CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

83900

CORRESPONDENCE

NDA 83-900
AF 14-395

OCT 29 1975

Smith Kline & French Laboratories
Attention: J. F. Cassin
1500 Spring Garden Street
Philadelphia, PA 19101

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 Benzedrine (Amphetamine Sulfate) Tablets, 5 mg. and 10 mg.

Reference is also made to your communications dated February 22, September 17, October 15, 1973, July 26, December 10, 1974, and October 15, 1975.

The application is inadequate under section 505(b)(4) of the Act in that it fails to contain the following information required in an application:

Adequate information concerning the methods used in the synthesis, extraction, isolation or purification of the amphetamine base and its final conversion to the sulfate.

Adequate information concerning the methods used in, and the facilities and controls used for the manufacturing, processing, packing and holding of the drug dosage form. In this regard include a fully completed set of production work records and related quality control reports from an actual production size run of this product.

Submit the printed package insert and all container labels in use with this product.

Please let us have your response promptly.

Sincerely yours,

[S] 10/29/75

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

cc:
PHI-DO
dup
HFD-614 HFD-616 MJarski 10/28/75
OMCarroll/JLMeyer/MAJarski
R/D init. JLMeyer, MSeife
OMCarroll 10/28/75 10/21/75
Final typing bho 10/23/75
Inadequate

[S] 10/29/75

FEB 9 1973

NDA 17-072

AF 14-395

Smith, Kline and French Laboratories
Attention: Robert L. Dean
1500 Spring Garden Street
Philadelphia, Pennsylvania 19101

Gentlemen:

Reference is made to your new drug application dated August 6, 1971 submitted pursuant to section 505(b) of the Federal Food, Drug , and Cosmetic Act for the preparation Benzedrine (amphetamine sulfate) Tablets.

We also acknowledge receipt of your additional communications dated November 15, 1971, April 6, 1972, May 5, 1972, July 7, 1972 and October 11, 1972.

We have completed our review of this application. However, before we are able to reach a conclusion the following additional information is necessary:

Revised labeling to conform to the enclosed draft copy.

Specify the talc used in the final dosage form. The designation " or equivalent" is too general. In addition, it is recommended that the talc be tested for presence of asbestos either by you or your supplier.

Clarify the averaging of three ultraviolet scans in the final dosage form assay.

A commitment to continue the stability studies on the final dosage form packaged in polyethylene bottles.

Please submit the above information within 60 days of the date of this letter.

Sincerely yours,

cc:
PHI-DO
Orig., Dup.
BD-100, BD-120
Init:BScoville:
WCCrabbs:
R/D:REJoyce:
F/T:cm/2/8/73

Elmer A. Gardner, M.D.
Director
Division of Neuropharmacological
Drug Products
Office of Scientific Evaluation
Bureau of Drugs

Our Reference
NDA 17-072
AF 14-935

FEB 3 1972

Smith Kline and French Laboratories
Attention: Robert L. Dean
1500 Spring Garden Street
Philadelphia, Pennsylvania 19101

Gentlemen:

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

Name of Drug: Benzedrine Tablets

Date of Application: August 6, 1971

Date of Receipt: August 9, 1971

In view of the large number of applications submitted for various formulations of amphetamines and related products, and in view of the unusual public health problems involved, we have found it necessary to develop special criteria and procedures for the review and evaluation of the safety and efficacy of anorectic agents, including amphetamines, prior to taking any action on individual new drug applications.

Because of the magnitude of this review and evaluation and in accordance with section 505(c) of the Federal Food, Drug and Cosmetic Act, we request an extension of time to August 3, 1972 for the completion of our review of your application.

We regret the delay in acknowledging the receipt of your submission. We will correspond with you further after we have had the opportunity to complete our review and evaluation.

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

Sincerely yours,

Elmer A. Gardner, M.D.
Director
Division of Neuropharmacological
Drug Products
Office of Scientific Evaluation
Bureau of Drugs

cc:
PHI-DO
OSE (BD-100)
DND (BD-120)
Med (BD-22)
IAS (BD-242)
WCCrabbs 1/20/72:abc/1/26/72
R/D init. by BScoville 1/19/72
MJFinkel 1/21/72
ELucas 1/25/72

1/31/72 E Lucas 1/27/72

OCT 11 1988

NDA 83-900

Smith Kline & French Laboratories
Attention: Raymond Ragland, Jr., Ph.D.
1500 Spring Garden Street, P.O. Box 7929
Philadelphia, PA 19101

Dear Sir:

We acknowledge the receipt of your communication dated August 24, 1988 requesting withdrawal of approval of your abbreviated new drug application for Benzedrine® (Amphetamine Sulfate) Tablets.

In compliance with your request and in accord with section 314.150(c) of the Federal Food, Drug, and Cosmetic Act, action will be taken to withdraw approval of the application. Appropriate notice will be given by publication in the Federal Register in accord with section 314.152.

This withdrawal will not prejudice any future filing of the application. You may request that the information in this application be considered in connection with any resubmission.

Sincerely yours,

/S/ 10/11/88

Marvin Seife, M.D.
Director
Division of Generic Drugs
Office of Drug Standards
Center for Drug Evaluation and Research

cc:
HFD-232
DRosen/KFUrnkranz 10/11/88
kl/10-7-88/1776b
approved withdrawal

1500 Spring Garden Street, P.O. Box 7929, Philadelphia, Pennsylvania 19101

Smith Kline &French Laboratories

A SMITHKLINE BECKMAN COMPANY

Regulatory Affairs
(215) 751-3868

August 24, 1988

Benzedrine® (amphetamine sulfate) Tablets
NDA 83-900
(Vol. 12, p. 69)

WITHDRAWN

Marvin Seife, M.D., Director
Division of Generic Drug Monographs
Center for Drugs and Biologics (HFN-530)
Document Control Room 17B-45
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Seife:

Please refer to our Abbreviated New Drug Application for Benzedrine® (amphetamine sulfate) Tablets ANDA 83-900.

