DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

JUN 7 1989

Dear Sir or Madam:

This is the second in a series of policy letters on the implementation of the Generic Animal Drug and Patent Term Restoration Act, which was signed into law by the President on November 16, 1988. The first policy letter was issued on November 23, 1988.

Under the provisions of the Act, the sponsor of a generic animal drug product must submit an Abbreviated New Animal Drug Application (ANADA) for approval before the product can legally be marketed. The generic product and its uses must be the same as those of an approved animal drug, with certain exceptions, and it must be demonstrated that the generic product is bioequivalent to the approved product. If the generic product differs in certain specific ways from the approved product, then the sponsor must first seek permission to file an ANADA by submitting a Suitability Petition.

The attached document, entitled "Generic Animal Drug and Patent Term Restoration Act - Implementation," describes the Agency's proposed procedures for the handling of ANADAs, Suitability Petitions and other related submissions. The document describes the general organizational structure in the Center for Veterinary Medicine and provides the names and phone numbers of responsible persons and who to contact for further information. Generally, wherever possible, the Center has tried to utilize its currently standing review divisions and administrative procedures in the approval process for generic animal drug products. A Generic Animal Drug Staff is proposed to administratively coordinate the review process and assure consistency within the Center. The document also contains drafts of three documents: Abbreviated New Animal Drug Applications - Manufacturing Requirements; Bioequivalence Guideline; and Environmental Review of Generic Animal Drugs.

The attached document is a draft document in its entirety and is, therefore, subject to change. The Act requires that no ANADAs be approved before January 1, 1991. We anticipate that a number of changes in this document may occur as we begin to review applications and petitions for generic animal drugs. When and if such changes occur, a copy of the revised document will be placed on public display and a notice of availability will be published in the Federal Register. Comments and questions regarding this document are solicited and welcome.

Comments may be addressed to:

Dr. Richard B. Talbot
Office of New Animal Drug Evaluation
Center for Veterinary Medicine
5600 Fishers Lane
Rockville, Maryland 20857
(301) 443-4313

As we in the Center continue to develop our implementation policies and procedures for generic animal drugs, we will continue to keep the public informed through written communications and through meetings with professional societies and associations. We welcome any input from all interested parties.

Sincerely yours,

Gerald B. Guest, DVM
Director, Center for
Veterinary Medicine

Attachment

DRAFT

JUN 7 1989

GENERIC ANIMAL DRUG AND PATENT TERM RESTORATION ACT

IMPLEMENTATION

I. INTRODUCTION

The objective of this document is to provide guidance for the implementation of the Generic Animal Drug and Patent Term Restoration Act. The Act provides the legal basis for the marketing of generic new animal drugs by allowing the substitution of bioequivalence information for the full safety and effectiveness information that is normally required for approval of a new animal drug product. Our activities have centered around developing administrative procedures for processing abbreviated new animal drug application (ANADAs), and drafting scientific and technical guidelines which address the requirements for demonstration of bio-equivalence between an approved drug and a proposed generic drug.

We have divided the approval process into two major areas: pre-ANADA activities and ANADA review activities.

The pre-ANADA activities may be grouped into three areas: Suitability Petitions, Requests for Waivers of In Vivo Testing and Protocols for Bioequivalence Studies. The procedures for submitting and processing these documents are described in Section II of this document.

Section III describes in detail our procedures for evaluating an ANADA.

The Appendix provides copies of draft documents regarding chemistry and manufacturing, bioequivalence and environmental considerations. Flow charts outlining the handling of Suitability Petitions and ANADAs are also provided in the Appendix.

The Generic Animal Drug Staff in the Office of New Animal Drug Evaluation (NADE) will co-ordinate ANADA activities.

To provide consistency across the various administrative units, we have established a standing Generic Drug Committee. It is anticipated that this committee will be chaired by the Deputy Director of the Office of New Animal Drug Evaluation. The committee members will include the Deputy Director, New Animal Drug Evaluation, the primary review Division Directors, and a representative of the Office of General Counsel. The responsibilities of the committee are described in Sections II and III. A Bioequivalence Committee will address the scientific aspects of bioequivalence, as described in Section III.

All inquires dealing with policy issues should be directed to:

Dr. Richard Talbot
Associate Director
Office of New Animal Drug Evaluation
Center for Veterinary Medicine
(301) 443-4313

Questions related to procedural or technical matters should be directed to Dr. Melanie Berson or to Dr. Tom McKay, of the Generic Animal Drug Staff at (301) 443-4500.

II. Pre-ANADA Activities

Pre-ANADA activities may include the submission of suitability petitions, requests for waivers of *in vivo* testing, and/or protocols for bioequivalence studies.

