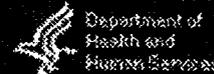




U.S. Food and Drug Administration



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Generic Animal Drugs and the Generic Animal Drug and Patent Term Restoration Act (GADPTRA)

Under the provisions of the Generic Animal Drug and Patent Term Restoration Act (GADPTRA), the sponsor of a generic animal drug product must submit an Abbreviated New Animal Drug Application (ANADA) for review and approval before the product can be legally 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. This page lists the laws, forms, Policy Letters, and Guidance Documents necessary for the submission of a generic animal drug application.

A brief explanation of the process is provided in CVM Memo 50 "[Information on Approval of Generic Animal Drugs](#)"

Information on the review and approval process for a New Animal Drug Application can be found on the [New Animal Drug Application Page](#).

Please note that many of the documents are not posted on the CVM Home Page due to their age. Paper copies are available from:

Food and Drug Administration
Center for Veterinary Medicine
Communications Staff
7500 Standish Place, HFV-12
Rockville, Maryland 20855
(301) 594-1755

Generic Animal Drug and Patent Term Restoration Act (GADPTRA)

- [Public Law 100-670, Nov. 16, 1988, 102 Stat. 3971](#)

Forms

- [New Animal Drug Application - FDA Form 356V](#)

Policy Letters

1. [Describes patent and exclusivity information to be submitted to FDA by holders of approved NADAs and NADA applicants. \(11/23/88\)](#)
2. [Describes format and content for suitability petitions, format and content for ANADAs, manufacturing requirements for ANADAs, and environmental review of generic animal drugs. \(6/7/89\) | pdf |](#)
3. "Exclusivity for human food safety data submitted in supplemental application"
 - "Withdrawal period for generic drugs"
 - "Substitution of an active ingredient in a combination drug or in a feed use combination"

"Labeling Requirements for Generic Drugs"

"Can a generic animal drug sponsor obtain exclusivity for an innovation approved under a supplement to an ANADA and can the pioneer drug sponsor copy the generic innovation without submitting additional data?" (8/2/89) | [pdf](#) | | [doc](#) |

4. "Actions concerning ANADAs when a pioneer drug has been withdrawn from sale"
"Effect of GADPTRA on approval of pre-62 drugs under the DESI program"
"Generic feed use combination drugs" (11/2/89) | [pdf](#) | | [doc](#) |
5. "Letter introducing the Revised Bioequivalence Guideline" (4/12/90)"
Revised Bioequivalence Guideline, (revised 10/09/02) | [pdf](#) | | [doc](#) |
6. "Withdrawal period for generic animal drug products"
"Eligibility of a new salt or ester for a pioneer animal drug" (10/17/90)
| [pdf](#) | | [doc](#) |
7. "Guidance for analytical methods for ANADAs"
"ANADAs, NADAs and supplemental approvals for subtherapeutic antibiotics"
"Hybrid applications"
"Waivers of In Vivo bioequivalence studies for topical products"
(3/20/91) | [pdf](#) | | [doc](#) |
8. Generic copying of certain drugs that were subject to review under the Drug Efficacy Study
Implementation (DESI) program.
(7/23/91) | [pdf](#) | | [doc](#) |
9. "Policy Statement on Environmental Review of Generic Animal Drugs" (Revision of a policy statement of the same title in Generic Policy Letter #2) - (6/27/95)

Guidance Documents

- Guideline #6 - Guidelines for Submitting NADA's for Generic Drugs Reviewed by NAS/NRC 10/20/71; rev. 3/19/76
- Guidance for Industry #35 - Bioequivalence Guideline, revised October 9, 2002 | [pdf](#) | | [doc](#) |
- Draft Guideline #43 - Draft Guideline for Generic Animal Drug Products Containing Fermentation-Derived Drug Substances, 10/95

Updated Monday, January 13, 2003 @ 11:00 AM by swd

November 23, 1988

Dear Sir or Madam:

On November 16, 1988, the President signed the Generic Animal Drug and Patent Term Restoration Act (copy enclosed). Among other things, it extends eligibility for the submission of abbreviated New Animal Drug Applications (ANADAs) to drug products first approved as New Animal Drug Applications (NADAs) after the 1962 Amendments to the Federal Food, Drug, and Cosmetic Act (the Act). Sponsors may submit ANADAs starting 60 days after enactment of the new law, or January 15, 1989.

The new Act requires that within 30 days of enactment each sponsor of a currently approved NADA submit to us patent and exclusivity information on these approved products. This letter provides preliminary guidance on the listing of drugs that are approved and the procedures you should follow for submitting patent and exclusivity information. We are in the process of preparing additional interim guidance on how FDA intends to implement the new statute, which we intend to make available within 90 days. During this initial implementation phase, FDA will follow existing regulations, policies and procedures, except as noted below, or where the statutory language dictates otherwise.

In all cases where a certification, statement, or waiver is to be submitted, the certification, statement, or waiver should be signed by the applicant or patent owner, or by its attorney, agent or other authorized official. It is the responsibility of applicants and patent owners to instruct their employees as to the scope of their duties and whether or not each is authorized to make any required certification or statement.

Submission of Patent Information by NADA Holders

Language added to section 512 of the Food, Drug, and Cosmetic Act (the Act) by section 102 of the Generic Animal Drug and Patent Term Restoration Act requires holders of approved NADAs, and NADA applicants, to submit certain patent information. The information that is required to be submitted includes the patent number and expiration date of any effective patent which claims the new animal drug for which the application was filed or a method of using such drug. The information that is to be submitted includes information on formulation patents and composition patents for the new animal drug product. However, information should not be submitted on process patents (patents that cover a method of manufacturing). A suggested format for the submission of this material is attached.

The relevant patent information must be submitted as follows:

- Holders of currently approved NADAs for drugs for which patents have been issued must submit the required patent information within 30 days after enactment of the generic act, i.e. by December 16, 1988.
- Holders of currently approved NADAs for drugs for which patents have not been issued but for which patents are issued in the future must submit the required patent information within 30 days after the issuance of the patents.
- Sponsors of pending NADAs for drugs for which patents have been issued, and sponsors of pending NADAs for drugs which patents are issued prior to approval, should submit the required patent information prior to approval.
- Sponsors of NADAs that are submitted in the future for drugs which patents have been issued must submit the patent information with the application.
- Sponsors of NADAs that are submitted in the future for drugs for which patents have not been issued at the time of NADA submission, but that are issued prior to approval, should submit the patent information prior to approval.
- Sponsors of NADAs that are approved in the future for drugs for which patents are issued after approval must submit the required patent information within 30 days after the issuance of the patents.

The procedures described above also apply to supplemental NADAs for changes that are covered by patents or become the subject of patents that are issued in the future.

The patent information that is to be submitted must be filed in a supplement to the approved or pending NADA. However, we also request that a copy of the patent information be sent to the Office of New Animal Drug Evaluation (see below). All patent information that is submitted with respect to approved applications will be published in the list of currently approved drugs, and will be updated in the monthly supplements to the list. FDA will not publish patent information prior to the approval of the NADA or supplemental NADA.

If the patent owner is different than the NADA holder or applicant, the submission should state the name of the patent owner as well as that of the applicant or NADA holder. If the patent owner or NADA holder or applicant does not reside or have a place of business in the United States, the submission should also name an agent of each non-resident patent owner and NADA holder applicant in the United States authorized to receive notice under section 512(n)(1)(H).

If information on a patent is not timely filed, e.g., is filed more than 30 days after enactment of the Act or more than 30 days after issuance of the patent, the agency could refuse to publish the untimely information, or (as provided by new section 512(d)(1)(D)) could withdraw the NADA if the patent holder failed to respond within 30 days to a notice from the agency. FDA has concluded, however, that while Congress clearly intended to encourage timely filing, a less severe penalty for late filing would effectuate Congress' intent without eliminating all statutory patent protection or withdrawing the NADA itself. Therefore, if an NADA applicant files required patent information on an untimely basis, FDA will publish the untimely information but will not require generic applicants with pending applications, who have previously submitted a correct certification, to re-certify as to the new patent information. Only applicants who submit ANADA's after the filing of the patent information will be required to submit a certification as to that patent.

In all cases, the date that FDA receives the patent information will be considered the date the information was filed.

Exclusive Approval for Certain Drugs

The new legislation establishes various periods of time during which ANADAs for certain products may not be submitted or approved if a pioneer application qualifies for exclusivity. Exclusivity applies to applications that are approved following enactment of the new law. If in the future you believe one or more of your approved products qualify for such exclusive approval status, please notify us promptly upon approval of the application. We plan to publish these and all other data required by the statute in supplements to the approved drug list.

The List of Currently Approved Drugs

The new legislation provides that within 60 days of enactment, FDA must make publicly available a list of all drugs which have been approved for safety and effectiveness before the date of enactment. The agency must update the list every 30 days. To comply with this requirement, FDA will initially file a copy of the list with the Dockets Management Branch and publish a notice of availability in the FEDERAL REGISTER. Supplements to the list will be used to explain in more detail how this requirement is being implemented, and to publish required patent information and information on periods of exclusivity for submission or approval of ANADAs for specific products. Copies of the list and its supplements may be obtained from the Industry Information Staff (HFV-12), Center for Veterinary Medicine, Food and Drug Administration, 5600 Fishers Lane, Rockville, Maryland 20857.

Patent Certification for ANADAs

In addition to the other requirements listed in the new law, all ANADA applicants must, as outlined in new section 512(n)(H) of the Act, certify regarding the patent status of the listed drugs referred to in the NADAs. All ANADAs must contain patent certification information. If this patent information is not included in the ANADA, the application will be considered incomplete. For all relevant patents on the approved drug, an applicant must certify one of the following:

- (1) no patent information has been filed under subsection (b)(1) or (c)(3);
- (2) the patent has expired;
- (3) the date on which the patent will expire; or
- (4) the patent filed is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted.

If the applicant seeks approval for a method of use which is not claimed in a method of use patent for the listed drug, the applicant must certify that the method of use patent does not claim the use for which the applicant seeks approval.