Smith Kline &French Laboratories discontinued marketing of Benzedrine® Tablets in September 1982; the expiration date for the last lot of product manufactured was December 1987. In accordance 21 CFR §314.150(c) we are hereby requesting withdrawal of ANDA 83-900.

Since the situation described above also applies to NDA 17-071 for Benzedrine® Spansule Capsules, we are making a simultaneous request to the Division of Neuropharmacological Drug Products for withdrawal of that NDA as well.

Please call me at (215) 751-6545 if you have any questions about this matter.

RECEIVED
AUG 29 1988
GENERIC DRUGS

Sincerely,

Raymond Ragland Jr

Raymond Ragland, Jr., Ph.D.
Director
Regulatory Affairs

RR/DS

0975r/10

069

SK&F

obert L. Dean, Vice President, Regulatory and Government Affairs - U.S. Pharmaceuticals

NEW DRUG APPLICATION 17-072

SK&F

SMITH KLINE & FRENCH LABORATORIES

500 Spring Garden Street, Philadelphia, Pa. 19101 • 215 LOcust 4-2400

August 6, 1971

Elmer A. Gardner, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Scientific Evaluation, Bureau of Drugs
Department of Health, Education and Welfare
Food and Drug Administration
Parklawn Building
5600 Fishers Lane
Rockville, Maryland 20852

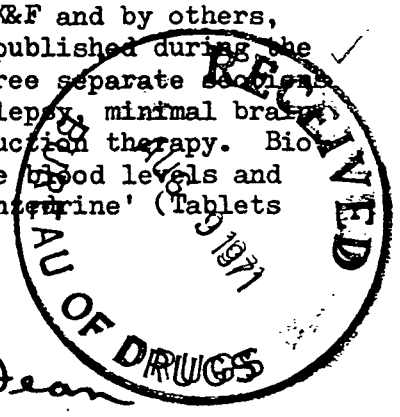
Dear Doctor Gardner:

This 'Benzedrine' Tablet NDA has been prepared in response to the Federal Register Notice 35:12652 of August 8, 1970, which calls for new drug applications to be submitted for amphetamine drugs within one year.

We continue to believe that the 'Benzedrine' tablet is not a "new drug" as that term is defined in Section 201(p) of the Federal Food, Drug & Cosmetic Act and, moreover, is covered by the grandfather clause enacted in Section 107(c)(4) of the Drug Amendments of 1962. This submission is made without prejudice to that position. Specifically, we do not concede the validity of the August 8, 1970 notice as it purports to apply to this product, and we reserve the right to urge in any appropriate proceeding that an approved NDA is not required for the product's continued marketing.

Since 'Benzedrine' (d,l amphetamine sulfate) was marketed in 1936, physicians have found it to be safe and effective in the treatment of narcolepsy, minimal brain dysfunction in children, and as an adjunct in weight reduction therapy. In the past several decades, hundreds of reports of animal studies, controlled and uncontrolled clinical studies have appeared in the published literature, and 'Benzedrine', being the first available amphetamine, became the standard against which other amphetamines and stimulants were compared.

Because 'Benzedrine' has been available for so many years, this NDA is not the usual summary of new data from an organized investigational program, but rather, it is a summary of animal studies conducted by SK&F and by others, and of the controlled and uncontrolled clinical studies published during the years of clinical use. For clarity, we have prepared three separate sections (E1 through E8), one for each of the indications: narcolepsy, minimal brain dysfunction in children; and as an adjunct in weight reduction therapy. Bioavailability studies have been included which compare the blood levels and urinary excretion obtained with both dosage forms of 'Benzedrine' (Tablets and 'Spansule' Sustained Release Capsules).



Sincerely yours,

Robert L Dean

Robert L. Dean

RLD/ams

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

Form Approved
OMB No. 57-R0003

NEW DRUG APPLICATION *(DRUGS FOR HUMAN USE)*
(Title 21, Code of Federal Regulations, § 130.4)

NEW DRUG APPLICATION

Name of applicant Smith Kline & French Laboratories

Address 1500 Spring Garden Street, Philadelphia, Pa. 19101

Date August 6, 1971

Name of new drug 'Benzedrine' Tablet

- [X] Original application (regulation § 130.4).
- [ ] Amendment to original, unapproved application (regulation § 130.7).
- [ ] Abbreviated application (regulation § 130.4(f)).
- [ ] Amendment to abbreviated, unapproved application (regulation § 130.7).
- [ ] Supplement to an approved application (regulation § 130.9).
- [ ] Amendment to supplement to an approved application.

The undersigned submits this application for a new drug pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act. It is understood that when this application is approved, the labeling and advertising for the drug will prescribe, recommend, or suggest its use only under the conditions stated in the labeling which is part of this application; and if the article is a prescription drug, it is understood that any labeling which furnishes or purports to furnish information for use or which prescribes, recommends, or suggests a dosage for use of the drug will contain the same information for its use, including indications, effects, dosages, routes, methods, and frequency and duration of administration, any relevant warnings, hazards, contraindications, side-effects, and precautions, as that contained in the labeling which is part of this application in accord with §1.106(b) (21 CFR 1.106(b)). It is understood that all representations in this application apply to the drug produced until an approved supplement to the application provides for a change or the change is made in conformance with other provisions of §130.9 of the new-drug regulations.

