CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

19-044 / S-002

Trade Name: Indium In-111 Oxyquinoline

Generic Name:

Sponsor: GE Healthcare

Approval Date: December 12, 1989

Indications: For a reduction in the number of vials for sterility testing from 20% to 10% of each production batch of the drug product.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-044 / S-002

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	**X**
Other Action Letters	**X**
Labeling	
Summary Review	
Officer/Employee List	
Office Director Memo	
Cross Discipline Team Leader Review	
Medical Review(s)	
Chemistry Review(s)	**X**
Environmental Assessment	
Pharmacology Review(s)	
Statistical Review(s)	
Microbiology Review(s)	**X**
Clinical Pharmacology/Biopharmaceutics Review(s)	
Other Reviews	
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	**X**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-044 / S-002

APPROVAL LETTER

NDA 19-044/S-002

DEC 12 1989

Amersham Corporation
2636 South Clearbrook Drive
Arlington Heights, Illinois 60005-4692

Attention: John H. Waterman
Manager, Scientific and Regulatory Affairs

Dear Mr. Waterman:

Reference is made to your supplemental new drug application dated May 27, 1986 submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for the diagnostic radiopharmaceutical indium In 111 oxyquinoline solution ~~NDA 19-044~~.

The supplemental new drug application provides for a reduction in the number of vials for sterility testing from 20% to 10% of each production batch of the drug product.

We have completed our review of this supplemental new drug application as submitted and it is approved as of the date of this letter.

We remind you that you must comply with the requirements set forth under 21 CFR 314.80 and 314.81 for an approved NDA.

Sincerely yours,

J Palmer 12-11-89

John F. Palmer, M.D.
Acting Director
Division of Medical Imaging,
Surgical and Dental Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Orig. NDA 19-044/S-002
HFD-160/Div. File
HFD-161/Lange/Stone
HFD-160/Ruby
HFD-160/Greenman
HFD-80
R/D Init. by:
S. Lange 11.30.89
E. Ruby 11.30.89 12.01.89
E. Sheinin,Ph.D. 12.01.89
V. Greenman 12.01.89
P. Cooney,Ph.D. 12.01.89
A.E. Jones, M.D. 12.04.89
R.D. Joyce, ASCSO 12.05.89
drafted by: S. Lange 11.30.89
To printing 12.5.89
ft:mah:12.06.89
Wang 0327B
SUPPLEMENT APPROVAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-044 / S-002

OTHER ACTION LETTER(s)

NDA 19-044/S-002

Amersham Corporation
2636 South Clearbrook Drive
Arlington Heights, Illinois 60005-4692
(312) 593-6300

JUN 8 1987

Attention: Donald E. Baker, Manager
Medical Regulatory Affairs

Dear Mr. Baker:

Please refer to your supplemental new drug application of May 27, 1986, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Indium In 111 Oxyquinoline Solution.

The supplemental application provides for revision of the USP XXI sterility test sampling in the lot release schedule from 20% to 10% of the batch size.

Changes of the kind which you have described are not, in our opinion, the kind of changes permitted by regulation to be put into effect in advance of approval of a supplement.

This letter is to notify you that an approved supplement is required for the proposed change and that the supplement is under review.

Please provide data derived from the manufacturing process sterility assurance validation studies and from in-process controls that lots meet the required low probability of containing a contaminated unit in spite of using a decreased number of test samples.

Sincerely yours,

Robert A. Jerussi 6/4/87

Robert A. Jerussi, Ph.D.
Deputy Director
Division of Oncology and
Radiopharmaceutical Drug Products
Office of Drug Research and Review
Center for Drugs and Biologies

cc:
Orig. NDA 19-044
HFN-150/Division File
HFN-150/Leak/3-23-87 JerG/1/87
HFN-150/West
R/D Init. by: RHWood/3-27-87
F/T by tag/5-28-87
revised by: RHWood/6-1-87
F/T by tag/6-1-87
Wang # 09840
Not approvable

H. J. Kelly, Acting Supervising Chemist
6-1-87

Robert L. West
6/3/87

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-044 / S-002

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW

Organization
HFD-160

NDA Number
19-044/S-002

Name and Address of Applicant
Amersham Corporation
2636 S. Clearbrook Dr.
Arlington Heights, IL 60005-4692
(312) 593-6300

AF Number

Supplements
Number Date
S-002 27May86

Name of Drug
Indium In-111 Oxyquinoline Solution

Non-Proprietary
same

Amendments
19Jun87
06Apr89

Supplement Provides For:
Reduction of the number of samples to be used in the sterility test from 20% of the batch [redacted] (b) (4) to 10% of the batch [redacted].