Where to Submit Patent and Exclusivity Information

As previously explained this information is to be filed in a supplement to an approved or pending NADA. Additionally, to expedite the compilation and the publication of the patent and exclusivity information by the Agency, currently approved NADA holders are requested to submit patent and exclusivity information to:

Office of New Animal Drug Evaluation (HFV-100)
Center for Veterinary Medicine
5600 Fishers Lane
Rockville, Maryland 20857

In response to industry requests we are enclosing a suggested format for the submission of this patent and exclusivity information.

Additional Information

For general question regarding the ANADA aspects of the new legislation contact:

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

For information on the patent extension aspects of the new legislation contact:

Charles VanHorn
Box 8 Patent and Trademarks Office
Washington, D.C. 20201
Phone: (703) 557-4035

or Ronald Wilson
Director, Health Assessment
Policy Staff, (HFV-20)
Office of Health Affairs
5600 Fishers Lane
Rockville, Maryland 20857
Phone: (301) 443-1382

FDA plans to issue proposed procedural regulations to implement the new law and will, at that time, comply with applicable provisions of the Paperwork Reduction Act.

We will keep you informed of additional guidance through written communication and through meetings of appropriate legal and professional associations on a continuing basis. We welcome your input and interest.

Sincerely yours,

/s/

Gerald B. Guest
Director, Center for
Veterinary Medicine

Suggested Format for Patent and Exclusivity Information

- 1) NADA Number
- 2) Applicant Firm Name
- 3) Approval Date
- 4) Trade Name
- 5) Active Ingredient(s)
- 6) Strength(s)
- 7) Dosage Form
- 8) Route of Administration
- 9) Exclusivity – Date
first ANADA could be approved and length of exclusivity period
- 10) Applicable patent
numbers and expiration date of each *
- 11) Identification of U.S. Agent if held by foreign person

* The above information should be supplied for each product.



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.

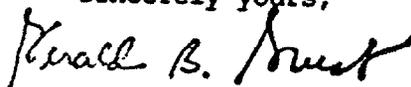
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Comments may be addressed to:

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

GENERIC ANIMAL DRUG AND PATENT TERM RESTORATION ACT

IMPLEMENTATION

I. INTRODUCTION

II. PRE-ANADA SUBMISSIONS

- A. Suitability Petitions
- B. Requests for Waiver of In vivo Testing
- C. Protocols for Bioequivalence Studies

III. ANADA REVIEW PROCESS

- A. Administrative Procedures
- B. ANADA Content

APPENDIX

- A. Abbreviated New Animal Drug Applications for Generic Animal Drugs -
Manufacturing Requirements
- B. Bioequivalence Guideline
- C. Environmental Review of Generic Animal Drugs
- D. Flow Charts

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 inquiries 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)(11)]

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)

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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 spectrometric (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 of 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.

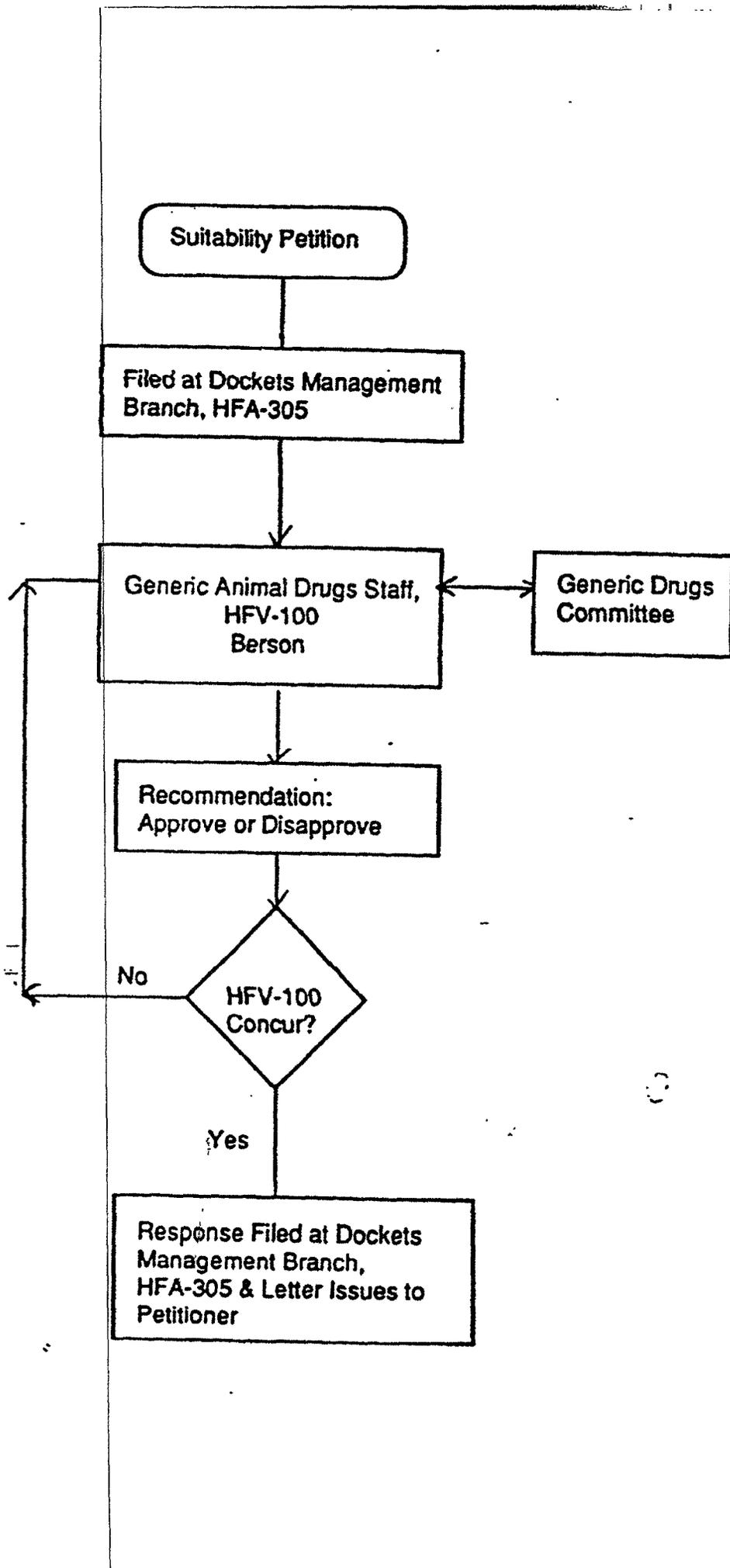
Chapter ____ . Environmental Review of Generic Animal Drugs.

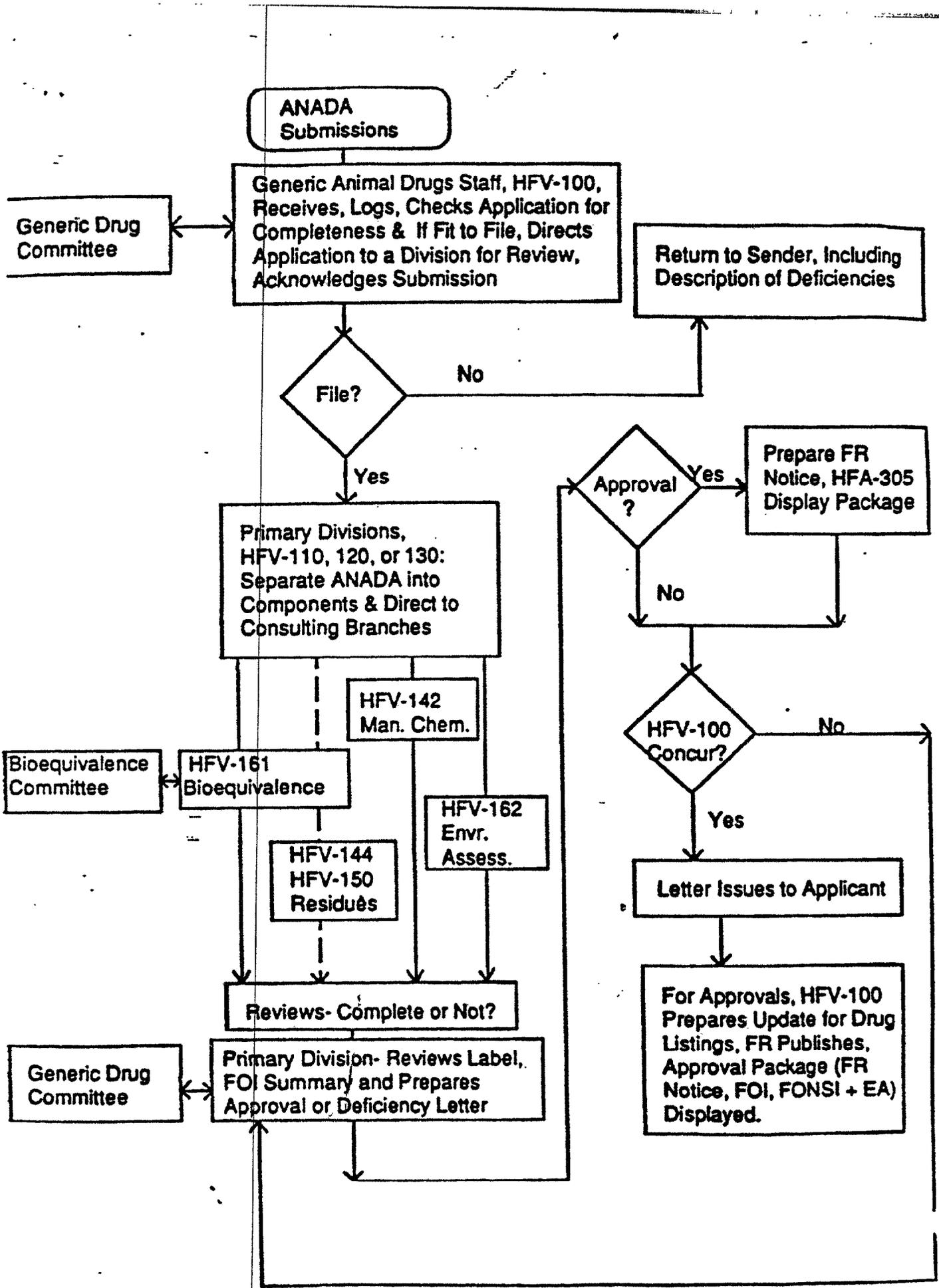
The National Environmental Policy Act (NEPA) requires that the Food and Drug Administration consider in its decisionmaking and disclose to the public the environmental impact that may be expected from a proposed action. The FDA's procedures for implementing NEPA are contained in 21 CFR Part 25. This 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





ANADA Submissions

Generic Drug Committee

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

Return to Sender, Including Description of Deficiencies

File?

