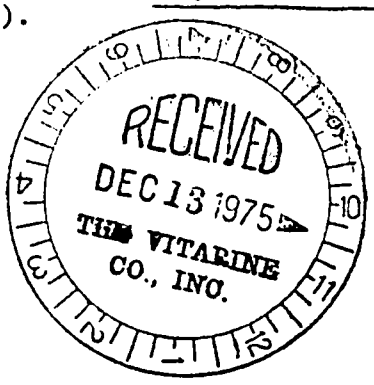
IV. Relative to stability, include (a) testing for rate of release of active ingredient in your procedures and (b) your intent with respect to expiration dating.

To expedite the processing of this application, we are requesting samples of the final dosage form and full information pertaining to them.

We have the following comments on the labeling submitted under Section 505(b)(6) of the Act:

The insert labeling is unsatisfactory, as supportative data is required to support all day suppresion of appetite (HOW SUPPLIED). The insert labeling should be revised in accord with the accompanying labeling guidelines (also note the comma after "hyperthyroidism" at the end of line 2, under CONTRAINDICATIONS).

Since the application is incomplete under section 505(1)(2)(3)(4) and (6) of the Act, it may not be filed as an application provided for in section 505(b).



Sincerely yours,

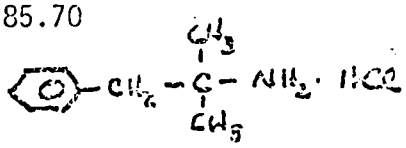
Marvin Seife, M.D.
Director
Division of Generic Drug Monographs
Office of Drug Monographs
Bureau of Drugs

Enclosures: labeling guidelines
physical/chemical parameters

(2)

Modifications to Specifications and Tests for Phentermine Hydrochloride:

1. Provide for a Descriptive Section including:

Generic name	Phentermine Hydrochloride
Chemical name	α,α -Dimethylphenethylamine Hydrochloride
Empirical formula	$C_{10}H_{15}N.HCl$
Molecular weight	185.70
Structural formula	
Description	White hygroscopic crystalline powder with slight bitter taste
Storage	e.g.:Stable if stored in a temperate place protected from moisture

2. Revise melting range to: 202 - 205°C

Phentermine Hydrochloride Finished Dosage - Long Acting

Phentermine Hydrochloride Dosage forms contain not less than 90.0% and not more than 110% of the labeled amount of $C_{10}H_{15}N.HCl$.

Description	To be added: physical properties
Storage	To be added: N.B. procedures/precautions
Identification	To be added. Methodology is requested for validation
Rate of release of active ingredient	To be added. Specifications to be developed in conjunction with studies
Content uniformity	To be added: compendium standards
Weight variation	To be added; compendium standards
Assay	90.0 - 110.0% (as above). Methodology is requested for validation.

(3)

PROLONGED, CONTINUOUS OR SUSTAINED RELEASE PREPARATIONS
Oral Administration

DESCRIPTION SECTION:

- List ingredients

ACTIONS SECTION:

Firm is to submit studies comparing blood levels occurring with the controlled release form with blood levels occurring with single units of the conventional form given multiple times.

DOSAGE AND ADMINISTRATION:

Time of administration is important. Length of prolonged activity determines dosage times.

Addendum to Labeling Guidelines
(11-5-74)

DRAFT: 1/25/73

CONTINUATION SHEET
IDENTIFYING CHANGES
AS REQUIRED

GUIDELINE LABELING FOR ANORECTIC DRUGS

PHENTERMINE HCl

DESCRIPTION

(To be confined to a statement of the physical and chemical properties of the drug.)

ACTIONS

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.

INDICATION

Phentermine HCl 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.

CONTRAINDICATIONS

Advanced arteriosclerosis, symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism, known hypersensitivity, or idiosyncrasy to the sympathomimetic amines, glaucoma.

Agitated states.

Patients with a history of drug abuse.

During or within 14 days following the administration of monoamine oxidase inhibitors, (hypertensive crises may result.)

WARNINGS

Tolerance to the anorectic effect usually develops within a few weeks. When this occurs, the recommended dose should not be exceeded in an attempt to increase the effect: rather, the drug should be discontinued.

Phentermine HCl may impair the ability of the patient to engage in potentially hazardous activities such as operating machinery or driving a motor vehicle; the patient should therefore be cautioned accordingly.