A. ANADA Suitability Petitions

The filing of a Suitability Petition provides a means by which a firm may request permission to file an ANADA for a product which differs from the approved pioneer product.

The specific variances under the Act for which a Suitability Petition may be submitted are as follows:

1. Change of one ingredient in a combination product or premix
2. Change of a dosage form
3. Change of a strength of an ingredient
4. Change in the route of administration
5. Change in use with other animal drugs in animal feed

The required components of the Suitability Petition have been adapted from the Citizen's Petition, as defined in 21 CFR Section 10.30, and are as follows:

1. Identification of Petitioner and appropriate citation of the relevant statutory sections of the Federal Food, Drug, and Cosmetic Act. For ANADA Suitability Petitions, the section is 512 (n) (3).

2. An "Action Requested" section detailing the proposed action that the petitioner is requesting the Agency to take, i.e., for the Commissioner to permit the filing of an ANADA for a proposed product, which differs from the approved pioneer product by the specifically defined characteristics. The proposed product should be identified and characterized.

3. A "Statement of Grounds" section that provides a comprehensive justification for the proposed variance from the pioneer drug product.

4. "Environmental Impact" We have determined that the action of submitting and reviewing the Suitability Petition will not normally be expected to have an environmental impact. Therefore, the Suitability Petition should include a request under 21 CFR 25.24(a)(8) for categorical exclusion from the requirement for an environmental assessment.

5. An "Economic Impact" section is required only when requested by the Commissioner; however, the petitioner should indicate that such an analysis will be provided upon request.

6. A "Certification" section stating that the petitioner has included all information known to him/her which is unfavorable to the petition. The certification must be signed and should contain a mailing address and telephone number.

Additional essential elements of a petition are:

1. Identification of a single listed drug which is the basis of the petition. (Multiple products may be cited to develop a justification in the "Statement of Grounds" section).

2. Inclusion of labeling for the proposed product and labeling of the approved pioneer drug product, noting and explaining all differences.

The Suitability Petitions will be evaluated by the Generic Animal Drug Staff with the assistance of the Generic Drug Committee. Petitions will be approved or denied within 90 days of the date the petition is filed.

The Act requires that the Suitability Petitions will be approved unless the Secretary finds that:

1. "investigations must be conducted to show the safety and effectiveness, in animals to be treated with the drug, of the active ingredients, route of administration, dosage form, strength, or use with other animal drugs in animal feed which differ from the approved new animal drug, or

2. investigations must be conducted to show the safety for human consumption of any residues in food resulting from the proposed active ingredients, route of administration, dosage form, strength, or use with other animal drugs in animal feed for the new animal drug which is different from the active ingredients, route of administration, dosage form, strength, or use with other animal drugs in animal feed of the approved new animal drug."

ANADA Suitability Petitions may be filed by submitting 4 copies to:

Dockets Management Branch
HFA-305, Room 4-62
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Telephone inquiries and desk copies of Petitions should be directed to:

Office of the Associate Director
New Animal Drug Evaluation
Center for Veterinary Medicine
HFV-100, Room 6B-03
Attention: Dr. Melanie Berson
Telephone Number: (301)443-4500

B. Request for Waivers of In Vivo Testing

When the proposed product meets specific criteria, a waiver of the requirement for in vivo testing may be requested. If the waiver is granted, the generic product will be considered to be bioequivalent to the reference product. Additionally, if the waiver is granted, any withdrawal period established for the reference product will be accepted for the new generic product. The criteria for waivers include the following:

1. The proposed generic product is a solution intended solely for intravenous injection, and it contains an active drug ingredient or therapeutic moiety combined with the same solvent, in the same concentration as an intravenous solution that is the subject of an approved full new animal drug application.

2. The drug product is a true solution intended for oral administration, contains the same therapeutic moiety in the same concentration as the reference product, and it contains no inactive ingredient that affects the absorption of any active ingredient.

3. The proposed generic product is a topically applied product which is intended for local therapeutic effect.

All requests for waivers should be submitted to the Center's Document Control Unit, HFV-16. They will be forwarded to the Generic Animal Drug Staff for evaluation and issuance of a decision. If the waiver is granted, a copy of the decision letter should be included as part of the subsequent ANADA submission.

C. Bioequivalence Studies: Bioequivalence studies may be blood level, physiological endpoint, or clinical endpoint studies.

The Agency encourages sponsors to submit protocols that define the nature and extent of the required experimental studies. Details regarding protocol development can be found in the Bioequivalence Guideline (Section 5), which is presented in Appendix B of this document.

Protocols should be submitted to the Center for Veterinary Medicine, Document Control Unit, HFV-16. The protocols will be assigned an INAD number and assigned to the appropriate primary division (HFV-110, 120 or 130) for review. The Generic Animal Drug Staff will review comments on protocols for consistency with Center policies.