Primary Divisions, HFV-110, 120, or 130: Separate ANADA into Components & Direct to Consulting Branches

Approval?

Prepare FR Notice, HFA-305 Display Package

Bioequivalence Committee

HFV-161 Bioequivalence

HFV-142 Man. Chem.

HFV-162 Env. Assess.

HFV-144 HFV-150 Residues

HFV-100 Concur?

Generic Drug Committee

Primary Division - Reviews Label, FOI Summary and Prepares Approval or Deficiency Letter

Letter Issues to Applicant

For Approvals, HFV-100 Prepares Update for Drug Listings, FR Publishes, Approval Package (FR Notice, FOI, FONSI + EA) Displayed.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

AUG 2 1989

Dear Sir or Madam:

This is the third in a series of policy letters regarding the implementation of the Generic Animal Drug and Patent Term Restoration Act (the new law), which was signed into law on November 16, 1988.

As part of our continuing implementation of the new law, we are introducing five draft policy statements (refer to attachment) which are entitled as follows:

- 1) "Exclusivity for Human Food Safety Data Submitted in a Supplemental Application."
- 2) "Withdrawal Period for Generic Drugs."
- 3) "Substitution of an Active Ingredient in a Combination Drug or in a Feed Use Combination."
- 4) "Labeling Requirements for Generic Drugs."
- 5) "Can A Generic Animal Drug Sponsor Obtain Exclusivity for an Innovation Approved Under a Supplement to an ANADA and Can the Pioneer Drug Sponsor Copy the Generic Innovation Without Submitting Additional Data?"

The policy statements are issued as draft statements. Comments and questions regarding the statements are invited from all interested parties. If any changes are made, the revised draft policy statements will be placed on public display, and a notice of availability will be published in the Federal Register.

Comments on the draft policy statements may be addressed to:
Dr. Richard B. Talbot
Office of New Animal Drug Evaluation
Center for Veterinary Medicine
5600 Fishers Lane
Rockville, MD 20857
(301) 443-4313

Additional policy statements will be forthcoming as we continue the development of our policies regarding the new law.

Sincerely yours,

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

Attachment

Generic Animal Drug and Patent Term Restoration Act (GADPTRA)
Draft Policy Statements

1) Exclusivity for Human Food Safety Data Submitted in a Supplemental Application

GADPTRA (the new law) provides that a sponsor of an approved NADA obtains exclusivity for a change approved in a supplement if that sponsor submitted human food safety studies other than bioequivalence or residue studies in support of the change. However, the Center for Veterinary Medicine (CVM) believes that this provision does not apply in the case of human food safety studies submitted to obtain a different tolerance,* because a tolerance for a drug substance necessarily applies to all products containing that same drug substance. In such cases, a newly established tolerance will apply immediately to generic drug products as well as the pioneer drug product. If a new withdrawal time is established in connection with the establishment of a new tolerance, the sponsor will not obtain exclusivity for that new withdrawal time.

- * CVM uses the term "tolerance" to include "safe concentration." Thus, where CVM establishes only a safe concentration and not a tolerance, the new safe concentration will apply immediately to generic drug products as well as the pioneer drug product.

2) Withdrawal Period for Generic Drugs

A generic sponsor will ordinarily be granted the same withdrawal period as the pioneer sponsor if bioequivalence, using blood level data, is demonstrated. However, even if bioequivalence is demonstrated using blood level data, a generic sponsor may still attempt to get a shorter withdrawal period than that granted to the pioneer sponsor. The shorter withdrawal period shall be granted if appropriate tissue depletion data, using methods of statistical analysis and interpretation described in the guidelines entitled "General Principles for Evaluating the Safety of Compounds used in Food-Producing Animals" justify a shorter withdrawal period.

If bioequivalence is demonstrated using pharmacological or clinical endpoint studies, then the generic sponsor must ordinarily collect tissue residue depletion data to establish the appropriate withdrawal period. The withdrawal period established in this manner need not be the same as the withdrawal period for the pioneer drug.

This policy will apply to all generic applications, whether or not the data and information that supports the pioneer approval meets current standards. As long as the pioneer drug is eligible for listing under the new law, the pioneer drug is considered to be safe and effective regardless of the adequacy of the underlying data in the NADA.

3) Substitution of an Active Ingredient in a Combination Drug or in a Feed Use Combination

The new law allows a generic sponsor to request substitution, under certain circumstances, of an active ingredient in a combination drug (or in a feed-mixed combination) with another active ingredient. The generic sponsor must submit to CVM a suitability petition requesting permission to file an ANADA with the proposed change from the pioneer drug. If CVM approves the petition, the generic sponsor must — in lieu of submitting bioequivalence information — show that the substituted active ingredient is of the same pharmacological or therapeutic class as the active ingredient for which it is substituted, and that the generic drug can be expected to have the same therapeutic effect as the pioneer.

CVM is required to disapprove the suitability petition if it finds that the generic sponsor must conduct investigations to show the effectiveness, safety to the animal, or safety for human consumption of the proposed combination. ("Investigations" do not include bioequivalence or residue depletion studies.) Although each petition will be examined on its individual merits, CVM has concluded that such investigations must ordinarily be conducted unless there are clearly no concerns that the proposed substitution will adversely affect the combination's effectiveness, target animal safety, and human food safety.

4) Labeling Requirements for Generic Drugs

The new law requires the labeling of a generic drug product to be the same as the pioneer's labeling, except for changes resulting from an approved suitability petition, differences in withdrawal periods, or differences in the manufacturers distributing or producing the products. In addition, labeling differences may be required because of patent or exclusivity provisions that apply to the pioneer product.

CVM will require that the labeling of a generic drug product be the same as the labeling of the pioneer drug product, except for the differences listed above. This means, for example, that the generic drug must be labeled for all the species and claims for which the pioneer is labeled (minus species and claims covered by patent or exclusivity protection).

- 5) Can a Generic Animal Drug Sponsor Obtain Exclusivity for an Innovation Approved Under a Supplement To an ANADA and Can the Pioneer Drug Sponsor Copy the Generic Innovation Without Submitting Additional Data?

CVM has considered whether the exclusivity provisions in the new law can be applied to innovations in the generic animal drug product approved under a supplement to an ANADA, and whether the pioneer drug sponsor can copy the generic innovation without submitting additional data.

The issue of exclusivity for a generic drug product may arise if the generic sponsor wishes to obtain approval under a supplement for a different dosage form, strength, route of administration or active ingredient, for which a suitability petition can not be approved because studies are necessary for approval of the innovations. Similarly, the generic sponsor may file a supplement to an ANADA to obtain approval for claims or species which differ from those of the pioneer product.

The position can be taken that the new law does not provide for the generic product to obtain exclusivity for an innovation, and the pioneer can not copy a generic innovation without the pioneer submitting its own data. Under Section 512(c)(2)(F), exclusivity specifically applies only to applications filed under Section 512(b)(1) [i.e. NADAs as distinguished from ANADAs filed under Section 512(b)(2) of the new law]. With respect to copying, it could be argued that a pioneer sponsor can not copy a generic innovation on the grounds that a generic drug is not a "listed" drug under Section 512(n)(4) because it has not been approved for safety and effectiveness. Under that section, only drugs that have been so approved may be listed, and only listed drugs may be copied.

However, CVM has tentatively decided to adopt interpretations of the new law which would provide exclusivity for innovation by the generic sponsor, and which would permit the pioneer sponsor to copy a generic innovation without submission of additional data. CVM believes that these interpretations would meet important goals of the generic legislation: to avoid duplicative research, to provide incentive for generic sponsors to innovate, and to make the conditions of use of the pioneer and generic drugs the same to the maximum extent possible. Because the generic sponsor would submit safety and effectiveness data to support the proposed innovation, the supplemental application would be considered to have been filed under section 512(b)(1), thus making it eligible for exclusivity. Moreover, the generic drug would be considered to be "approved for safety and effectiveness," both on the basis of its having been shown to be bioequivalent to a drug that has been approved as safe and effective, and because of the safety and effectiveness data submitted to support the innovation. Thus, the generic drug would be a "listed" drug, eligible for copying.

Because the generic law does not definitively resolve these issues, CVM will consider comments from interested parties before deciding whether to adopt finally its tentative position on the issues.



November 2, 1989

Dear Sir or Madam:

This is the fourth in a series of policy letters regarding the implementation of the Generic Animal Drug and Patent Term Restoration Act (GADPTRA), which was signed into law on November 16, 1988.

We are introducing three policy statements (refer to attachment) which address our continuing implementation of the new law. The policy statements are entitled as follows:

- 1) "Actions Concerning ANADAs When a Pioneer Drug Has Been Withdrawn from Sale"
- 2) "Effect of GADPTRA on Approval of Pre-62 Drugs Under the DESI Program"
- 3) "Generic Feed Use Combination Drugs (Type A Article, Type B or Type C Medicated Feeds)"

We welcome comments and questions on the policy statements from all interested parties. If any changes are made, the revised policy statements will be placed on public display, and a notice of availability will be published in the Federal Register.

Comments on the draft policy statements may be addressed to:

Dr. Robert C. Livingston
Office of New Animal Drug Evaluation
Center for Veterinary Medicine (HFV-100)
5600 Fishers Lane
Rockville, MD 20857
(301) 443-4313

Generic Animal Drug and Patent Term Restoration Act (GADPTRA)
Draft Policy Statements

1) Actions Concerning ANADAs When a Pioneer Drug Has Been
Withdrawn from Sale

Section 512(c)(2)(G) of the Act provides that the approval of an abbreviated new animal drug application (ANADA) is to be suspended if the ANADA refers to a drug which has been withdrawn from sale, for the period of withdrawal from sale or, if earlier, the period ending on the date the Secretary determines that the withdrawal from sale was not for safety or effectiveness reasons. Section 512(n)(4)(C) provides that a pioneer drug may not be listed if the Secretary determines that the drug has been withdrawn from sale for safety or effectiveness reasons. If the listed drug is withdrawn from sale subsequent to the listing, the drug is to be removed from the list until either its sale resumes, or the Secretary determines that the withdrawal from sale is not for safety or effectiveness reasons.