Attached hereto, submitted in the form described in §130.4(e) of the new-drug regulations, and constituting a part of this application are the following:

1. Table of contents. The table of contents should specify the volume number and the page number in which the complete and detailed item is located and the volume number and the page number in which the summary of that item is located (if any).

2. Summary. A summary demonstrating that the application is well-organized, adequately tabulated, statistically analyzed (where appropriate), and coherent and that it presents a sound basis for the approval requested. The summary should include the following information: (In lieu of the outline described below and the evaluation described in Item 3, an expanded summary and evaluation as outlined in §130.4(d) of the new-drug regulations may be submitted to facilitate the review of this application.)

a. Chemistry.

i. Chemical structural formula or description for any new-drug substance.

ii. Relationship to other chemically or pharmacologically related drugs.

iii. Description of dosage form and quantitative composition.

b. Scientific rationale and purpose the drug is to serve.

c. Reference number of the investigational drug notice(s) under which this drug was investigated and of any notice, new-drug application, or master file of which any contents are being incorporated by reference to support this application.

d. Preclinical studies. (Present all findings including all adverse experiences which may be interpreted as incidental or not drug-related. Refer to date and page number of the investigational drug notice(s) or the volume and page number of this application where complete data and reports appear.)

i. Pharmacology (pharmacodynamics, endocrinology, metabolism, etc.).

ii. Toxicology and pathology: Acute toxicity studies; subacute and chronic toxicity studies; reproduction and teratology studies; miscellaneous studies.

e. Clinical studies. (All material should refer specifically to each clinical investigator and to the volume and page number in the application and any documents incorporated by reference where the complete data and reports may be found.)

i. Special studies not described elsewhere.

ii. Dose-range studies.

iii. Controlled clinical studies.

iv. Other clinical studies (for example, uncontrolled or incompletely controlled studies).

v. Clinical laboratory studies related to effectiveness.

vi. Clinical laboratory studies related to safety.

vii. Summary of literature and unpublished reports available to the applicant.

3. Evaluation of safety and effectiveness. a. Summarize separately the favorable and unfavorable evidence for each claim in the package labeling. Include references to the volume and page number in the application and in any documents incorporated by reference where the complete data and reports may be found.

b. Include tabulation of all side effects or adverse experience, by age, sex, and dosage formulation, whether or not considered to be significant, showing whether administration of the drug was stopped and showing the investigator's name with a reference to the volume and page number in the application and any documents incorporated by reference where the complete data and reports may be found. Indicate those side effects or adverse experiences considered to be drug-related.

4. Copies of the label and all other labeling to be used for the drug (a total of 12 copies if in final printed form, 4 copies if in draft form):

a. Each label, or other labeling, should be clearly identified to show its position on, or the manner in which it accompanies, the market package.

b. If the drug is to be offered over the counter, labeling on or within the retail package should include adequate directions for use by the layman under all the conditions for which the drug is intended for lay use or is not to be prescribed, recommended, or suggested in any labeling or advertising sponsored by or on behalf of the applicant and directed to the layman. If the drug is intended or offered for uses under the professional supervision of a practitioner licensed by law to administer it, the application should also contain labeling that includes adequate information for all such uses, including all the purposes for which the over-the-counter drug is to be advertised to, or represented for use by, physicians.

c. If the drug is limited in its labeling to use under the professional supervision of a practitioner licensed by law to administer it, its labeling should bear information for use under which such practitioners can use the drug for the purposes for which it is intended, including all the purposes for which it is to be advertised or represented, in accord with §1.106(b) (21 CFR 1.106(b)). The application should include any labeling for the drug intended to be made available to the layman.

d. If no established name exists for a new-drug substance, the application shall propose a nonproprietary name for use as the established name for the substance.

e. Typewritten or other draft labeling copy may be submitted for preliminary consideration of an application. An application will not ordinarily be approved prior to the submission of the final printed label and labeling of the drug.

f. No application may be approved if the labeling is false or misleading in any particular.

(When mailing pieces, any other labeling, or advertising copy are devised for promotion of the new drug, samples shall be submitted at the time of initial dissemination of such labeling and at the time of initial placement of any such advertising for a prescription drug (see §130.13 of the new-drug regulations). Approval of a supplemental new-drug application is required prior to use of any promotional claims not covered by the approved application.)

5. A statement as to whether the drug is (or is not) limited in its labeling and by this application to use under the professional supervision of a practitioner licensed by law to administer it.

6. A full list of the articles used as components of the drug. This list should include all substances used in the synthesis, extraction, or other method of preparation of any new-drug substance, and in the preparation of the finished dosage form, regardless of whether they undergo chemical change or are removed in the process. Each substance should be identified by its established name, if any, or complete chemical name, using structural formulas when necessary for specific identification. If any proprietary preparation is used as a component, the proprietary name should be followed by a complete quantitative statement of composition. Reasonable alternatives for any listed substance may be specified.

7. A full statement of the composition of the drug. The statement shall set forth the name and amount of each ingredient, whether active or not, contained in a stated quantity of the drug in the form in which it is to be distributed (for example, amount per tablet or per milliliter) and a batch formula representative of that to be employed for the manufacture of the finished dosage form. All components should be included in the batch formula regardless of whether they appear in the finished product. Any calculated excess of an ingredient over the label declaration should be designated as such and percent excess shown. Reasonable variations may be specified.