The objective is to review the protocols within 45 days.

III. ANADA Review Process

A. Administrative Procedures

All abbreviated applications will be forwarded from the CVM Document Control Unit (HFV-16) to the Generic Animal Drug Staff (HFV-100).

The primary function of this staff will be to perform an initial review of the ANADA to determine the general content of the application and to determine the general acceptability of the application as an ANADA.

1. General Content: The standard form FDA-356V will be used as the basic application. The application will be examined to determine that all parts required by Subparagraphs 512(n)(1)(A) through (H) of the Act are provided. Refer to Part III B of this document.

2. Acceptability for Consideration: A review will be conducted of the information provided concerning the proposed product, its composition and its labeling to determine: (A) that the active ingredients, route of administration, dosage form and strength are the same as those of the pioneer product, or, if any of these are different a suitability petition has been submitted and approved in accordance with the Act (refer to Part II B of this document); (B) if the proposed uses are with other animal drugs in feed and one of the other animal drugs is different than the other approved animal drug in feed, a suitability petition has been submitted and approved in accordance with the Act (refer to Part II B of this document); (C) that the conditions of use, or similar limitations, have been previously approved.

Documentation submitted that the above conditions have been met will include copies of approved labeling and copies of approval letters for Suitability Petitions referenced in support of differences between the proposed and approved products. This documentation will be required in the original ANADA submission.

The Generic Animal Drug Staff will rely on the assistance and opinions of the Center's Generic Drug Committee in determining the acceptability of the ANADA for consideration of the proposed product as a generic new animal drug product.

Once it is determined that the application is suitable for consideration as a generic application, it will be forwarded to the appropriate primary review division for evaluation.

1. The Division of Therapeutic Drugs for Non-Food Animals (HFV-110) if the ANADA relates to a drug for non-food animals.

2. The Division of Production Drugs (HFV-120) if the ANADA relates to a drug for production purposes in food animals.

3. The Division of Therapeutic Drugs for Food Animals (HFV-130) if the ANADA relates to a drug for therapeutic purposes in food animals.

The scientific/technical review of the ANADA will be the administrative responsibility of the above divisions. These divisions will coordinate the input from the four major areas of scientific/technical review:

(1) Manufacturing and Quality Control - The draft guideline provided in Appendix A of this document should be used in the development of the manufacturing and quality control procedures. The appropriate material submitted in the ANADA will be reviewed by the Division of Chemistry, Manufacturing and Quality Control Branch (HFV-142) in the Division of Chemistry. The standards for the approval of an ANADA are essentially the same as for a NADA.

(2) Bioequivalence - The draft guideline included as Appendix B of this document should have been followed in developing this information. The material dealing with bioequivalence included in the ANADA will be reviewed for qualitative biological and/or medical aspects within the appropriate divisions mentioned above.

The quantitative aspects of this material will be reviewed by the Center's Biometrics Branch, HFV-161. In addition to the regular review units, the Bioequivalence Committee will establish scientific policy in this area. They will also evaluate and recommend solutions for any issues that are not covered by existing policy.

(3) National Environmental Policy Act (NEPA). The standards defined in Appendix C of this document should be met for approval. This area will be reviewed by the Environmental Staff (HFV-162).

(4) Food Safety - If a generic product covered by an ANADA is judged to be bioequivalent by the Agency, using appropriate blood level studies, then no tissue residue studies will be required. If the proposed drug product is the subject of an approved suitability petition, appropriate tissue residue data may be required. If bioequivalence has been determined by a pharmacologic or therapeutic endpoint, or, if the ANADA sponsor wishes to request a shorter withdrawal period than previously established, tissue residue data must be developed. These data will be reviewed by the Residue Evaluation Branch (HFV-144).

As previously stated each ANADA will be the responsibility of HFV-110, 120 or 130. The routing of the information pertaining to the above areas will be accomplished by the responsible division. These divisions will also be responsible for reviewing all aspects of the ANADA for appropriateness of the reviews received from each consulting unit, for the label review and for the FOI summary reviews. They will also be responsible for summarizing and drafting the Agency's response to each ANADA.

The decision packages from the divisions will be routed back through the Office of New Animal Drug Evaluation (HFV-100) for final concurrence.

B. ANADA Content

Each submission shall contain a cover letter and a signed and dated Form FDA 356V. The application must contain the following parts (citations in brackets refer to Section 512 of the Food, Drug and Cosmetic Act, as amended):

1. Identification.

The identification section should include the name and address of the sponsor and official and proprietary names of the proposed new animal drug.