Thus the Food and Drug Administration (FDA) is required, in several circumstances, to determine whether the discontinued marketing of a drug covered by a new animal drug application (NADA) was for safety or effectiveness reasons. Pending the adoption of its own regulations, the Center for Veterinary Medicine (CVM) intends to follow generally the principles and procedures that are contained in the regulations that FDA has proposed for the implementation of the human drug generic law. See 54 Fed. Reg. 28872 (July 10, 1989), in particular proposed 21 CFR 314.153 and 314.161, and the discussion at 54 Fed. Reg. at 28907-08. Among other things, the proposal provides for the deferral of the safety and effectiveness determinations until the time that the determinations are actually needed as determined by certain "triggering" circumstances (e.g. the submission of an ANADA that references the drug).

CVM has also decided to provide guidance as to one particular situation that is not specifically addressed by the July 10 proposal. This is the circumstance in which (a) a sponsor of a listed NADA voluntarily requests withdrawal of the approval of its NADA, after having discontinued marketing of the drug, and (b) the safety and effectiveness determination has not yet been made. In that case, the request to withdraw approval will not, *per se*, be a triggering circumstance. That is, the Center will withdraw approval of the drug but will defer the safety or effectiveness determination until such time as a triggering circumstance does occur. (However, if an approved

ANADA references the particular pioneer drug, the safety and effectiveness determination will be made at that time). In the meantime, the pioneer drug will remain a listed drug, although it will be placed on a separately identified list. CVM believes that it is permissible to continue to list the drug, even though its approval is withdrawn, because the act provides that a listed drug is to be delisted only when the approval is withdrawn on the grounds stated in 512(e). A voluntary withdrawal of approval based only on discontinuance of sale is not based on section 512(e).

CVM has, in supplements to the original list published in accordance with section 512(n)(4), removed from the list NADAs whose approvals have been voluntarily withdrawn since the list was first published. Because safety and effectiveness determinations have not been made as to these NADAs, the NADAs will be restored to the list. However, as explained in the previous paragraph, they will be placed in a separate category along with the NADAs whose approvals are voluntarily withdrawn in the future.

Finally, ANADA sponsors should be aware that the list that the Center originally published included all NADAs that had been approved for safety and effectiveness as of the effective date of the GADPTRA, including those whose marketing had been discontinued but whose approval had not been withdrawn. Although the NADAs in the latter category (along with NADAs for drugs whose marketing has been discontinued since the effective date of the GADPTRA) are not separately identified, ANADAs that reference those NADAs will not be approved until CVM determines that the marketing was not discontinued for safety and effectiveness reasons. Accordingly, ANADA sponsors are cautioned of the need to inquire, in cases where there is doubt as to whether marketing of a drug they wish to reference has been discontinued, to determine whether in fact marketing has been stopped. (As time and resources permit, CVM will identify those drugs that are on the list whose marketing has been discontinued.) In addition, as explained in the July 10 human drug proposal, ANADA sponsors will bear the burden of establishing that marketing of a discontinued drug was not stopped for safety or effectiveness reasons.

2) Effect of GADPTRA on Approval of Pre-62 Drugs Under
the DESI Program

The Generic Animal Drug and Patent Term Restoration Act (GADPTRA) provides for the generic copying of pioneer animal drugs that have been approved for safety and effectiveness by FDA. The new law, therefore, covers drugs that were approved for safety by FDA prior to 1962, and subsequently approved for effectiveness under the Drug Effectiveness Study Implementation (DESI). FDA has approved generic copies of such drugs, under the DESI program, for a number of years. Requirements and procedures for approval of generic drugs under the DESI program differ in some respects from those for approval of generic drugs under GADPTRA.

Under GADPTRA, FDA is not permitted to approve abbreviated new animal drug applications (ANADAs) for generic animal drugs until January 1, 1991. In passing GADPTRA, Congress did not revoke the authority for FDA to approve generic copies of pre-62 drugs under the DESI program. It is clearly not the intention of the agency to have two separate policies for the approval of generic animal drugs, once generic drugs can be approved under GADPTRA. However, the Center for Veterinary Medicine (CVM) will in the interim continue to process and approve generic drugs under the DESI program subject to the following provisions:

- CVM will not accept a DESI application unless it believes that is likely that the application can be approved prior to January 1, 1991.
- Generic equivalents of pre-62 drugs will not be approved under the DESI program after December 31, 1990, but will be approved under GADPTRA after that date. However, the foregoing statement will not apply to a DESI application that is pending on that date, provided that the sponsor has exercised due diligence in pursuing the approval and continues to do so. In such a case, the application will be approved as a DESI application.
- The Center's current bioequivalence guidelines will be applied to all pending and future DESI applications, unless commitments have already been made for different bioequivalence requirements.

3) Generic Feed Use Combination Drugs (Type A Article, Type B or Type C Medicated Feeds)

Following the approval of an abbreviated new animal drug application (ANADA) for a generic Type A Article, the generic sponsor is entitled to approval for all of the combination products (Type B or Type C Medicated Feeds), for which the pioneer product is approved. Bioequivalency and tissue residue studies are not required for the approval of the generic feed use combinations (Type B or Type C Medicated Feeds). However, after the ANADA has been approved for the generic Type A Article, an ANADA must be submitted for each feed use combination product for which the generic sponsor seeks approval. The ANADA for each feed use combination should provide medicated feed labeling (Blue Bird labeling) which copies the pioneer medicated feed labeling, environmental assessment, and a Freedom of Information (FOI) Summary. The application should also identify the specific subsection of the CFR Section 500 that must be amended to include the generic drug sponsor on the list of approved sponsors for each feed use combination product.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, Maryland 20857

April 12, 1990

Dear Sir or Madam:

This is the fifth in a series of policy letters regarding the implementation of the Generic Animal Drug and Parent Term Restoration Act (GADPTRA), which was signed into law on November 16, 1988.

We are introducing the revised Bioequivalence Guideline dated April 12, 1990. The April 12, 1990 Bioequivalence Guideline is a revision of the April 19, 1989 Bioequivalence Guideline, announced in the June 21, 1989 Federal Register as part of the second generic animal drug policy letter. The current Guideline was revised with due consideration given to comments received on the April 19, 1989 Guideline.

Copies of the April 12, 1990 Bioequivalence Guideline may be obtained by contacting:

Industry Information Staff (HfV-12)
Room 7-85
Center for Veterinary Medicine
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857
(301) 443-4557

We welcome comments on the April 12, 1990 Bioequivalence Guideline from all interested parties. If any changes are made, availability of the revised Guideline will be announced in the Federal Register.

Page 2

Comments of the Guideline may be submitted to:

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

We will continue to announce the availability of policy letters regarding implementation of the new law.

Sincerely yours,

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

Attachment

NOTE: The April 12, 1990 Bioequivalence Guideline has been updated. The current copy is available from our web site.

Guidance for Industry

BIOEQUIVALENCE GUIDANCE

**(THIS VERSION OF THE GUIDANCE REPLACES THE VERSION TITLED
“BIOEQUIVALENCE GUIDANCE” THAT WAS MADE AVAILABLE ON
OCTOBER 10, 2000)**

Section III.A. of this guidance has been superceded by CDER's guidance entitled "Bioanalytical Method Validation". Any general questions regarding the application of the Bioanalytical Method Validation guidance to new animal drugs should be directed to Marilyn Martinez, Center for Veterinary Medicine, Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, (301)827-7577, mmartin1@cvm.fda.gov. Any questions regarding analytical methods for tissue residues should be directed to Valerie Reeves, 7500 Standish Pl., Rockville, MD 20855, (301)827-6973, vreeves@cvm.fda.gov.

This document is intended to provide guidance for the design and analysis of in vivo bioequivalence studies. This revision to the version that was made available in April 1996 adds an illustrative example of how to calculate confidence bounds when log transformed data are used.

Comments and suggestions regarding this guidance document should be submitted to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the Docket Number (94D-0401). Additional information on the 1996 guidance document can be found in the Federal Register (Vol. 61, No. 102, May 24, 1996). Comments will be accepted at any time.

For questions regarding this guidance document, contact Lonnie Luther, Center for Veterinary Medicine (HFV-100), Food and Drug Administration, 7500 Standish Place, Rockville, MD 20855.

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Veterinary Medicine (CVM)
October 9, 2002**

BIOEQUIVALENCE GUIDANCE

CENTER FOR VETERINARY MEDICINE
FOOD AND DRUG ADMINISTRATION
7500 STANDISH PLACE
ROCKVILLE, MD 20855

Docket No. 94D-0401

This guidance document represents the agency's current thinking on this matter. It does not create or confer any rights for or on any person and does not operate to bind the FDA or public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations or both.

PREAMBLE

In 1996, the Center for Veterinary Medicine (CVM) revised a document entitled "April 1990 Bioequivalence Guideline." The revised document, "Bioequivalence Guidance (Final) 1996", was issued in final form following notice and comment.

Many of the changes in the "Bioequivalence Guidance (Final) 1996" were based upon reports from panel presentations at the 1993 Veterinary Drug Bioequivalence Workshop in Rockville, Maryland, sponsored by the Center for Veterinary Medicine (CVM), the Animal Health Institute (AHI), the American Academy of Veterinary Pharmacology and Therapeutics (AAVPT), and the Animal Drug Alliance¹. Some new topics were introduced into the guidance as a result of issues identified in the review of bioequivalence protocols and studies.

The major new topics in the guidance were as follows:

1. Higher than approved dose bioequivalence studies.
2. Bioequivalence testing for multiple strength solid oral dosage forms.
3. Assay considerations for bioequivalence studies.
4. AUC and CMAX as the pivotal parameters for bioequivalence determination.
5. Blood level bioequivalence studies to be accompanied by tissue residue depletion studies for generic products for food-producing animals.