8. A full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of the drug. Included in this description should be full information with respect to any new-drug substance and to the new-drug dosage form, as follows, in sufficient detail to permit evaluation of the adequacy of the described methods of manufacture, processing, and packing and the described facilities and controls to determine and preserve the identity, strength, quality, and purity of the drug:

a. A description of the physical facilities including building and equipment used in manufacturing, processing, packaging, labeling, storage, and control operations.

b. A description of the qualifications, including educational background and experience, of the technical and professional personnel who are responsible for assuring that the drug has the safety, identity, strength, quality, and purity it purports or is represented to possess, and a statement of their responsibilities.

c. The methods used in the synthesis, extraction, isolation, or purification of any new-drug substance. When the specifications and controls applied to such substance are inadequate in themselves to determine its identity, strength, quality, and purity, the methods should be described in sufficient detail, including quantities used, times, temperatures, pH, solvents, etc., to determine these characteristics. Alternative methods or variations in methods within reasonable limits that do not affect such characteristics of the substance may be specified.

d. Precautions to assure proper, identity, strength, quality, and purity of the raw materials, whether active or not, including the specifications for acceptance and methods of testing for each lot of raw material.

e. Whether or not each lot of raw materials is given a serial number to identify it, and the use made of such numbers in subsequent plant operations.

f. If the applicant does not himself perform all the manufacturing, processing, packaging, labeling, and control operations for any new-drug substance or the new-drug dosage form, his statement identifying each person who will perform any part of such operations and designating the part; and a signed statement from each such person fully describing, directly or by reference, the methods, facilities, and controls in his part of the operation.

g. Method of preparation of the master formula records and individual batch records and manner in which these records are used.

h. The instructions used in the manufacturing, processing, packaging, and labeling of each dosage form of the new drug, including any special precautions observed in the operations.

i. Adequate information with respect to the characteristics of and the test methods employed for the container, closure, or other component parts of the drug package to assure their suitability for the intended use.

j. Number of individuals checking weight or volume of each individual ingredient entering into each batch of the drug.

k. Whether or not the total weight or volume of each batch is determined at any stage of the manufacturing process subsequent to making up a batch according to the formula card and, if so, at what stage and by whom it is done.

l. Precautions to check the actual package yield produced from a batch of the drug with the theoretical yield. This should include a description of the accounting for such items as discards, breakage, etc., and the criter used in accepting or rejecting batches of drugs in the event of an unexplained discrepancy.

m. Precautions to assure that each lot of the drug is packaged with the proper label and labeling, including provisions for labeling storage and inventory control.

n. The analytical controls used during the various stages of the manufacturing, processing, packaging, and labeling of the drug, including a detailed description of the collection of samples and the analytical procedures to which they are subjected. The analytical procedures should be capable of determining the active components within a reasonable degree of accuracy and of assuring the identity of such components. If the article is one that is represented to be sterile, the same information with regard to the manufacturing, processing, packaging, and the collection of samples of the drug should be given for sterility controls. Include the standards used for acceptance of each lot of the finished drug.

o. An explanation of the exact significance of the batch control numbers used in the manufacturing, processing, packaging, and labeling of the drug, including the control numbers that appear on the label of the finished article. State whether these numbers enable determination of the complete manufacturing history of the product. Describe any methods used to permit determination of the distribution of any batch if its recall is required.

p. A complete description of, and data derived from, studies of the stability of the drug, including information showing the suitability of the analytical methods used. Describe any additional stability studies underway or contemplated. Stability data should be submitted for any new-drug substance, for the finished dosage form of the drug in the container in which it is to be marketed, including any proposed multiple-dose container, and if it is to be put into solution at the time of dispensing, for the solution prepared as directed. State the expiration date(s) that will be used on the label to preserve the identity, strength, quality, and purity of the drug until it is used. (If no expiration date is proposed, the applicant must justify its absence.)

q. Additional procedures employed which are designed to prevent contamination and otherwise assure proper control of the product.

(An application may be refused unless it includes adequate information showing that the methods used in, and the facilities and controls used for, the manufacturing, processing, and packaging of the drug are adequate to preserve its identity, strength, quality, and purity in conformity with good manufacturing practice and identifies each establishment, showing the location of the plant conducting these operations.)

9. Samples of the drug and articles used as components, as follows: a. The following samples shall be submitted with the application or as soon thereafter as they become available. Each sample shall consist of four identical, separately packaged subdivisions, each containing at least three times the amount required to perform the laboratory test procedures described in the application to determine compliance with its control specifications for identity and assays:

i. A representative sample or samples of the finished dosage form(s) proposed in the application and employed in the clinical investigations and a representative sample or samples of each new-drug substance, as defined in §130.1(g), from the batch(es) employed in the production of such dosage form(s).

ii. A representative sample or samples of finished market packages of each dosage form of the drug prepared for initial marketing and, if any such sample is not from a commercial-scale production batch, such a sample from a representative commercial-scale production batch; and a representative sample or samples of each new-drug substance as defined in §130.1(g), from the batch(es) employed in the production of such dosage form(s).

iii. A sample or samples of any reference standard and blank used in the procedures described in the application for assaying each new-drug substance and other assayed components of the finished drug: *Provided, however,* That samples of reference standards recognized in the official U.S. Pharmacopeia or The National Formulary need not be submitted unless requested.

b. Additional samples shall be submitted on request.

c. Each of the samples submitted shall be appropriately packaged and labeled to preserve its characteristics, to identify the material and the quantity in each subdivision of the sample, and to identify each subdivision with the name of the applicant and the new-drug application to which it relates.

d. There shall be included a full list of the samples submitted pursuant to Item 9a; a statement of the additional samples that will be submitted as soon as available; and, with respect to each sample submitted, full information with respect to its identity, the origin of any new-drug substance contained therein (including in the case of new-drug substances, a statement whether it was produced on a laboratory, pilot-plant, or full-production scale) and detailed results of all laboratory tests made to determine the identity, strength, quality, and purity of the batch represented by the sample, including assays. Include for any reference standard a complete description of its preparation and the results of all laboratory tests on it. If the test methods used differed from those described in the application, full details of the methods employed in obtaining the reported results shall be submitted.

e. The requirements of Item 9a may be waived in whole or in part on request of the applicant or otherwise when any such samples are not necessary.

f. If samples of the drug are sent under separate cover, they should be addressed to the attention of the Bureau of Medicine and identified on the outside of the shipping carton with the name of the applicant and the name of the drug as shown on the application.