2. Summary and Table of Contents. [(n)(1)(A) - (D), (F)]

The summary should contain a description of the proposed product, its active ingredients, route of administration, dosage form and strength. It should describe all of the proposed conditions of use or similar limitations prescribed, recommended or suggested on the labeling for the new animal drug and should contain a copy of the approved labeling for the pioneer product. It should contain a proposed withdrawal period at which residues of the new animal drug will be consistent with the tolerances established for the approved new animal drug, and whether this proposed withdrawal period is the same as the withdrawal period for the approved new animal drug. A summary of each study provided in the application and a list of references should also be provided in this part of the application.

If a Suitability Petition has been approved in accordance with the Act, a copy of the approval letter should be included in this part of the application.

Certification that no patent infringements will occur due to the manufacture, use or sale of the proposed new animal drug product should be included. Certification that proper notice has been given to holders of any patents such as the Act may require should be included. [(n)(1)(H) - (I)]

Any appropriate statements regarding exclusivity should be addressed in this part of the application, if applicable (1).

3. Proposed Labeling. [(n)(1)(F), (G)]

As stated in the FDA-356V.

4. Components and Composition. [(n)(1)(B), (G)]

As stated in the FDA-356V. Batch formula information should be included in this part of the application. Refer to Appendix A of this document.

5. Manufacturing Methods, Facilities and Controls. [(n)(1)(D), (G)]

As stated in the FDA-356V. All manufacturing information required for a pioneer product is also required for a generic product. Refer to Appendix A of this document.

6. Samples. [(n)(1)(G)]

As stated in the FDA-356V. Samples should be provided only on request by FDA.

7. Analytical Methods for Residues. [(n)(1)(A)(ii)]

Appropriate information dealing with human food safety should be provided in this section. Refer to Appendix B, Section IV of this document.

8. Bioequivalency Information. [(n)(1)(E)]

Complete information on Bioequivalency Studies should be provided in this Section.

Refer to Appendix B of this document regarding Bioequivalency requirements. If a waiver of in vivo testing was granted, a copy of the decision letter should be included in this part of the application.

9. Good Laboratory Practice Compliance.

If applicable. Refer to Appendix B of this document.

10. Environmental Assessment.

Refer to Appendix C of this document.

11. Freedom of Information Summary.

As required by the FDA-356V.

12. Other.

(1) Presumably the exclusivity for generic products may only be obtained if the pioneer's patent is challenged and found to be invalid. The exclusivity will be for 180 days and will be granted to the first patent challenger.

APPENDIX A

Manufacturing Requirements

ABBREVIATED NEW ANIMAL DRUG APPLICATIONS
FOR
GENERIC ANIMAL DRUGS

MANUFACTURING INFORMATION

MANUFACTURING AND QUALITY CONTROL BRANCH

DIVISION OF CHEMISTRY

CENTER FOR VETERINARY MEDICINE

FOOD & DRUG ADMINISTRATION

(CVM 142-051189)

TABLE OF CONTENTS

NOTE: The information presented is a DRAFT of proposed items. The information contained herein does not represent a complete presentation of all the specific and relevant information in each area.

(CVM 142-051189)

I. INTRODUCTION

This document provides information regarding the manufacturing process and the accompanying quality control system intended for raw materials, in-process materials, and the finished dosage form.

The information is intended to provide guidance to establish the identity, strength, quality, and purity of the new drug substance, drug product components, and dosage form and the procedures to assure that all batches conform to appropriate specifications.

Specific information related to product composition, specifications and stability is provided. This information is not intended to be all inclusive since there will be many issues that will be product dependent. These will need to be addressed with the sponsor.

The information presents guidance on acceptable approaches to meeting regulatory requirements. An applicant is encouraged to discuss different approaches or variations in advance with FDA reviewers to preclude expending time and effort in preparing a submission that FDA may later determine to be unacceptable.

Protocols or requests for advisory opinions may be submitted to the Center if the applicant so desires.

II. MANUFACTURING, CONTROL AND PACKAGING INFORMATION

Complete information on the manufacturing process, control procedures and packaging and labeling procedures is required.

A. NADA Submissions

The information for the manufacture of a generic animal drug product is the same as required in an original NADA submission for a new animal drug. The information is listed in Sections 4 and 5 of Form FDA-356V.

The information required includes the following:

Product Composition
Components
Manufacturer
Personnel
Equipment
  Manufacturing
  Laboratory
New Drug Substance
  Synthesis/Supplier
  Fermentation/Supplier
Raw Material
  Controls
Specifications/Methods
Manufacturing Process
  Production Batch Record
  In-process Controls
Container/Closure
Packaging Procedures
Labeling Procedures
Lot Control Number System

Analytical Controls
  Finished Product
    Specifications/Methods

Stability

B. Master File Submissions

Master files which contain any or all of the above information may be used as support documentation. An authorization letter permitting FDA to review the master file in support of an NADA must be submitted by the master file holder. All information in the master file must be current.