CVM has revised the "1996 Bioequivalence Guidance" to add an illustrative example of how to

calculate confidence bounds when log transformed data are used. The guidance has also been revised in accordance with FDA's Good Guidance Practices (GGPs, found in the Federal Register of February 27, 1997, 62 FR 8961). With the exception of the addition of information on how to calculate confidence bounds when log transformed data are used, minor revisions made to comply with the GGPs (e.g., addition of a cover sheet), and revisions to the Preamble, the document is the same as the document issued in 1996. In September 2000, FDA revised the guidance to clarify sources of information more clearly.

A person may follow the guidance or may choose to follow alternate procedures or practices. If a person chooses to use alternate procedures or practices, that person may wish to discuss the matter further with the agency to prevent an expenditure of money and effort on activities that may later be determined to be unacceptable to FDA. Although this guidance document does not bind the agency or the public, and it does not create or confer any rights, privileges, or benefits for or on any person, it represents FDA's current thinking on bioequivalence testing for animal drugs. When a guidance document states a requirement imposed by statute or regulation, the requirement is law and its force and effect are not changed in any way by virtue of its inclusion in the guidance.

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I. INTRODUCTION

This document is intended to provide guidance for the design and analysis of *in vivo* bioequivalence studies. The guidance is an update of the April 12, 1990 Bioequivalence Guideline. Many of the changes in the guideline are based upon reports from panel presentations at the 1993 Veterinary Drug Bioequivalence Workshop¹.

Two products are considered to be bioequivalent when they are equally bioavailable; that is, equal in the rate and extent to which the active ingredient(s) or therapeutic ingredient(s) is (are) absorbed and become(s) available at the site(s) of drug action.

The Generic Animal Drug and Patent Term Restoration Act (GADPTRA) signed into law on November 16, 1988, permits sponsors to submit an Abbreviated New Animal Drug Application (ANADA) for a generic version of any off-patent approved animal drug (with certain exceptions noted in the law) regardless of whether the drug was approved prior to 1962 and subject to the National Academy of Sciences / National Research Council / Drug Effectiveness Study Implementation (NAS/NRC/DESI) review.

Bioequivalence studies are used in a variety of situations, most often when a sponsor proposes manufacturing a generic version of an approved off-patent product. A bioequivalence study may also be part of a new animal drug application (NADA) or supplemental NADA for approval of an alternative dosage form, new route of administration, or a significant manufacturing change which may affect drug bioavailability.

The Center has concluded that the tissue residue depletion of the generic product is not adequately addressed through bioequivalence studies. Therefore, sponsors of ANADA's for drug products for food-producing animals will generally be asked to include bioequivalence and tissue residue studies (21 USC 360 b (n) (1) (E)). A tissue residue study should generally accompany clinical end-point and pharmacologic end-point bioequivalence studies, and blood level bioequivalence studies that can not quantify the concentration of the drug in blood throughout the established withdrawal period (21 USC 360 b (n) (1) (A) (ii)).

Bioequivalence studies (*i.e.*, blood level, pharmacologic end-point, and clinical end-point studies) and tissue residue depletion studies should be conducted in accordance with good laboratory practice (GLP) regulations (21 CFR Part 58).

Whereas the focus of the guidance is bioequivalence testing for ANADA approval, the general principles also apply to relative bioavailability studies conducted for NADA's.

Sponsors should consult with the Center early in the product development process to facilitate the design of studies adequate for drug approval. The Center urges sponsors to submit protocols for review prior to conducting studies.

II. GENERAL CONSIDERATIONS

A. Selection of Reference Product for Bioequivalence Testing

As a general rule, the proposed generic product should be tested against the original pioneer product.

If the original pioneer product is no longer marketed, but remains eligible to be copied, then the first approved and available generic copy of the pioneer should be used as the reference product for bioequivalence testing against the proposed new generic product.

If several approved NADA's exist for the same drug product, and each approved product is labeled differently (*i.e.*, different species and/or claims), then the generic sponsor must clearly identify which product label is the intended pioneer. Bioequivalence testing should be conducted against the single approved product which bears the labeling that the generic sponsor intends to copy.

The generic sponsor should consult with CVM regarding selection of the appropriate reference product before conducting the bioequivalence study.

B. Criteria for Waiver of *In Vivo* Bioequivalence Study

The requirement for the *in vivo* bioequivalence study may be waived for certain generic products (21 USC 360 b (n) (1) (E)). Categories of products which may be eligible for waivers include, but are not limited to, the following:

1. Parenteral solutions intended for injection by the intravenous, subcutaneous, or intramuscular routes of administration.
2. Oral solutions or other solubilized forms.
3. Topically applied solutions intended for local therapeutic effects. Other topically applied dosage forms intended for local therapeutic effects for non-food animals only.
4. Inhalant volatile anesthetic solutions.

In general, the generic product being considered for a waiver contains the same active and inactive ingredients in the same dosage form and concentration and has the same pH and physico-chemical characteristics as an approved pioneer product.

However, the Center will consider bioequivalence waivers for non-food animal topical products with certain differences in the inactive ingredients of the pioneer and generic products.

If a waiver of the *in vivo* bioequivalence and/or the tissue residue study/studies is granted for a food animal drug product, then the withdrawal period established for the pioneer product will be assigned to the generic product.

Sponsors may apply for waivers of *in vivo* bioequivalence studies prior to submission of the ANADA's.

C. Selection of Blood Level, Pharmacologic End-point, or Clinical End-point Study

In vivo bioequivalence may be determined by one of several direct or indirect methods. Selection of the method depends upon the purpose of the study, the analytical method available, and the nature of the drug product. Bioequivalence testing should be conducted using the most appropriate method available for the specific use of the product.

The preferred hierarchy of bioequivalence studies (in descending order of sensitivity) is the blood level study, pharmacologic end-point study, and clinical end-point study. When absorption of the drug is sufficient to measure drug concentration *directly* in the blood (or other appropriate biological fluids or tissues) and systemic absorption is relevant to the drug action, then a blood (or other biological fluid or tissue) level bioequivalence study should be conducted. The blood level study is generally preferred above all others as the most sensitive measure of bioequivalence. The sponsor should provide justification for choosing either a pharmacologic or clinical end-point study over a blood-level (or other biological fluids or tissues) study.

When the measurement of the rate and extent of absorption of the drug in biological fluids can not be achieved or is unrelated to drug action, a pharmacologic end-point (*i.e.*, drug induced physiologic change which is related to the approved indications for use) study may be conducted. Lastly, in order of preference, if drug concentrations in blood (or fluids or tissues) are not measurable or are inappropriate, and there are no appropriate pharmacologic effects that can be monitored, then a clinical end-point study may be conducted, comparing the test (generic) product to the reference (pioneer) product and a placebo (or negative) control.

D. Species Selection

A bioequivalence study generally should be conducted for each species for which the pioneer product is approved on the label, with the exception of "minor" species (as defined in section 514.1 (d) (1) of Title 21 of the Code of Federal Regulations) on the label.

E. Dose Selection

Dose selection will depend upon the label claims, consideration of assay sensitivity, and relevance to the practical use conditions of the reference product. A blood level bioequivalence study should generally be conducted at the highest dose approved for the pioneer product.

However, the Center will consider a bioequivalence study conducted at a higher than approved dose in certain cases. Such a study may be appropriate when a multiple of the highest approved dose achieves measurable blood levels, but the highest approved dose does not. In general, the study would be limited to 2-3x the highest dose approved for the pioneer product. The pioneer product should have an adequate margin of safety at the higher than approved dose level. The generic sponsor should also confirm (*e.g.*, through literature) that the drug follows linear kinetics. A higher than approved dose bioequivalence study in food animal species would be accompanied by a tissue residue withdrawal study conducted at the highest approved dose for the

pioneer product.

For products labeled for multiple claims involving different pharmacologic actions at a broad dose range (*e.g.*, therapeutic and production claims), a single bioequivalence study at the highest approved dose will usually be adequate. However, multiple bioequivalence studies at different doses may be needed if the drug is known to follow nonlinear kinetics. The sponsor should consult with CVM to discuss the bioequivalence study or studies appropriate to a particular drug.

F. Multiple Strengths of Solid Oral Dosage Forms

The generic sponsor should discuss with CVM the appropriate *in vivo* bioequivalence testing and *in vitro* dissolution testing to obtain approval for multiple strengths (or concentrations) of solid oral dosage forms.

CVM will consider the ratio of active to inactive ingredients and the *in vitro* dissolution profiles of the different strengths, the water solubility of the drug, and the range of strengths for which approval is sought.

One *in vivo* bioequivalence study with highest strength product may suffice if the multiple strength products have the same ratio of active to inactive ingredients and are otherwise identical in formulation.

In vitro dissolution testing should be conducted, using an FDA approved method, to compare each strength of the generic product to the corresponding strength of the reference product.

G. Manufacturing of Pilot Batch ("Biobatch")

A pilot batch or "biobatch" should be the source of the finished drug product used in the pivotal studies (*i.e.*, bioequivalence studies and tissue residue studies), stability studies and the validation studies for the proposed analytical and stability indicating methods (refer to CVM's guidance number 42, "Animal Drug Manufacturing Guidelines").

III. BLOOD LEVEL STUDIES

Blood level bioequivalence studies compare a test (generic) product to a reference (pioneer) product using parameters derived from the concentrations of the drug moiety and/or its metabolites, as a function of time, in whole blood, plasma, serum (or in other appropriate biological fluids or tissues). This approach is particularly applicable to dosage forms intended to deliver the active drug ingredient(s) to the systemic circulation (*e.g.*, injectable drugs and most oral dosage forms). Generally, the study should encompass the absorption, distribution, and depletion (elimination) phases of the drug concentration vs time profiles.

A. Assay Consideration

A properly validated assay method is pivotal to the acceptability of any pharmacokinetic study. Sponsors should discuss any questions or problems concerning the analytical methodology with CVM before undertaking the bioequivalence studies. The ANADA submission should contain adequate information necessary for the CVM reviewer to determine the validity of the analytical

method used to quantitate the level of drug in the biological matrix (*e.g.*, blood).