Drug Dependence:
Phentermine HCl is related chemically and pharmacologically to the amphetamines. Amphetamines and related stimulant drugs have been extensively abused, and the possibility of abuse of phentermine HCl 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 dep

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 dermatosis, marked insomnia, irritability, hyperactivity, and personality changes. The most severe manifestation of chronic intoxications is psychosis, often clinically indistinguishable from schizophrenia.

Usage in Pregnancy: (This section should identify whether reproduction studies, including teratology studies, have been done in animals and state briefly the results. A similar statement should be made concerning human studies. The section should contain an accurate concluding statement as to the factors which must be weighed by the physician in judging whether to use the drug in a particular pregnant patient. A general concluding statement which would be acceptable in most cases is the following: Use of Phentermine HCl by women who are or may become pregnant requires that the potential benefit be weighed against the possible hazard to mother and infant.

Usage in Children: Phentermine HCl is not recommended for use in children under 12 years of age.

PRECAUTIONS

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

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

Phentermine HCl 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, constipation, other gastrointestinal disturbances.

Allergic: Urticaria.

Endocrine: Impotence, changes in libido.

DOSAGE AND ADMINISTRATION

(As appropriate to drug involved.)

Phentermine HCl is not recommended for use in children under 12 years of age.

OVERDOSAGE

Manifestations of acute overdosage with Phentermine HCl include restlessness, tremor, hyperreflexia, rapid respiration, confusion, assaultiveness, hallucinations, panic states.

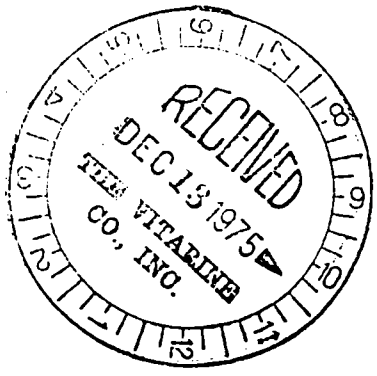
Fatigue and depression usually follow the central stimulation.

Cardiovascular effects include arrhythmias, 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 Phentermine HCl intoxication is largely symptomatic and includes lavage and sedation with a barbiturate. Experience with hemodialysis or peritoneal dialysis is inadequate to permit recommendation in this regard. Acidification of the urine increases Phentermine HCl excretion. Intravenous phentolamine (Regitine) has been suggested for possible acute, severe hypertension, if this complicates Phentermine HCl overdosage.

HOW SUPPLIED

(Information to be supplied by the firm).



DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
ROCKVILLE, MARYLAND 20852

NDA 84-842

The Vitarine Company, Inc.
Attention: Mr. Norman Porter
227-15 N. Conduit Avenue
Springfield Gardens, NY 11413

JUN 27 1975

Gentlemen:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

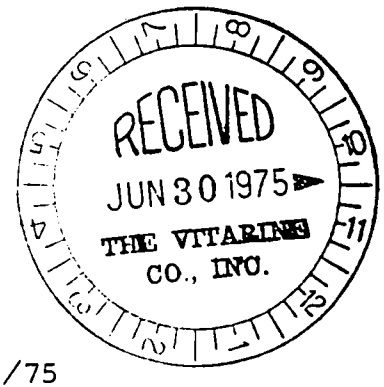
NAME OF DRUG: Phentermine Hydrochloride Capsules, 30 mg.

DATE OF APPLICATION: June 10, 1975

DATE OF RECEIPT: June 17, 1975

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the NDA number shown above.



Sincerely yours,

Marvin Seife, M.D.
Director
Division of Generic Drug Monographs
Office of Drug Monographs
Bureau of Drugs

6/30/75

Dist: Dr. S. Most
Mr. Shaw → Mr. Smedresman → Mr. Mazon
N.P.

(4)

VOLUME 2.1

NEW DRUG APPLICATION

NDA No. ANDA #86-945

NAME OF APPLICANT

The Vitarine Co., Inc.
227-15 No. Conduit Ave.
Springfield Gardens, N.Y. 11413

NAME OF NEW DRUG

PHENTERMINE HCl 30 mg.
BLUE/CLEAR UNTIMED CAPS

SUBMISSION VOL _____ OF _____ VOLS.