Pharmacological Category
diagnostic radiopharmaceutical

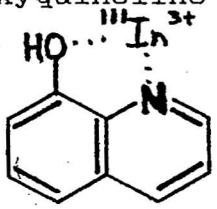
How Dispensed
Rx

Records/Reports
current through Dec 1988

Dosage Form
injectable solution

Potency
1.0 mCi/mL,
[redacted] (b) (4) ug 8-hydroxyquinoline/mL

Chemical Name and Structure
Complex of 8-hydroxyquinoline and Indium [redacted] (b) (4)



Comments

[redacted] (b) (4)

[redacted] S-002 [redacted] propose to alter the sample size for the sterility test.

Conclusions and Recommendations

A microbiology review of this supplement will be neccessary. S-002 [redacted] could be reviewed [redacted] (b) (4). However, the firm has requested a meeting to discuss [redacted]. In case there is a delay in scheduling the meeting or for some other reason, and since the supplement has been pending since May1986, I am requesting that a microbiology review of S-002 be done as soon as possible.

Reviewer E. Ruby
Eric Ruby, Chemist, HFD-160

Date Completed 030ct89

8 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-044 / S-002

MICROBIOLOGY REVIEW(S)

ORIGINAL 81

OCT 23 1989

MICROBIOLOGIST'S REVIEW #1	1. Organization	2. NDA Number
	HFD-160	19-044

3. Name and Address of Applicant (City & State)	4. AF Number	5. Supplement(s) Number(s)	Date(s)
Amersham Corporation Arlington Heights, Illinois 60005-4692		S-002 assigned	05-27-86 10/11/89

6. Name of Drug	7. Nonproprietary Name
Indium IN 111 Oxyquinoline Solution	

8. Supplement(s) Provides For:	9. Amendments & Other (Reports, etc) Dates
A change in the USP XXI Sterility Test sampling procedure for lot release.	SNC - 06/19/87 Amendment - 04/06/89

10. Pharmacological Category	11. How Dispensed	12. Related IND/NDA/DMF
Radiopharmaceutical	/X/ RX / / OTC	(b)(4) - 03/14/87 DMF (b)(4)

13. Dosage Form(s)	14. Potency(ies)
Sterile solution for injection supplied in (b)(4) vials, 1.0 ml/vial	

15. Chemical Name and Structure	16. Records & Reports
	Current / / Yes / / No Reviewed / / Yes / / No

17. Comments

1. The supplement provides for reduction in the number of samples for testing sterility of batches for lot release. The applicant has changed the sampling schedule from 20% to 10% of the batch size.

2. The supplement was submitted as a special supplement - "Special Supplement - Changes Being Effected". The Administration's letter of of June 8, 1987 informed the applicant that the proposed change required prior approval and that appropriate data should be submitted in support of sterility assurance (e.g., process validation studies and in-process controls). (continued on page 2)

18. Conclusions and Recommendations

The application is approvable for the proposed reduction in the sampling schedule from 20% (USP XXI) to 10% of batch size.

19. REVIEWER

Name	Signature	Date Completed
V. Greenman	V Greenman	October 19, 1989

Distribution CSO /X/ Original Jacket /X/ /X/ Reviewer /X/ Div. File

Wang # 4246N

17. Continued

(b) (4)

The Administration's letter of March 13, 1989 informed the applicant that since (b) (4), S-002 remains nonapprovable. Notwithstanding the fact that S-002 was put into effect at the time the supplement was submitted, the applicant was requested to perform the USP XXI sterility test, not the revised test (sampling schedule of 10% of batch size).