The following aspects should be addressed in assessing method performance:

1. Concentration Range and Linearity

The quantitative relationship between concentration and response should be adequately characterized over the entire range of expected sample concentrations. For linear relationships, a standard curve should be defined by at least 5 concentrations. If the concentration response function is non-linear, additional points would be necessary to define the non-linear portions of the curve. Extrapolation beyond a standard curve is not acceptable.

2. Limit of Detection (LOD)

The standard deviation of the background signal and LOD should be determined. The LOD is estimated as the response value calculated by adding 3 times the standard deviation of the background response to the average background response.

3. Limit of Quantitation (LOQ)

The initial determination of LOQ should involve the addition of 10 times the standard deviation of the background response to the average background response. The second step in determining LOQ is assessing the precision (reproducibility) and accuracy (recovery) of the method at the LOQ. The LOQ will generally be the lowest concentration on the standard curve that can be quantified with acceptable accuracy and precision (see items 5. and 6. below).

4. Specificity

The absence of matrix interferences should be demonstrated by the analysis of 6 independent sources of control matrix. The effect of environmental, physiological, or procedural variables on the matrix should be assessed. Each independent control matrix will be used to produce a standard curve, which will be compared to a standard curve produced under chemically defined conditions. The comparison of curves should exhibit parallelism and superimposability within the limits of analytical variation established for the chemically defined standard curve.

5. Accuracy (Recovery)

This parameter should be evaluated using at least 3 known concentrations of analyte freshly spiked in control matrix, one being at a point 2 standard deviations above the LOQ, one in the middle of the range of the standard curve ("mid-range") and one at a point 2 standard deviations below the upper quantitative limit of the standard curve. The accuracy of the method, based upon the mean value of 6 replicate injections, at each concentration level, should be within 80-120% of the nominal concentration at each level (high, mid-range, and LOQ).

6. Precision

This parameter should be evaluated using at least 3 known concentrations of analyte freshly spiked in control matrix, at the same points used for determination of accuracy. The coefficient of variation (CV) of 6 replicates should be $\pm 10\%$ for concentrations at or above 0.1 ppm (0.1 μ g/mL). A CV of $\pm 20\%$ is acceptable for concentrations below 0.1 ppm.

7. Analyte Stability

Stability of the analyte in the biological matrix under the conditions of the experiment (including any period for which samples are stored before analyses) should be established. It is recommended that the stability be determined with incurred analyte in the matrix of dosed animals in addition to, or instead of, control matrix spiked with pure analyte. Also, the influence of 3 freeze-thaw cycles at 2 concentrations should be determined.

Stability samples at 3 concentrations should be stored with the study samples and analyzed through the period of time in which study samples are analyzed. These analyses will establish whether or not analyte levels have decreased during the time of analysis.

8. Analytical System Stability

To assure that the analytical system remains stable over the time course of the assay, the reproducibility of the standard curve should be monitored during the assay. A minimal design would be to run analytical standards at the beginning and at the end of the analytical run.

9. Quality Control (QC) Samples

The purpose of QC samples is to assure that the complete analytical method, sample preparation, extraction, clean-up, and instrumental analysis perform according to acceptable criteria. The stability of the drug in the test matrix for the QC samples should be known and any tendency for the drug to bind to tissue or serum components over time should also be known.

Drug free control matrix, *e.g.*, tissue, serum, etc. that is freshly spiked known quantities of test drug, should be analyzed contemporaneously with test samples, evenly dispersed throughout each analytical run. This can be met by the determination of accuracy and precision of each analytical run (Items 5 and 6).

10. Replicate and Repeat Analyses

Single rather than replicate analyses are recommended, unless the reproducibility and/or accuracy of the method are borderline. Criteria for repeat analyses should be determined prior to running the study and recorded in the method SOP.

11. Summary of Samples to Be Run With Each Analysis

- a. Accuracy estimate (Item 5)
- b. Precision estimate (Item 6)
- c. Analytical system stability (Item 8)
- d. Analyte stability samples (Item 7)

B. General Experimental Design Considerations

1. Dosing by Labeled Concentration

The potency of the pioneer and generic products should be assayed prior to conducting the bioequivalence study to ensure that FDA or compendial specifications are met. The Center recommends that the potency of the pioneer and generic lots should differ by no more than $\pm 5\%$ for dosage form products.

The animals should be dosed according to the labeled concentration or strength of the product, rather than the assayed potency of the individual batch (*i.e.*, the dose should not be corrected for the assayed potency of the product). The bioequivalence data or derived parameters should not be normalized to account for any potency differences between the pioneer and generic product lots.

2. Single Dose vs Multiple Dose Studies

A single dose study at the highest approved dose will generally be adequate for the demonstration of bioequivalence. A single dose study at a higher than approved dose may be appropriate for certain drugs (refer to the section on Dose Selection).

A multiple dose study may be appropriate when there are concerns regarding poorly predictable drug accumulation, (*e.g.*, a drug with nonlinear kinetics) or a drug with a narrow therapeutic window. A multiple dose study may also be needed when assay sensitivity is inadequate to permit drug quantification out to 3 terminal elimination half-lives beyond the time when maximum blood concentrations (C_{MAX}) are achieved, or in cases where prolonged or delayed absorption² exist. The determination of prolonged or delayed absorption (*i.e.*, flip-flop kinetics) may be made from pilot data, from the literature, or from information contained with FOI summaries pertaining to the particular drug or family of drugs.

3. Subject Characteristics

Ordinarily, studies should be conducted with healthy animals representative of the species, class, gender, and physiological maturity for which the drug is approved. The bioequivalence study may be conducted with a single gender for which the pioneer product is approved, unless there is a known interaction of formulation with gender.

An attempt should be made to restrict the weight of the test animals to a narrow range in order to maintain the same total dose across study subjects.

The animals should not receive any medication prior to testing for a period of two weeks or more, depending upon the biological half-life of the ancillary drug.

4. Fed vs Fasted State

Feeding may either enhance or interfere with drug absorption, depending upon the characteristics of the drug and the formulation. Feeding may also increase the inter- and intrasubject variability in the rate and extent of drug absorption. The rationale for conducting each bioequivalence study under fasting or fed conditions should be provided in the protocol.

Fasting conditions, if used, should be fully described, giving careful consideration to the pharmacokinetics of the drug and the humane treatment of the test animals.

The protocol should describe the diet and feeding regime which will be used in the study.

If a pioneer product label indicates that the product is limited to administration either in the fed or fasted state, then the bioequivalence study should be conducted accordingly. If the bioequivalence study parameters pass the agreed upon confidence intervals, then the single study is acceptable as the basis for approval of the generic drug.

However, for certain product classifications or drug entities, such as enteric coated and oral sustained release products, demonstration of bioequivalence in both the fasted and the fed states may be necessary, if drug bioavailability is highly variable under feeding conditions, as determined from the literature or from pilot data. A bioequivalence study conducted under fasted conditions may be necessary to pass the confidence intervals. A second smaller study may be necessary to examine meal effects. CVM will evaluate the smaller study with respect to the means of the pivotal parameters (AUC, CMAX). The sponsors should consult with CVM prior to conducting the studies.

C. Pharmacokinetic and Statistical Considerations in Study Design

1. Sampling Time Considerations

The total number of sampling times necessary to characterize the blood level profiles will depend upon the curvature of the profiles and the magnitude of variability associated with the bioavailability data (including pharmacokinetic variability, assay error and interproduct differences in absorption kinetics).

The sampling times should adequately define peak concentration(s) and the extent of absorption. The sampling times should extend to at least 3 terminal elimination half-lives beyond TMAX. The sponsor should consult with CVM prior to conducting the pivotal bioequivalence study if the assay is unable to quantify samples to 3 half-lives.

Maximum sampling time efficiency may be achieved by conducting a pilot investigation. The pilot study should identify the general shapes of the test and reference curves, the magnitude of the difference in product profiles, and the noise associated with each blood sampling time (*e.g.*, variability attributable to assay error and the variability between subjects, for parallel study designs, or within subjects, for crossover study designs). This information should be applied to the determination of an optimum blood sampling

schedule. Depending upon these variability estimates, it may be more efficient to cluster several blood samples rather than to have samples which are periodically dispersed throughout the duration of blood sampling.³

2. Protein Binding

In general, product bioequivalence should be based upon total (free plus protein bound) concentrations of the parent drug (or metabolite, when applicable). However, if nonlinear protein binding is known to occur within the therapeutic dosing range (as determined from literature or pilot data), then sponsors may need to submit data on both the free and total drug concentrations for the generic and pioneer products.

Similarly, if the drug is known to enter blood erythrocytes, the protocol should address the issue of potential nonlinearity in erythrocyte uptake of the drug administered within the labeled therapeutic dosing range.

The bioequivalence protocol or completed study report should provide any information available from the literature regarding erythrocyte uptake and protein binding characteristics of the drug or drug class, including the magnitude of protein binding and the type of blood protein to which it binds.

3. Subject Number

Pilot studies are recommended as a means of estimating the appropriate sample size for the pivotal bioequivalence study. Estimated sample size will vary depending upon whether the data are analyzed on a log or linear scale. Useful references for sample size estimates include Westlake⁴, Hauschke⁵, and Steinijans⁶.

4. Cross-over and Parallel Design Considerations

A two-period cross-over design is commonly used in blood level studies. The use of cross-over designs eliminates a major source of study variability: between subject differences in the rates of drug absorption, drug clearance, and the volume of drug distribution.

In a typical two-period cross-over design, subjects are randomly assigned to either sequence A or sequence B with the restriction that equal numbers of subjects are initially assigned to each sequence. The design is as follows:

	Sequence A	Sequence B
Period 1	Test	Reference
Period 2	Reference	Test

A crucial assumption in the two-period cross-over design is that of equal residual effects. Unequal residual effects may result, for example, from an inadequate washout period. Another assumption of the cross-over (or extended period) design is that there is no subject by formulation interaction. In other words, the assumption is that all subjects are from a relatively homogeneous population and will exhibit similar relative bioavailability of the test and reference products. If there are subpopulations of subjects, such that the relationship between product bioavailability is a function of the subpopulation within which they are being tested, then a subject by formulation interaction is said to exist.