III. PRODUCT INFORMATION

This section provides guidance in certain critical areas. It should be pointed out that there will be issues within the subject areas that will be product dependent and need to be addressed on a case by case basis with the sponsor.

Products will fall into one of two categories:

1.- Pharmaceutical dosage forms

2.- Medicated feed forms:

- Type A Medicated Articles

  Premixes
  dry
  liquid

- Type B and C Medicated Products

  Finished Feeds
  dry
  liquid
  blocks

A. Product Composition

(i) Active Ingredient(s):

A generic product must contain the same active ingredient(s) as the pioneer product. The same salt form (e.g., sulfate, hydrochloride) must be used.

Information to demonstrate that the generic product contains the same active ingredient(s) must be provided. This information must include the results of testing using recognized standards and methods, e.g. CFR, USP/NF, AOAC, when available. Where standards are not publicly available, methods and specifications must be proposed to ensure the strength, quality, purity and identity of the active ingredient. Tests and methods (with appropriate validation data*) must be submitted.

*Validation data - See pg 5, Section C(ii)

The methods used should be appropriate for the specific active ingredient(s). Accepted analytical procedures include:

Infrared (IR) analysis
Mass spectometric (MS) analysis,
NMR (nuclear magnetic resonance) analysis
Chromatographic procedures (HPLC, GLC, TLC, GPC, etc),
UV spectrophotometric analysis
Microbiological procedures

The generic active ingredient need not be purchased from the same source as the pioneer. The source must be listed in the application. All information relative to the synthesis or fermentation process and manufacture of the ingredient must be submitted.

(ii) Inactive Ingredients:

The inactive ingredients need not be the same as used in the pioneer product.

All inactive ingredients must meet current compendial or established standards. Where none are available, standards with appropriate tests and methods (including appropriate validation data*)must be proposed.

B. Biomass products

The complete fermentation and manufacturing process for the preparation of the generic biomass product must be submitted.

A generic biomass product need not be produced by the same process as the pioneer biomass product.

The generic biomass "active" ingredient(s) must be fully characterized and demonstrated to be the same active ingredient(s) contained in the pioneer biomass product. A profile characterization of the biomass product may require identification of inactive ingredients.

C. Finished Product Specifications

(i) Standards:

Generic products must meet recognized regulatory standards when available.

Available sources may be the current edition of the USP/NF, the Code of Federal Regulations (where standards have been published), or publications where pioneer producers have published such standards.

*Validation data - See pg 5, Section C(ii)

When recognized regulatory standards are not available, the generic sponsor must establish appropriate standards to assure the strength, identity, purity and quality of the product can be maintained.

(ii) Analytical Methods:

Any assay (analytical) method presented must be validated by the sponsor. A complete "validation package" containing all methods, specifications and validation data must be submitted.

Validation data shall include recovery data, accuracy, precision, linearity, specificity, sensitivity and a statistical report.

The need for FDA laboratory testing to verify any proposed new or previously validated method will be determined on a case-by-case basis.

Premix and complete feed methods may be subjected to a method trial. This procedure is to ensure that product matrix variations do not adversely effect the suitability of the methods. The Center will determine the need for a method trial.

Samples should not be sent unless they are requested.

D. Stability

Stability data and a post-approval stability commitment are required for each generic product. Stability requirements will not be waived. Stability data is required per 21 CFR 514(b)(5)(x) for all animal drug products and feeds. 21 CFR 211.166 specifically provides stability requirements for pharmaceutical dosage forms.

Stability data must be presented for batches of drug products and medicated animal feeds of sufficient size to be representative of full size production lots.

Stability studies must be consistent with the requirements outlined in the Center for Veterinary Medicine Drug Stability Guidelines (12/1/87 edition).

Consideration will be given for stability data provided on actual production lots of proposed products (with the same formula as proposed) considered as "Generic" in the U.S. but approved and manufactured in a foreign country.

E. Expiration Dates

Expiration date periods are required and must be proposed for each generic animal drug dosage form and Type A medicated product. The expiration date is to be determined by the generated stability data.

IV. CONFORMANCE TO cGMPs

All manufacturing sites (domestic and foreign) will be required to conform to the appropriate cGMP regulatory requirements prior to final approval of the NADA.