The referenced (b) (4)

S-002.

3. The supplements S-002, (b) (4) were discussed at a meeting held on October 18, 1989 between representatives of Amersham, Compliance and HFD-160. The latter supplement provides for (b) (4)

cc:
Orig. NDA 19-044
HFD-160/Division File
HFD-160/VGreenman/10-19-89
HFD-161//F.Stone
R/D Init. by: P.H.Cooney/10-23-89
F/T by:DFlannigan
Wang (#) 4246N

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-044 / S-002

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Amersham Corporation
2636 South Clearbrook Drive
Arlington Heights, Illinois 60005-4692
(312) 593-6300

amend
SUPPL NEW CORRES (b) (4)
TO S-0021
SBC

Amersham

April 6, 1989

Eric B. Sheinin, Ph.D.
Supervisory Chemist
Division of Oncology and
Radiopharmaceutical Drug Products (HFD-150)
Office of Drug Evaluation I
Center for Drugs Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Md 20857

CENTER FOR DRUGS AND BIOLOGICS
REC'D
APR 10 1989
HFN-150

Re: NDA 19-044/S-002 - Indium ^{111}In Oxyquinoline
Reduced Sterility Test Sample Size

Dear Doctor Sheinin:

Please refer to your letter dated March 13, 1989 concerning our pending Supplement S-002 providing for reduced sterility test sample size for Indium ^{111}In Oxyquinoline. Your letter also made reference to (b) (4) (b) (4), (b) (4). Each of the issues you raised will be addressed separately.

S-002

The reduced sample size described in our immediately effective Supplement dated May 27, 1986 has, in fact, been employed since that date. The response to this Supplement from Doctor Jerussi, dated June 8, 1987, noted that it was the Division's opinion that such changes required prior approval, and requested submission of additional data in support of such approval. Our reply dated June 19, 1987 reviewed the rationale for implementing the changes provided for by the Supplement and requested that the Division review the process validation data submitted with pending (b) (4), dated (b) (4).

While we understand that (b) (4) (b) (4), we do not believe that this precludes the Division's review of Supplement S-002.

However, of greater importance are the recommendations of the USP monograph on Sterilization and Sterility Assurance <1211>. The Section headed Sterility Testing of Lots reviews the philosophy of process validation and sterilizer overkill cycles as the "primary means of supporting the claim that a lot of finished articles purporting to be sterile meets that specification."

The following paragraph notes:

> If data derived from the manufacturing process sterility assurance validation studies and from in-process controls are judged to provide greater assurance that the lot meets the

> required low probability of containing a contaminated unit (compared to sterility testing results from finished units drawn from that lot), any sterility test procedures adopted may be minimal, or dispensed with on a routine basis.

This position is strengthened by a footnote to this paragraph (6) which reads:

> Radioactive Pharmaceutical Products - Because of rapid radioactive decay, it is not feasible to delay the release of some radioactive pharmaceutical products in order to complete sterility tests on them. In such cases, results of sterility tests provide only retrospective confirmatory evidence for sterility assurance, which therefore depends on the primary means thereto established in the manufacturing and validation/ certification procedures.

Finally, the monograph further states, under Performance, Observation and Interpretation:

(b) (4) [redacted]

We believe, therefore, that our current sampling plan meets the requirements of USP XXI and that the Supplement may be approved following review of the validation data provided.

(b) (4) [redacted] Supplement S-002.

We look forward to your prompt consideration of these comments, and approval of pending Supplement S-002. We appreciate your continued interest in our Application.

Yours truly,

Jack Waterman

John H. Waterman
Manager, Scientific and Regulatory Affairs

mc
2679P

to JL 8/7/86

Amersham Corporation
2636 South Clearbrook Drive
Arlington Heights, Illinois 60005-4692
(312) 593-6300

NDA NO. 19 044 REF. NO. 5002
NDA SUPPL FOR 3 - SCS

JUN 1986

May 27, 1986

Amersham

Department of Health, Education and Welfare
Food and Drug Administration
HFN-150
Attention: Document Control Room #17B-34
5600 Fishers Lane
Rockville, MD 20857

Re: NDA #19-044
Indium In 111 Oxyquinoline Solution
SPECIAL SUPPLEMENT - CHANGES BEING EFFECTED

Gentlemen:

Reference is made to Indium Oxyquinoline Solution, NDA #19-044, approved on December 24, 1985.