A one-period parallel design may be preferable in the following situations:

- a. The drug induces physiological changes in the animal (e.g., liver microsomal enzyme induction) which persist after total drug clearance and alter the bioavailability of the product administered in the second period.
- b. The drug has a very long terminal elimination half-life, creating a risk of residual drug present in the animal at the time of the second period dosing.
- c. The duration of the washout time for the two-period cross-over study is so long as to result in significant maturational changes in the study subjects.
- d. The drug follows delayed or prolonged absorption (flip-flop kinetics²), where the slope of the $[\beta]$ -elimination phase is dictated by the rate of drug absorption rather than the rate of drug elimination from one or both products.

Other designs, such as the two-period design with four treatment sequences (Test/Test, Reference/Reference, Test/Reference and Reference/Test) or the extended period design may be appropriate depending on the circumstances. The use of alternative study designs should be discussed with CVM prior to conducting the bioequivalence study. Pilot data or literature may be used in support of alternative study designs.

5. Duration of Washout Time for Cross-over Study

For drugs which follow a one or two compartment open body model, the duration of the washout time should be approximately 10x the plasma apparent terminal elimination half-life, to provide for 99.9% of the administered dose to be eliminated from the body.

If more highly complex kinetic models are anticipated (e.g., drugs for which long withdrawal times have been assigned due to prolonged tissue binding), or for drugs with the potential for physiologic carryover effects, the washout time should be adjusted accordingly.

The washout period should be sufficiently long to allow the second period of the cross-over study to be applicable in the statistical analysis. However, if sequence effects are noted, the data from the first period may be evaluated as a parallel design study.

6. Pivotal Parameters for Blood Level Bioequivalence

The sponsor is encouraged to calculate parameters using formulas which involve only the raw data (*i.e.*, so-called model independent methods).

a. Area Under the Curve (AUC) Estimates

The extent of product bioavailability is estimated by the area under the blood concentration vs time curve (AUC). AUC is most frequently estimated using the linear trapezoidal rule. Other methods for AUC estimation may be proposed by the sponsor and should be accompanied by appropriate literature references during protocol development.

For a single dose bioequivalence study, AUC should be calculated from time 0 (predose) to the last sampling time associated with quantifiable drug concentration AUC(0-LOQ). The comparison of the test and reference product value for this noninfinity estimate provides the closest approximation of the measure of uncertainty (variance) and the relative bioavailability estimate associated with AUC(0-INF), the full extent of product bioavailability⁷.

The relative AUC values generally change very little once the absorption of both products has been completed^{8,9}. However, because of the possibility of multifunctional absorption kinetics, it can not always be determined when the available drug has been completely absorbed. Therefore, CVM recommends extending the duration of sampling until such time that $AUC(0-LOQ)/AUC(0-INF) \geq 0.80$. Generally, the sampling times should extend to at least 3 multiples of the drug's apparent terminal elimination half-life, beyond the time when maximum blood concentrations are achieved.

AUC(0-INF) should be used to demonstrate that the concentration-time curve can be quantitated such that $AUC(0-LOQ)/AUC(0-INF) \geq 0.80$. The method for estimating the terminal elimination phase should be described in the protocol and the final study report. The $AUC(0-LOQ)/AUC(0-INF)$ is calculated to determine whether AUC(0-LOQ) adequately reflects the extent of absorption.

The sponsor should consult with CVM if $AUC(0-LOQ)/AUC(0-INF)$ is determined to be < 0.80 . If $AUC(0-LOQ)/AUC(0-INF)$ is < 0.80 , then a multiple dose study to steady state may be needed to allow an accurate assessment of AUC(0-INF) (where $AUC(0-INF) = AUC(0-t)$ at steady state and t is the dosing interval).

In a multiple dose study, the AUC should be calculated over one complete dosing interval AUC(0-t). Under steady state conditions, AUC(0-t) equals the full extent of bioavailability of the individual dose AUC(0-INF) assuming linear kinetics. For drugs which are known to follow nonlinear kinetics, the sponsor should consult with CVM to determine the appropriate parameters for the bioequivalence determination.

b. Rate of Absorption

The rate of absorption will be estimated by the maximum observed drug concentration

(C_{MAX}) and the corresponding time to reach this maximum concentration (T_{MAX}).

When conducting a steady-state investigation, data on the minimum drug concentrations (trough values) observed during a single dosing interval (C_{MIN}) should also be collected. Generally, three successive C_{MIN} values should be provided to verify that steady-state conditions have been achieved. Although C_{MIN} most frequently occurs immediately prior to the next successive dose, situations do occur with C_{MIN} observed subsequent to dosing. To determine a steady state concentration, the C_{MIN} values should be regressed over time and the resultant slope should be tested for its difference from zero.

c. Determination of Product Bioequivalence

Unless otherwise indicated by CVM during the protocol development for a given application, the pivotal bioequivalence parameters will be C_{MAX} and AUC(0-LOQ) (for a single dose study) or AUC(0-t) (for a multiple dose study). To be indicative of product bioequivalence, the pivotal metrics should be associated with confidence intervals which fall within a set of acceptability limits (see Statistical Analysis section of this Guidance.

The sponsor and CVM should agree to the acceptable bounds for the confidence limits for the particular drug and formulation during protocol development.

If studies or literature demonstrate that the pioneer drug product exhibits highly variable kinetics, then the generic drug sponsor may propose alternatives to the generally acceptable bounds for the confidence limits.

T_{MAX} in single dose studies and C_{MIN} in multiple dose studies will be assessed by clinical judgment.

D. Statistical Analysis

CVM advocates the use of 90% confidence intervals, as the best available method for evaluating bioequivalence study data. Papers by Schuirmann¹⁰ and Westlake⁴ compare various methodologies for assessing drug product equivalence and describe the confidence interval approach.

The confidence interval approach should be applied to the individual parameters of interest (e.g., AUC and C_{MAX}). The sponsor may use untransformed or log transformed data. However, the choice of untransformed or log transformed data should be made by the sponsor with concurrence by the Center prior to conducting the study.

1. Untransformed Data

A discussion of how the confidence interval approach should be applied to (normally distributed) untransformed data from a two-period crossover design is given below.

If we let \bar{X}_{T1} be the mean for the test drug in period 1, \bar{X}_{T2} the mean for the test drug in period 2, and \bar{X}_{R1} and \bar{X}_{R2} the respective means for the reference drug, then the estimates for the drugs averaged over both periods are $\bar{X}_T = (1/2)(\bar{X}_{T1} + \bar{X}_{T2})$ for the test drug and $\bar{X}_R = (1/2)(\bar{X}_{R1} + \bar{X}_{R2})$ for the reference drug. Although both sequence groups usually start with the same number of animals, the number of animals in each sequence group (n_A and n_B) that successfully finish the study may not be equal. The formulas above utilize the marginal or least squares estimates of μ_T and μ_R , the corresponding means in the target population. These means are not a function of the sample size in each sequence.

An analysis of variance is needed to obtain the estimate of σ^2 , the error variance. The estimator, s^2 , which will be used in the calculation of the 90% confidence interval should be obtained from the "error" mean square term found in the following ANOVA table.

Source	Degrees of Freedom
Sequence	1
Animal (Sequence)	n_A+n_B-2
Period	1
Formulation	1
Error	n_A+n_B-2
Total	$2n_A+2n_B-1$

Lower and upper 90% confidence intervals are then found by formulas based on Student's t-distribution.

$$L = (\bar{X}_T - \bar{X}_R) - t_{n_A+n_B-2;0.05} s \sqrt{\frac{1}{2} \left(\frac{1}{n_A} + \frac{1}{n_B} \right)}$$

$$U = (\bar{X}_T - \bar{X}_R) + t_{n_A+n_B-2;0.05} S \sqrt{\frac{1}{2} \left(\frac{1}{n_A} + \frac{1}{n_B} \right)}$$

The procedure of declaring two formulations bioequivalent if the 90% confidence interval is completely contained in some fixed interval, is statistically equivalent to performing two one-sided statistical tests ($\alpha = .05$) at the end-points of the interval.

Consider the following example with $L = 3$, $U = 17$, $\bar{X}_T = 110$ and $\bar{X}_R = 100$. By the traditional hypothesis testing approach, the result would be considered statistically significant since the confidence interval does not include 0. Using the confidence interval approach, the entire confidence interval lies within 17% of \bar{X}_R . (The lower end of the confidence interval lies within $L/\bar{X}_R = 3/100 = 3\%$ of \bar{X}_R , while the upper end of the confidence interval lies within $U/\bar{X}_R = 17/100 = 17\%$ of \bar{X}_R .) If it were determined by CVM that only differences larger than 20% were biomedically important, then using the confidence interval approach the results of this study would be considered adequate to demonstrate bioequivalence.

Now consider an example with $L = -4$, $U = 24$, $\bar{X}_T = 110$ and $\bar{X}_R = 100$. In this case, by the traditional hypothesis testing approach the result would not be considered statistically significant since the confidence interval includes 0. However, the confidence interval extends as far as 24% from \bar{X}_R . (The lower end of the confidence interval lies within $L/\bar{X}_R = -4/100 = -4\%$ of \bar{X}_R , while the upper end of the confidence interval extends to $U/\bar{X}_R = 24/100 = 24\%$ of \bar{X}_R .) If it were determined by CVM that only differences larger than 20% were biomedically important, then the results of this study would be considered inadequate to demonstrate bioequivalence, since the entire confidence interval is not within 20% of \bar{X}_R .

2. Logarithmically transformed data

This section discusses how the 90% confidence interval approach should be applied to log-transformed data. In this situation the individual animal AUC and CMAX values are log-transformed and the analysis is done on the transformed data. For a two-period crossover study, as described in D.1, the ANOVA model used to calculate estimates of the error variance and the least square means are identical for both transformed and untransformed data. The procedural difference comes after the lower and upper 90% confidence intervals are found by formulas based on Student's t-distribution.

The lower and upper confidence bounds of the log-transformed data will then need to be

back-transformed in order to be expressed on the original scale of the measurement. One thing to keep in mind when moving between the logarithm scale and the original scale is that the back-transformed mean of a set of data that has been transformed to the logarithm scale is not strictly equivalent to the mean that would be calculated from the data on the original scale of measurement. This back-transformed mean is known instead as the geometric mean.