New drug substances.....21 CFR 211
(Note: Although specific cGMP regulations are not available for the manufacture of new drug substances, the Agency uses the concepts of 21 CFR 211 as a control of the manufacturing process for a new drug substance.)
Pharmaceutical Dosage Forms.....21 CFR 211
Type A Medicated Articles.....21 CFR 226

V. ENVIRONMENTAL CONTROLS

All manufacturing sites will be required to provide environmental assessments (as per environmental guidelines) relative to the impact of the manufacturing operations on the environment.

APPENDIX B

Bioequivalency Guidelines

Please refer to the fifth generic animal drug policy letter to obtain the revised edition of the Bioequivalence Guideline (dated April 1990).

APPENDIX C

Environmental Review of Generic Animal Drugs

ENVIRONMENTAL ASSESSMENT
(Generic Animal Drug)

1. Date:

2. Name or applicant or petitioner:

3. Address:

4. Description of the proposed action: Briefly describe the requested action (i.e., approval of a generic drug product); the location where the product will be produced; and the types of environments present at and adjacent to the location where the production will occur. Include a discussion of the proposed indications for use of the product, a proposed label, or a reference to the section of 21 CFR Part 500 that describes the proposed conditions of use of the product.

5. Identification of the chemical substances that are the subject of the proposed action: Provide complete nomenclature, CAS Registry Number (if available), molecular weight, structural formulae, and physical description for the drug product to be produced. This information is required to allow accurate location of data about chemicals in the scientific literature and to allow identification of closely related chemicals.

6. Introduction of substances into the environment for the site(s) of production:

a. list the substances expected to be emitted;

b. state the controls exercised to modify emissions;

c. describe the applicable emission requirements and permits obtained (including occupational) at the Federal, State and local level;

d. provide a statement certifying compliance with all applicable emission requirements;

e. discuss the effects the approval of this ANADA will have upon compliance with current emissions requirements at the production site(s).

* See note below for optional alternative method for addressing this item available for foreign manufacturing sites.

7.-11. Documentation for items 7-11 of the EA format in 21 CFR 25.31a, concerning the fate, effects, resource and energy use, mitigation and alternatives, need not be provided for generic applications.

12. List of preparers: List those persons who prepared the assessment together with their qualification (expertise, experience, professional disciplines). Persons and agencies consulted should also be listed.

13. Certification: Include a statement signed by the responsible official of the applicant's firm that certifies that the information presented is true, accurate, and complete to the best of the knowledge of the firm.

(Date): _____
(Signature of responsible official): _____
(Title of responsible official): _____

14. References: List complete citations for all referenced material. Copies of referenced articles not generally available should be attached.

15. Appendices. Normally not needed for generic applications.

* Alternative for item 6 when part or all of the manufacture is located in a foreign country.

It is a common and incorrect assumption that, because a product is manufactured in a foreign country, no environmental review of that aspect of the application is required. Under NEPA, Executive Order 12114 "Environmental Effects Abroad of Major Federal Actions", and 21 CFR 25.50, the requirement for evaluation of the impact of agency actions on the global commons and on foreign countries is established.

The preferred method for addressing item 6 of the above format is to provide the information requested, substituting the requirements of the foreign country where the manufacturing will occur for Federal, State and local emissions requirements. Sometimes applicants have found that it is more convenient to obtain a letter or letters from the appropriate office(s) of the foreign government stating that the manufacture of the product that is the subject of the application has been evaluated by that government and that it meets their requirements for emissions and occupational controls. Provided that the letter(s) has some specificity about the drug product that would be manufactured under the ANADA and the government's requirements, such a letter can be used in lieu of the information requested in item 6a, b, c, and e, above.