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

TO : Laboratory Operations Branch/DFS/EDRO
Attn: Salvatore J. Pinella (HFO-610)

DATE: April 29, 1982

For forwarding to: HFD-530

FROM : Research Coordinator
New York Regional Laboratory (HFR-2161)

SUBJECT: ANDA 86-945

PRODUCT: Phentermine HCl Caps

FIRM: The Vitarine Co., Inc.
Springfield Gardens, NY 11413

All the analytical results appear to be satisfactory. Please note the analysts comments, especially with regard to the infra-red identification test.

5/6/82

WILLIAM M. PLANK

WILLIAM M. PLANK
WMP/ag
cc: HFR-2162 : File 463: 300
Lab I . 155 hours 4 exams, Analyst(s) R. Cohen, G. Lehr
Lab H (Monitor)
HFR-2161

1.

SAMPLES BEING FORWARDED

ITEM	QUANTITY	CONTROL NO. OR OTHER IDENTIFICATIC
Phentermine Hydrochloride Capsules, 30mg	4 x 25	Lot # 75-23-II
Phentermine Hydrochloride Reference Standard	4 x 1gm	# 23426

2. [illegible] of Determinations

Statement of Composition of Finished Dosage Form(s)	No. of Pages	NDA Reg. Number(s)
Specifications/Methods for New Drug Substance(s)		
[illegible]ifications/Methods for Finished Dosage Form(s)		
[illegible]ts of Determinations obtained by Applicant(s)		
Other (specify)		

3. REQUESTED DETERMINATIONS (Perform tests indicated below: (conduct ~~ASSAY~~ tests in DUPLICATE)

a. Drug Substance(s):

Assay - Identification
LOD

b. Dosage Form(s):

1) Assay - using reference standard provided
2) Identification -

4. SUMMARY OF RESULTS (Report individual and average ASSAY results)

Conforms to test

Found (on anhydrous basis) (1) 100.8% (2) 100.9%
Average: 100.9%

0.44%

Declared		Found	%
30mg	1	31.46	104.9
	2	32.23	107.4
	Av.		106.2

Conforms to test

SIGNATURE OF ANAL[illegible]

DATE 4/21/82

DISTRICT LABORATORY COPY ROUTING

Division of Drug Chemistry (HFD-420)

[illegible]

Field Sciences Branch (HFD- 610)

DIVISION OF DRUG CHEMISTRY COPY ROUTING

_____ Chemist (HFD- ____)

_____ [illegible]

Field Sciences Branch (HFD- 610)

FORM FD 2[illegible]

VOLUME 3.1

NEW DRUG APPLICATION

NDA No. 86945

NAME OF APPLICANT

Vitarine Pharm Inc.

NAME OF NEW DRUG

Phentermine HCl Capsules
30mg (Blue/Clear)

ARCHIVAL COPY

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APPLICATION REASSIGNMENT AUTHORIZATION FORM
OFFICE OF GENERIC DRUGS

ANDA/AADA#	DRUG	FIRM
40-083	Phentermine HCl Caps	King Pharms
87-301	" " "	Eon Manuf
87-208	" " "	" "
87-223	" " "	" "
86-945	" " "	" "
87-190	" " "	" "

1. REASSIGN FROM: Bernard

   DATE OF ORIGINAL ASSIGNMENT: _____

2. ASSIGN TO: Langowski AXL

   DATE OF REASSIGNMENT: 9/22/94

   REASON FOR REASSIGNMENT: Renewal needs work.

BRANCH SUPERVISOR (SIGNATURE) 9/28/94 DATE

CHEMISTRY/BIOEQUIVALENCE DIVISION DIRECTOR (SIGNATURE) CONCUR: ✓ NOT CONCUR: ___

DATE: 9/28/94

A COPY OF THIS FORM SHOULD BE PLACED IN EACH APPLICATION AND IN THE DIVISION FILE

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: SEP 26 1994

FROM: Division of Epidemiology and Surveillance, HFD-730

SUBJECT: Receipt and Referral of 15-Day Averse Reaction Information

TO : HFD- 510

The enclosed 15-Day adverse reaction information was sent to the Division of Epidemiology and Surveillance, in duplicate, as required under the new regulations (21 CFR 314.80). The original, official copy of the submission is being sent to you for processing and filing to the appropriate NDA/IND.

PRODUCT NAME: Phentermine

NDA/REGISTRATION NUMBER: 86-945

James W. Moore

James W. Moore, R.Ph., M.A.

VOLUME 4.1

NEW DRUG APPLICATION

NDA No. 86945

NAME OF APPLICANT

Eon Labs

NAME OF NEW DRUG

Phentermine HCL

ARCHIVAL COPY