10. Full reports of preclinical investigations that have been made to show whether or not the drug is safe for use and effective in use. a. An application may be refused unless it contains full reports of adequate preclinical tests by all methods reasonably applicable to a determination of the safety and effectiveness of the drug under the conditions of use suggested in the proposed labeling.

b. Detailed reports of the preclinical investigations, including all studies made on laboratory animals, the methods used, and the results obtained, should be clearly set forth. Such information should include identification of the person who conducted each investigation, a statement of where the investigations were conducted, and where the underlying data are available for inspection. The animal studies may not be considered adequate unless they give proper attention to the conditions of use recommended in the proposed labeling for the drug such as, for example, whether the drug is for short- or long-term administration or whether it is to be used in infants, children, pregnant women, or women of child-bearing potential.

c. Detailed reports of any pertinent microbiological and *in vitro* studies.

d. Summarize and provide a list of literature references (if available) to all other preclinical information known to the applicant, whether published or unpublished, that is pertinent to an evaluation of the safety or effectiveness of the drug.

11. List of investigators. a. A complete list of all investigators supplied with the drug including the name and post office address of each investigator and, following each name, the volume and page references to the investigator's report(s) in this application and in any documents incorporated by reference, or the explanation of the omission of any reports.

b. The unexplained omission of any reports of investigations made with the new drug by the applicant, or

submitted to him by an investigator, or the unexplained omission of any pertinent reports of investigations or clinical experience received or otherwise obtained by the applicant from published literature or other sources, whether or not it would bias an evaluation of the safety of the drug or its effectiveness in use, may constitute grounds for the refusal or withdrawal of the approval of an application.

12. Full reports of clinical investigations that have been made to show whether or not the drug is safe for use and effective in use. a. An application may be refused unless it contains full reports of adequate tests by all methods reasonably applicable to show whether or not the drug is safe and effective for use as suggested in the labeling.

b. An application may be refused unless it includes substantial evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling.

c. Reports of all clinical tests sponsored by the applicant or received or otherwise obtained by the applicant should be attached. These reports should include adequate information concerning each subject treated with the drug or employed as a control, including age, sex, conditions treated, dosage, frequency of administration of the drug, results of all relevant clinical observations and laboratory examinations made, full information concerning any other treatment given previously or concurrently, and a full statement of adverse effects and useful results observed, together with an opinion as to whether such effects or results are attributable to the drug under investigation and a statement of where the underlying data are available for inspection. Ordinarily, the reports of clinical studies will not be regarded as adequate unless they include reports from more than one independent, competent investigator who maintains adequate case histories of an adequate number of subjects, designed to record observations and permit evaluation of any and all discernible effects attributable to the drug in each individual treated and comparable records on any individuals employed as controls. An application for a combination drug may be refused unless there is substantial evidence that each ingredient designated as active makes a contribution to the total effect claimed for the drug combination. Except when the disease for which the drug is being tested occurs with such infrequency in the United States as to make testing impractical, some of the investigations should be performed by competent investigators within the United States.

d. Attach as a separate section a completed Form FD-1639, Drug Experience Report (obtainable, with instructions, on request from the Department of HEW. Food and Drug Administration. Bureau of Drugs *(BD-200)* Rockville, Maryland 20852), for each adverse experience or, if feasible, for each subject or patient experiencing one or more adverse effects, described in Item 12c, whether or not full information is available. Form FD-1639 should be prepared by the applicant if the adverse experience was not reported in such form by the investigator. The Drug Experience Report should be cross-referenced to any narrative description included in Item 12c. In lieu of a FD Form 1639, a computer-generated report may be submitted if equivalent in all elements of information with the identical enumerated sequence of events and methods of completion; all formats proposed for such use will require initial review and approval by the Food and Drug Administration.

e. All information pertinent to an evaluation of the safety and effectiveness of the drug received or otherwise obtained by the applicant from any source, including information derived from other investigations or commerical marketing (for example, outside the United States), or reports in the scientific literature, involving the drug that is the subject of the application and related drugs. An adequate summary may be acceptable in lieu of a reprint of a published report which only supports other data submitted. Reprints are not required of reports in designated journals, listed in §130.38 of the new-drug regulations, about related drugs; a bibliography will suffice. Include any evaluation of the safety or effectiveness of the drug that has been made by the applicant's medical department, expert committee, or consultants.

f. If the drug is a combination of previously investigated or marketed drugs, an adequate summary of preexisting information from preclinical and clinical investigation and experience with its components, including all reports received or otherwise obtained by the applicant suggesting side effects, contraindications, and ineffectiveness in use of such components. Such summary should include an adequate bibliography of publications about the components and may incorporate by reference information concerning such components previously submitted by the applicant to the Food and Drug Administration.

g. The complete composition and/or method of manufacture of the new drug used in each submitted report of investigation should be shown to the extent necessary to establish its identity, strength, quality, and purity if it differs from the description in Item 6, 7, or 8 of the application.