In accordance with 21 CFR Subpart B Section 314.70(c), Amersham wishes to supplement the application to revise the specification for the USPXXI Sterility Test sampling procedures.

1. Summary of Basis for Change:

Amersham International has revised the USPXXI Sterility Test sampling in the Lot Release Schedule from 20% to 10% of the batch size for the following reasons:

(b) (4)

(b) (4)

[redacted]

2. Date Change was Effected:

Therefore, based on the foregoing reasons and the continued (b) (4) (b) (4), on May 21, 1986, the specification for USPXXI retrospective Sterility Test sampling in the Lot Release Schedule was revised from 20% to 10% of the batch size.

A copy of the products revised specification, which appears on page 8.228 in Part 8(n) of the original NDA, is attached for your information.

Should you have any questions, please do not hesitate to contact the undersigned.

Sincerely,

Donald E. Baker
Manager, Medical Regulatory Affairs

DEB/cpd

8/4/86
Read from document
Room. 6 Reviewers
Robert Ludwest, CSO.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
5600 FISHERS LANE
ROCKVILLE, MARYLAND 20852

Form Approved
OMB No. 57-R0003

NEW DRUG APPLICATION *(DRUGS FOR HUMAN USE)*

(Title 21, Code of Federal Regulations, § 314.1)

Name of applicant AMERSHAM CORPORATION

Address 2636 South Clearbrook Drive; Arlington Heights, Illinois 60005

Date May 27, 1986

Name of new drug NDA #19-044 Indium In 111 Oxyquinoline Solution SPECIAL SUPPLEMENT - CHANGES BEING EFFECTED

☐ Original application (regulation § 314.1).

☐ Amendment to original, unapproved application (regulation § 314.6)

☐ Abbreviated application (regulation § 314.1(f)).

☐ Amendment to abbreviated, unapproved application (regulation § 314.6).

☐ Supplement to an approved application (regulation § 314.8).

☒ 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 §201.100 (21 CFR 201.100). 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 §314.8 of the new-drug regulations.

Attached hereto, submitted in the form described in §314.1(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, and expanded summary and evaluation as outlined in §314.1(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 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 it is to be advertised or represented, in accord with §201.100 (21 CFR 201.100). 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 nay such advertising for a prescription drug (see §310.300 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 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 control 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 criteria 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 sutitability of the analytical method 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 §310.3(g), from the batches(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 inital 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 §310.3(g) of the new-drug regulations, 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 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 Drugs 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 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, recommended, or suggested in the proposed labeling.

c. Reports of all clinical tests sponsored by the applicant or received or other wise 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 clincial 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 seperate section a completed Form FD-1639, Drug Experience Report (obtainable, with instructions, on request from the Food and Drug Administration, Department of HEW. 5600 Fishers Lane, 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 commercial 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 §310.9 of the new-drug regulations, about related drugs; a bibliography will suffice. Include the 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.

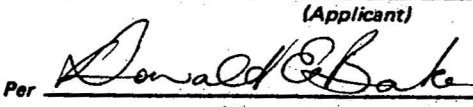
13. If this is a supplemental application, full information on each proposed change concerning any statement made in the approved application.
Observe the provisions of §314.8 of the new-drug regulations concerning supplemental applications.

14. [Reserved]

15. The applicant is required to submit an environmental impact analysis report analyzing the environmental impact of the manufacturing process and the ultimate use or consumption of the drug pursuant to §6.1 of this chapter.

AMERSHAM CORPORATION

(Applicant)

Per 

(Responsible official or agent)

Manager, Medical Regulatory Affairs

(Indicate authority)

(Warning: A willfully false statement is a criminal offense. U.S.C. Tittle 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.