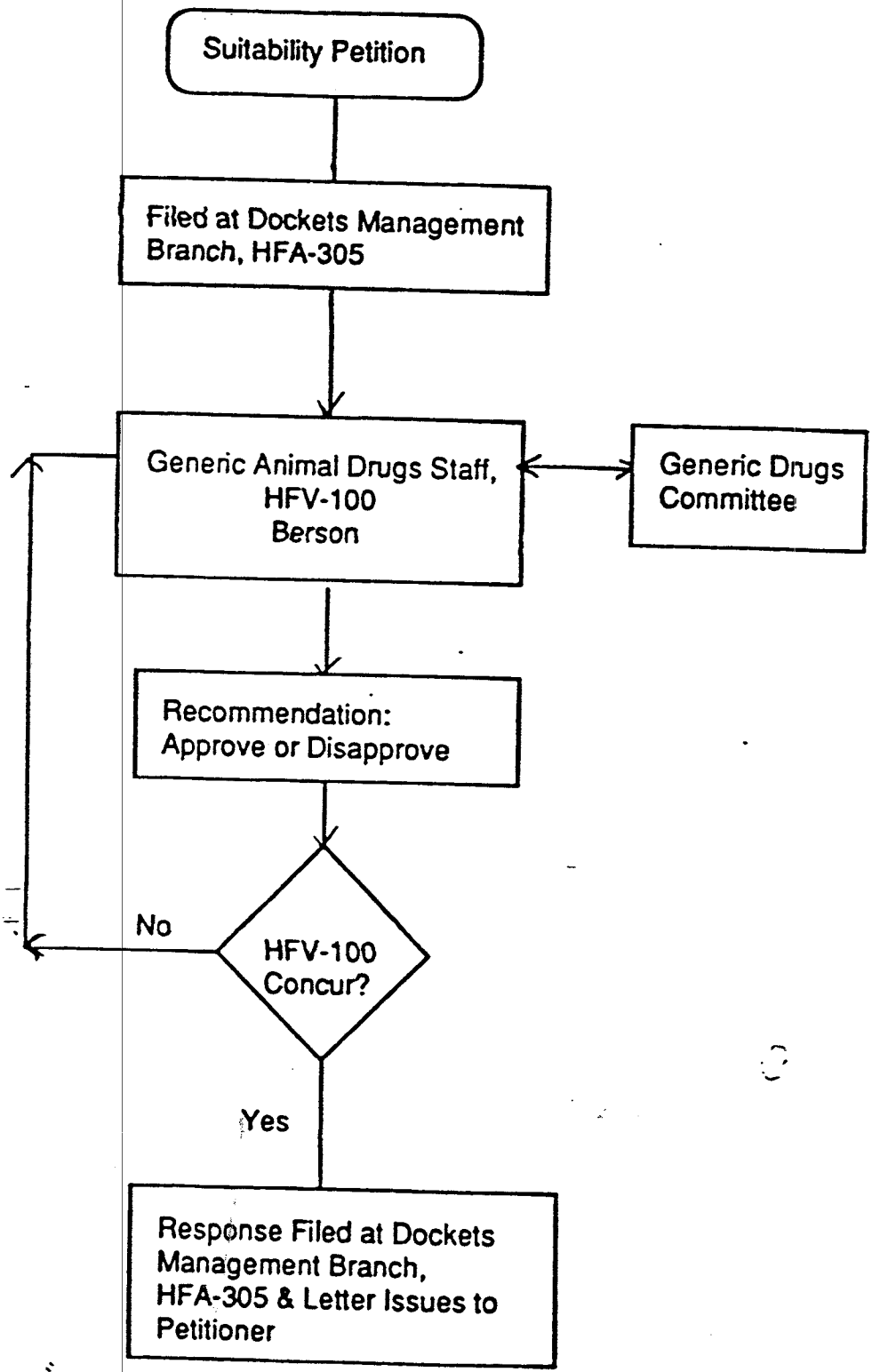
Chapter __. Environmental Review of Generic Animal Drugs.