13. If this is a supplemental application, full information on each proposed change concerning any statement made in the approved application.

Observe the provisions of §130.9 of the new-drug regulations concerning supplemental applications.

Smith Kline & French Laboratories
(Applicant)

Per Robert L. Dean
(Responsible official or agent)

Robert L. Dean, Vice President
~~Regulatory and Government Affairs~~
(Indicate authority)

(Warning: A willfully false statement is a criminal offense. U.S.C. Title 18, sec. 1001.)

NOTE: This application must be signed by the applicant or by an authorized attorney, agent, or official. If the applicant or such authorized representative does not reside or have a place of business within the United States, the application must also furnish the name and post office address of and must be countersigned by an authorized attorney, agent, or official residing or maintaining a place of business within the United States.

ORIG

SK&F

SMITH KLINE & FRENCH LABORATORIES
00 Spring Garden Street, P.O. Box 7929, Philadelphia, Pennsylvania 19101 • 215-854-4000
cable SMITHKLINE PHILADELPHIAPA
telex 83-4487

RESUBMISSION

NDA ORIG AMENDMENT.

FPL

February 19, 1976

NDA 83-900
'Benzedrine' Tablets

Division of Generic Drug Monographs
Office of Drug Monographs
Bureau of Drugs HFD #530
Attention: Document Control Room 16-72
Department of Health, Education and Welfare
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20852

Gentlemen:

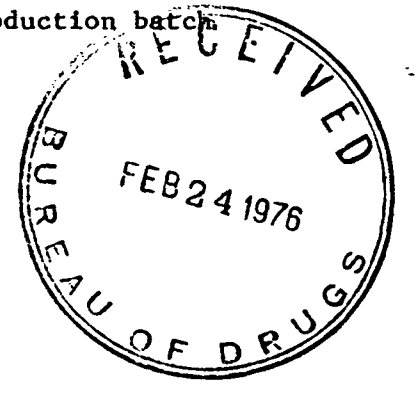
In response to Dr. Seife's communication dated October 29, 1975 in reference to our NDA 83-900 for 'Benzedrine' (amphetamine sulfate) Tablets, information is provided herewith to satisfy the following:

a) Adequate information concerning the methods used in the synthesis, extraction, isolation or purification of the amphetamine base and its final conversion to the sulfate

A Drug Master File describing the methods, facilities and controls used for our production of Amphetamine Sulfate has been submitted to the FDA. We will notify your Division upon receipt of notice of assignment of a Master File Number to that information.

b) Include a fully completed set of production work records and related quality control reports from an actual production size run of this product

Attachment A contains copies of production records and analytical laboratory data for a typical production batch of 'Benzedrine' Tablets.



c) The printed package insert and all container labels in use with this product

Attachment B contains twelve (12) copies of the Prescribing Information and Immediate Container Labels currently used for the two dosage strengths of this product.

In addition, to make them current, the revisions indicated below have been made in the Controls Sections of our New Drug Application as originally submitted August 6, 1971 and as updated July 5, 1972, April 6, 1973 and October 15, 1975.

Section 6 - Page 1 Section 8 - Page 5	Updated to reflect the use of Purified Water, USP rather than Water
Section 8 - Page 6, 6a	Updated to reflect the current use of high density polyethylene bottles for packaging
Section 8 - Page 10	Updated to reflect the use of a 5 year expiration date.

Sincerely,

J. F. Cassin

J. F. Cassin
Manager, Regulatory Affairs

Att.
kb

NDA ORIG AMENDMENT

FPL

Robert L. Dean, Vice President, Regulatory and Government Affairs-U.S. 215-854 5194

SMITH KLINE & FRENCH LABORATORIES

1500 Spring Garden Street, Philadelphia, Pennsylvania 19101

cable SMITHKLINE PHILADELPHIA PA
telex 83-4487

December 10, 1974

NDA ~~17-071~~ 13-700

Special new-drug application
supplement--changes being effected

Office of Scientific Evaluation
Bureau of Drugs
Department of Health, Education and Welfare
Food and Drug Administration
Parklawn Building, 5600 Fishers Lane
Rockville, Maryland 20852

Gentlemen:

In accordance with 314.8(d) and (e), I am enclosing 12 final printed copies each of the immediate container labels for 'Benzedrine' (brand of amphetamine sulfate) Spansule Capsules, 15 mg. (50s, placed in use in August, 1974), 5 mg. Tablets (100s, placed in use in September, 1974) and 10 mg. Tablets (100s, placed in use in October, 1974), revised to change "from this bulk package" to "this product" in the safety closure statement.

Sincerely yours,

Robert L. Dean

RLD/awd

Enclosures

RECEIVED
DEC 19 1974
(2)
BUREAU OF DRUGS

SmithKline

NDA ORIG AMENDMENT

Robert L. Dean, Vice President, Regulatory and Government Affairs-U.S. 215-854-5194

SMITH KLINE & FRENCH LABORATORIES

1500 Spring Garden Street, Philadelphia, Pennsylvania 19101

cable SMITHKLINE PHILADELPHIAPA
215/ 854-4487

FPD

July 26, 1974

NDA 17-071
83-900

Barrett Scoville, M.D., Director
Division of Neuropharmacological Drug Products
Office of Scientific Evaluation
Bureau of Drugs, DHEW
Food and Drug Administration
Parklawn Building - 5600 Fishers Lane
Rockville, Maryland 20852

Dear Doctor Scoville:

In accordance with the requests in your letter of April 30, 1974, I am submitting twelve final printed copies of prescribing information for 'Benzedrine' (brand of amphetamine sulfate) Spansule Capsules and Tablets revised to conform with the January 29, 1973 draft guideline labeling for single-entity amphetamine products (BZ:L17).

As requested, this labeling also includes, under ACTIONS, FDA's suggested statement regarding 'Benzedrine' Spansule capsules, and the following additional information:

1) Under "WARNINGS - Usage in Children," we have stated that amphetamines are not recommended in minimal brain dysfunction in children under three years of age.

2) Under "DOSAGE AND ADMINISTRATION - Narcolepsy," we have included specific dosage recommendations for pediatric and adult patients and suggested dosage increments and times of administration.

3) Under "DOSAGE AND ADMINISTRATION - Minimal Brain Dysfunction in Children," we have retained from our current labeling the paragraph stating that once symptoms have been controlled it may be possible to reduce dosage or interrupt therapy during summer months, since this information is useful to physicians. We have also included recommendations on the times of administration of tablet and 'Spansule' capsule dosage forms.

4) Similarly, under "DOSAGE AND ADMINISTRATION - Exogenous Obesity," we have adapted the guideline dosage recommendations to the use of 'Spansule' capsules, included suggested times of administration, and repeated the warning that 'Benzedrine' is not recommended for the treatment of obesity in children under 12 years of age.

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SmithKline

NDA 17-071

5) Under "OVERDOSAGE - Treatment," we have retained from our current labeling the paragraph dealing with overdosage of 'Spansule' capsules.

This labeling will be put into use next month.

In addition, as requested in your letter, I am enclosing twelve copies of the immediate container label for 15 mg. 'Benzedrine' Spansule capsules (50's). This label was placed in use in August, 1973, and submitted to FDA on October 15, 1973.

We noticed in the Federal Register of June 19, 1974, that the notice, "Drugs for Human Use — Drug Efficacy Study Implementation Certain Single Entity Oral Anoretic Drugs in Conventional or Controlled Release Dosage Forms" (39:26459), does not appear to require an initial box warning in the package insert, whereas the Guideline Labeling for Single-Entity Amphetamine Products, which we have followed in revising 'Benzedrine' labeling, does require a box warning. Is this box warning something we might omit in the next printing?

Sincerely yours,

Robert L. Dean

RLD:jh

Enclosures

NDA ORIG AMENDMENT SK&F

FPII

ORIG

Robert L. Dean, Vice President, Regulatory and Government Affairs-U.S.

SMITH KLINE & FRENCH LABORATORIES

1500 Spring Garden Street, Philadelphia, Pa. 19101 • 215 LOcust 4-2400

October 15, 1973

NDA 17-071

(-, 83-900)

"Special new drug application
supplement--changes being effected"

Office of Scientific Evaluation
Bureau of Drugs
Department of Health, Education and Welfare
Food and Drug Administration
5600 Fishers Lane, Parklawn Building
Rockville, Maryland 20852

Gentlemen:

In accordance with 130.9 (d) and (e), I am enclosing for your files 12 final printed copies each of the labels and labeling for 'Benzedrine' (brand of amphetamine sulfate):

1) revised prescribing information (BZ:L16) and immediate container label for 10 mg. Tablets (100s) to include the new corporate name, "Division of SmithKline Corporation," placed in use in September, 1973.

2) revised immediate container label for 15 mg. 'Spansule' Capsules (50s) to include the new corporate name and a change in the storage statement from "Keep in a cool, dry place" to "Store at controlled room temperature" to conform to standard compendial terminology. This was placed in use in August, 1973.

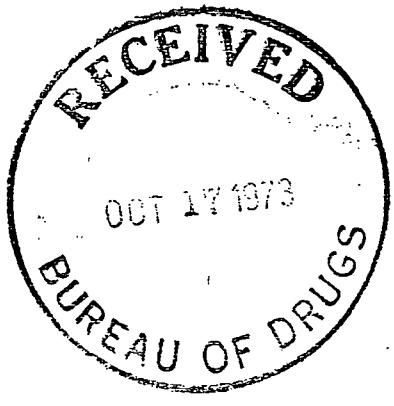
As stated in our letter of August 6, 1971, these submissions are made without prejudice to our position that 'Benzedrine' Spansule Capsules and Tablets are not "new drugs" as that term is defined in Section 201(p) of the Federal Food, Drug and Cosmetic Act and is covered by the grandfather clause enacted in Section 107 (c)(4) of the Drug Amendments of 1962.

Sincerely yours,

Robert L. Dean

RLD/awd

Enclosures



NDA ORIG AMENDMENT

SK&F

FPL

Robert L. Dean, Vice President, Regulatory and Government Affairs-U.S.

SMITH KLINE & FRENCH LABORATORIES
1500 Spring Garden Street, Philadelphia, Pa. 19101 • 215 LOcust 4-2400

September 17, 1973

ANDA 83-900

"Special new-drug application
supplement--changes being effected"

Office of Scientific Evaluation
Bureau of Drugs
Department of Health, Education and Welfare
Food and Drug Administration
Parklawn Building, 5600 Fishers Lane
Rockville, Maryland 20852

Gentlemen:

In accordance with 130.9 (d) and (e), I am enclosing for your files 12 final printed copies of a slightly revised immediate container label, placed in use in July, 1973, for 'Benzedrine' (brand of amphetamine sulfate) Tablets, 5 mg. (100s). The only change is the addition of the new corporate name -- Division of SmithKline Corporation.

As stated in our letter of August 6, 1971, these submissions are made without prejudice to our position that 'Benzedrine' Spansule Capsules and Tablets are now "new drugs" as that term is defined in Section 201(p) of the Federal Food, Drug and Cosmetic Act and is covered by the grandfather clause enacted in Section 107(c)(4) of the Drug Amendments of 1962.