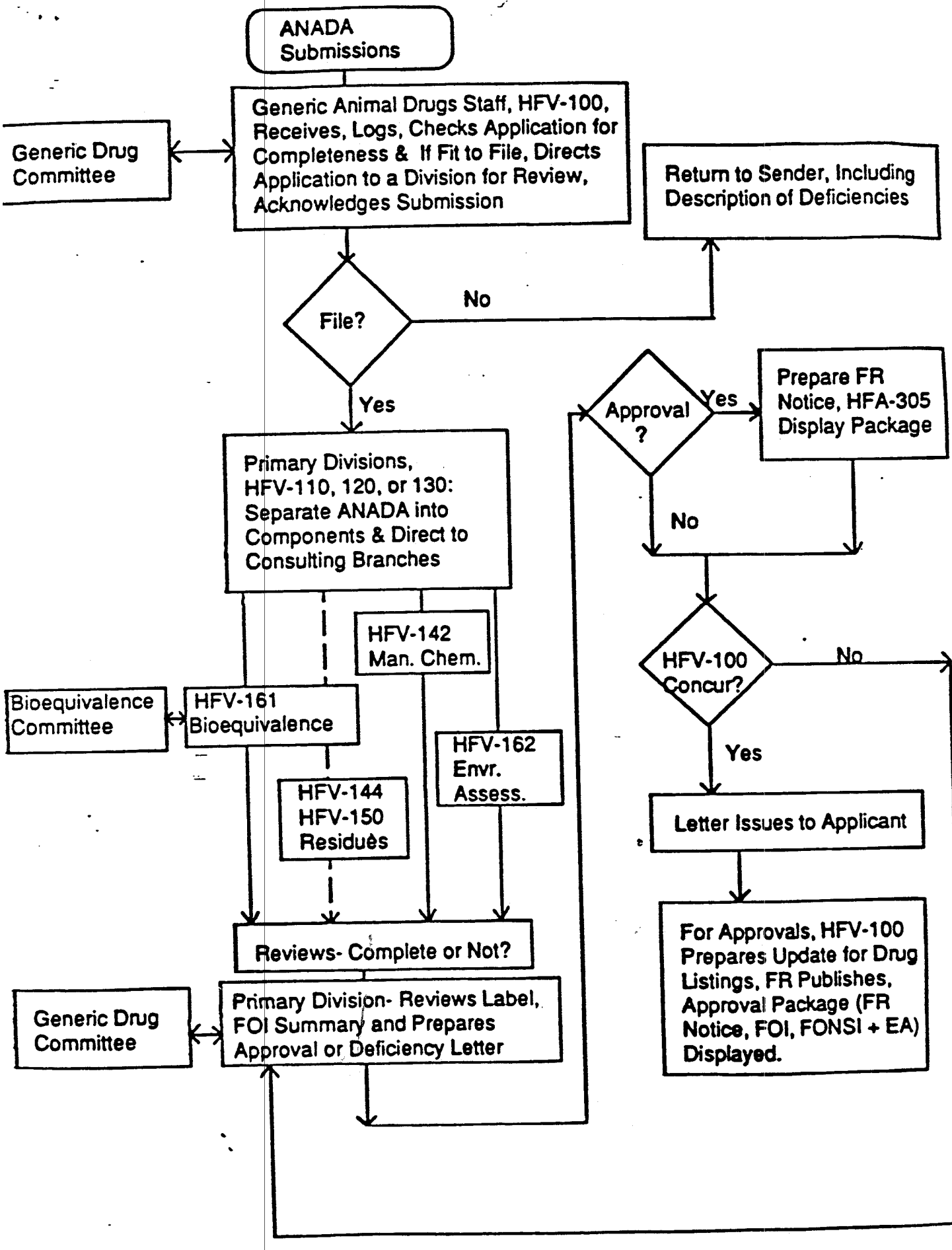
The National Environmental Policy Act (NEPA) requires that the Food and Drug Administration consider in its decisionmaking and disclose to the public the environmental impact that may be expected from a proposed action. The FDA's procedures for implementing NEPA are contained in 21 CFR Part 25. This discussion provides supplemental information specific to generic animal drugs that are the subject of an abbreviated new animal drug application (ANADA). Applicants must provide as part of each ANADA adequate information to objectively determine and verify the potential environmental impacts of the manufacture, but not the use, of the generic product. This information should be organized in the abbreviated environmental assessment format that follows. Such abbreviated EAs will be available for public review at the time of approval of ANADAs.

The format, which is based on the abbreviated EA formats for certain other classes of animal drugs contained in 21 CFR 25.31a(b), describes the types of information appropriate to the environmental review of generic animal drugs. ANADAs are anticipated to usually provide for new manufacturing sites controlled by different sponsors than those described in pioneer new animal drug applications. The abbreviated EA format is designed to examine this difference in manufacturing sites. Because the generic product will be used in the same manner as the pioneer and will be introduced into the same environments, in the same concentrations and under the same situations as already considered at the time of approval of the pioneer product, an abbreviated EA for a generic product need not contain information addressing or analysis of the potential environmental impacts due to use of the product.

APPENDIX D

Flow Charts


Suitability Petition
Filed at Dockets Management Branch, HFA-305
Generic Animal Drugs Staff, HFV-100 Berson
Generic Drugs Committee
Recommendation: Approve or Disapprove
HFV-100 Concur?
No
Yes
Response Filed at Dockets Management Branch, HFA-305 & Letter Issues to Petitioner


ANADA Submissions
Generic Animal Drugs Staff, HFV-100, Receives, Logs, Checks Application for Completeness & If Fit to File, Directs Application to a Division for Review, Acknowledges Submission
Generic Drug Committee
Return to Sender, Including Description of Deficiencies
File?
No
Yes
Primary Divisions, HFV-110, 120, or 130: Separate ANADA into Components & Direct to Consulting Branches
HFV-142 Man. Chem.
Bioequivalence Committee
HFV-161 Bioequivalence
HFV-162 Envr. Assess.
HFV-144 HFV-150 Residues
Reviews- Complete or Not?
Generic Drug Committee
Primary Division- Reviews Label, FOI Summary and Prepares Approval or Deficiency Letter
Approval ?
Yes
Prepare FR Notice, HFA-305 Display Package
No
HFV-100 Concur?
No
Yes
Letter Issues to Applicant
For Approvals, HFV-100 Prepares Update for Drug Listings, FR Publishes, Approval Package (FR Notice, FOI, FONSI + EA) Displayed.