Sincerely yours,

Robert L. Dean

RECEIVED
SEP 26 1973
BUREAU OF DRUGS

RLD/awd

Enclosures

NDA ORIG AMENDMENT

FPL

obert L. Dean, Vice President, Regulatory and Government Affairs - U.S. Pharmaceuticals

SMITH KLINE & FRENCH LABORATORIES

500 Spring Garden Street, Philadelphia, Pa. 19101 • 215 LOcust 4-2400

ORIG

NDA 17-071

February 22, 1973

"Special new-drug application
supplement--changes being effected"

Office of Scientific Evaluation
Bureau of Drugs
Food and Drug Administration
Department of Health, Education and Welfare
Parklawn Building - 5600 Fishers Lane
Rockville, Maryland 20852

Gentlemen:

In accordance with 130.9 (d) and (e) and with the Federal Register notice of April 27, 1972, for "Child Protection Packaging Standards for Preparations Subject to the Comprehensive Drug Abuse Prevention and Control Act of 1970," I am enclosing for your files 12 final printed copies each of slightly revised immediate container labels for 'Benzedrine' (brand of amphetamine sulfate) Spansule Capsules, 15 mg. (50s) and Tablets, 5 mg. and 10 mg. (100s). The only change is the addition of the following safety closure statement:

> "Important: Use safety closures when dispensing from this bulk package unless otherwise directed by physician or requested by purchaser."

This labeling was placed in use 1) for 'Spansules' in January, 1973, and 2) for Tablets in February, 1973.

As stated in our letter of August 6, 1971, these submissions are made without prejudice to our position that 'Benzedrine' Spansule Capsules and Tablets are not "new drugs" as that term is defined in Section 201(p) of the Federal Food, Drug and Cosmetic Act and is covered by the grandfather clause enacted in Section 107 (c)(4) of the Drug Amendments of 1962.

Sincerely yours,

Robert L Dean

RLD:db

Enclosures

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FEB 26 1973
BUREAU OF DRUGS

(2)

...t L. Dean, Vice President, Regulatory and Government Affairs-U.S. Pharmaceuticals NDA ORIG AMENDMENT

SK&F

SMITH KLINE & FRENCH LABORATORIES FPL

1500 Spring Garden Street, Philadelphia, Pa. 19101 • 215 LOcust 4-2400

October 11, 1972

NDA 17-071

"Special new-drug application supplement—changes being effected"

Office of Scientific Evaluation
Bureau of Drugs
Department of Health, Education and Welfare
Food and Drug Administration
Parklawn Building, 5600 Fishers Lane
Rockville, Maryland 20852

Gentlemen:

In accordance with 130.9 (d) and (e), I am enclosing for your files 12 final printed copies of a slightly revised prescribing information for 'Benzedrine' (brand of amphetamine sulfate) Spansule Capsules and Tablets. On page 2, paragraph 2 under WARNINGS has been revised to clarify the section concerning the operation of vehicles or machinery.

I am also enclosing 12 final printed copies of a slightly revised immediate container label for 'Benzedrine' Spansule Capsules, 15 mg. (50s). The 'Spansule' description has been changed to "...so prepared that an initial dose is released promptly and the remaining medication is released gradually over a prolonged period" to conform to the prescribing information submitted to FDA 5/5/72.

The above labeling was placed in use in August, 1972.

As stated in our letter of August 6, 1971, these submissions are made without prejudice to our position that the 'Benzedrine' Tablets and Spansule Capsules are not "new drugs" as that term is defined in Section 201(p) of the Federal Food, Drug and Cosmetic Act and is covered by the grandfather clause enacted in Section 107(c)(4) of the Drug Amendments of 1962.

Sincerely yours,

RECEIVED OCT 16 1972 BUREAU OF DRUGS

RLD:db

Enclosures

ENCLOSURES IN GENERAL ONLY

17-071

BOTH JACKETS

NDA ORIG AMENDMENT

SK&F

Robert L. Dean, Vice President, Regulatory and Government Affairs - U.S. Pharmaceuticals

SMITH KLINE & FRENCH LABORATORIES

FPL

1500 Spring Garden Street, Philadelphia, Pa. 19101 • 215 LOcust 4-2400

May 5, 1972

Orig

NDA 17-071

"Special new drug application
supplement--changes being effected"

Office of Scientific Evaluation
Bureau of Drugs
Department of Health, Education and Welfare
Food and Drug Administration
Parklawn Building, 5600 Fishers Lane
Rockville, Maryland 20852

Gentlemen:

In accordance with 130.9 (d) and (e), I am enclosing for your files twelve (12) final printed copies of a slightly revised prescribing information for 'Benzedrine' (brand of amphetamine sulfate) Spansule Capsules and Tablets. The only change is in the 'Spansule' DESCRIPTION on page 1: the phrase beginning "...so prepared that a therapeutic dose..." has been changed to "...so prepared that an initial dose is released promptly and the remaining medication is released gradually over a prolonged period" in order to improve product description. This labeling was placed in use in March, 1972.

As stated in our letter of August 6, 1971, these submissions are made without prejudice to our position that the 'Benzedrine' Tablet and Spansule Capsules are not "new drugs" as that term is defined in Section 201(p) of the Federal Food, Drug and Cosmetic Act and is covered by the grandfather clause enacted in Section 107(c)(4) of the Drug Amendments of 1962.

Sincerely yours,

Robert L. Dean

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MAY 10 1972
BUREAU OF DRUGS

RLD/awd

Enclosures: BZ:L14

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