It may help to see the calculations involved. If the AUC from each animal has been transformed to the logarithm scale, we can express the transformed AUC as $LnAUC$. Then the mean on the logarithm scale is as follows:

$$\overline{LnAUC}_t = \sum_{i=1}^n \frac{LnAUC_{it}}{n}$$

where the subscript t represents the AUC determinations for

the test article, i is the AUC of the i th animal, and n is the total number of animals receiving the text article. When this mean is back-transformed, it becomes the geometric

mean: $e^{(\overline{LnAUC}_t)}$. This geometric mean will be on the original scale of the measurement. It will be close to but not exactly equal to the mean obtained on the original scale of the measurement.

The back-transformation of the confidence bounds is accomplished in the following way:

$$\text{Lower bound (expressed as a percentage)} = (e^L - 1) \times 100$$

$$\text{Upper bound (expressed as a percentage)} = (e^U - 1) \times 100$$

Where

- L is the lower 90% confidence interval as given in Section III D 1 and calculated on the log-transformed data;
- U is the upper 90% confidence interval as given in Section III D 1 and calculated on the log-transformed data.

As an example, consider the data for AUC from a hypothetical crossover study in the following table:

Animal	Crossover	Reference Article		Test Article	
		AUC	LogAUC	AUC	LogAUC

	Sequence				
1	1	518.0	6.25	317.8	5.76
2	1	454.9	6.12	465.0	6.14
3	1	232.8	5.45	548.4	6.31
4	1	311.1	5.74	334.8	5.81
5	2	340.4	5.83	224.7	5.41
6	2	497.7	6.21	249.2	5.52
7	2	652.0	6.48	625.4	6.44
8	2	464.1	6.14	848.7	6.74
	Mean	433.8	6.03	451.7	6.02
	Standard deviation	133.3	0.33	214.3	0.47
	Geometric mean		414.7		410.5

The statistics for AUC will be calculated from the log-transformed data. In this example, L , the lower 90% confidence interval calculated on the log scale is -0.395. U , the upper 90% confidence interval calculated on the log scale is 0.372. To back-transform these intervals and express them as percentages, we do the following:

Back-transformed lower bound:

$$\left(e^{-0.395} - 1\right) \times 100 = (0.674 - 1) \times 100 = (-0.326) \times 100 = -32.6\%$$

Back-transformed upper bound:

$$\left(e^{0.372} - 1\right) \times 100 = (1.451 - 1) \times 100 = (0.451) \times 100 = 45.1\%$$

Therefore the lower end of the confidence bound lies within -32.6% of the geometric mean of the reference article, while the upper end of the confidence interval lies within 45.1% of the geometric mean of the reference article. If it were determined by CVM that the acceptable confidence bound was 80% to 125% of the geometric mean of the reference article in order to demonstrate bioequivalence, then the back-transformed lower bound can be as low as -20% and the back-transformed upper bound can be as high as 25%. In this example, we would determine that the study had not demonstrated an acceptable level of bioequivalence between the test article and the reference article.

A more detailed derivation of these expressions for upper and lower confidence bounds is found in the Appendix.

The width of the confidence interval is determined by the within subject variance (between subject variance for parallel group studies) and the number of subjects in the study. In general, the confidence interval for untransformed data should be 80-120% (the confidence interval should lie within $\pm 20\%$ of the mean of the reference product). For logarithmically transformed data, the confidence interval is generally 80-125% (the confidence interval should lie within -20% to $+25\%$ of the mean of the reference product). The sponsor and CVM should determine the acceptable bounds for confidence limits for the particular drug and formulation during protocol development.

IV. PHARMACOLOGIC END-POINT STUDIES

Where the direct measurement of the rate and extent of absorption of the new animal drug in biological fluids is inappropriate or impractical, the evaluation of a pharmacologic end-point related to the labeled indications for use will be acceptable.

A. General Design Aspects

Typically the design of a pharmacologic end-point study should follow the same general considerations as the blood level studies. However, specifics such as the number of subjects or sampling times will depend on the pharmacologic end-point monitored. The parameters to be measured will also depend upon the pharmacologic end-points and may differ from those used in blood level studies. As with blood level studies, when pharmacologic end-point studies are used to demonstrate bioequivalence, a tissue residue study will also be required in food-producing animals.

B. Statistical Analysis

For parameters which can be measured over time, a time *vs* effect profile is generated, and equivalence is determined with the method of statistical analysis essentially the same as for the blood level bioequivalence study.

For pharmacologic effects for which effect *vs* time curves can not be generated, then alternative procedures for statistical analysis should be discussed with CVM prior to conducting the study.

V. CLINICAL END-POINT STUDIES

If measurement of the drug or its metabolites in blood, biological fluids or tissues is inappropriate or impractical, and there are no appropriate pharmacologic end-points to monitor (*e.g.*, most production drugs and some coccidiostats and anthelmintics), then well-controlled clinical end-point studies are acceptable for the demonstration of bioequivalence.

A. General Design Aspects

Generally, a parallel group design with three treatment groups should be used. The groups should be a placebo (or negative) control, a positive control (reference/pioneer product) and the test (generic) product. The purpose of the placebo (or negative) control is to confirm the sensitivity or validity of the study.

Dosage(s) approved for the pioneer product should be used in the study. Dosage(s) should be selected following consultation with CVM and should reflect consideration for experimental sensitivity and relevance to the common use of the pioneer product.

B. Subject Characteristics and Data Collection

Studies should generally be conducted using the target animal species, with consideration for the sex, class, body weight, age, health status, and feeding and husbandry conditions, as described on the pioneer product labeling. In general, the length of time that the study is conducted should be consistent with the duration of use on the pioneer product labeling.

In general, the response(s) to be measured in a clinical end-point study should be based upon the labeling claims of the pioneer product and selected in consultation with CVM. It may not be necessary to collect data on some overlapping claims (*e.g.*, for a production drug which is added at the same amount per ton of feed for both growth rate and feed efficiency, data from only one of the two responses need be collected).

C. Statistical Analysis

When considering sample size, it is important to note that the pen, not the individual animal, is often the experimental unit.

As with blood level bioequivalence studies, CVM is advocating the use of 90% confidence intervals as the best method for evaluating clinical end-point studies. The bounds for confidence limits (*e.g.*, $\pm 20\%$ of the improvement over placebo [or negative] control) for the particular drug should be agreed upon with CVM prior to initiation of the study.

The analysis should be used to compare the test product and the reference product. In addition, a traditional hypothesis test should be performed comparing both the test and reference products separately to the placebo (or negative) control. The hypothesis test is conducted to ensure that the study has adequate sensitivity to detect differences when they actually occur. If no significant improvement ($\alpha = .05$) is seen in the parameter (*i.e.*, the mean of the test and the mean of the reference products are each not significantly better than the mean of the placebo [or negative] control), generally, the study will be considered inadequate to evaluate bioequivalence.

Assuming that the test and reference products have been shown to be superior to the placebo (or negative) control, the determination of bioequivalence is based upon the confidence interval of the difference between the two products.

Some clinical end-point studies may not include a placebo (or negative) control for ethical and/or practical considerations. If the placebo is omitted, then the response(s) to the test and reference products should each provide a statistically significant improvement over baseline.

If the results are ordered categorical data (*e.g.*, excellent, good, fair or poor), a non-parametric hypothesis test of no difference between test product and placebo (or negative) control and between the reference product and placebo (or negative) control should be performed. As above, if these tests result in significant differences between the test product and control and the reference product and control, then a non-parametric confidence interval on the difference between the test and reference products is calculated.

Another acceptable approach for categorical data is to calculate the confidence interval on the odds ratio between the test and reference products after showing that the test and reference products are significantly better than the control¹¹.

VI. HUMAN FOOD SAFETY CONSIDERATIONS

The toxicology and tolerance developed for the pioneer animal drug are applied to generic copies of the drug.

The Panel on Human Food Safety at the 1993 Veterinary Drug Bioequivalence Workshop addressed tissue residue depletion studies for generic animal drugs¹. The Center has concluded that in addition to a bioequivalence study, a tissue residue depletion study should be conducted for approval of a generic animal drug product in a food-producing species. Two drug products may have the same plasma disposition profile at the concentrations used to assess product bioequivalence, but may have very different tissue disposition kinetics when followed out to the withdrawal time for the pioneer product. Therefore, to show the withdrawal period at which residues of the generic product will be consistent with the tolerance for the pioneer product, a tissue residue depletion study is necessary.

The results of a bioequivalence study or tissue residue depletion study in one animal species can not generally be extrapolated to another species. Possible species differences in drug partitioning or binding in tissues could magnify a small difference in the rate or extent of drug absorbed into a large difference in marker residue concentrations in the target tissue. Therefore, for a pioneer product labeled for more than one food-producing species, a bioequivalence study and a tissue residue depletion study will generally be requested for each major food-producing species on the label.

A traditional withdrawal study, as described in CVM's guidance number 3, "General Principles for Evaluating the Safety of Compounds Used in Food-Producing Animals," is considered the best design for collecting data useful for the calculation of a preslaughter withdrawal period for drugs used in food-producing animals. In the traditional withdrawal study, twenty animals are divided into four or five groups of four to five animals each. Groups of animals are slaughtered

at carefully preselected time points following the last administration of the test product and the edible tissues are collected for residue analysis. A statistical tolerance limit approach is used to determine when, with 95% confidence, 99% of treated animals would have tissue residues below the codified limits.

For purposes of calculating a withdrawal period for a generic animal drug, only the generic product would be tested (i.e., not the pioneer product), and only the marker residue in the target tissue would be analyzed.

Other study designs will be considered on a case-by-case basis. Sponsors are encouraged to submit the proposed tissue residue depletion protocol for CVM concurrence before proceeding with the withdrawal study.

The generic animal drug will be assigned the withdrawal time supported by the residue depletion data, or the withdrawal time currently assigned to the pioneer product, whichever is the longer.

The generic animal drug sponsor may request a shorter withdrawal period for the generic product by supplementing the ANADA and providing tissue residue data necessary to support the shorter withdrawal period request. Such a supplement will be reviewed under the agency's policy for Category II supplements. For a Category II supplement, a reevaluation of the safety (or effectiveness) data in the parent application (i.e., the pioneer NADA) may be required (21 CFR 514.106 (b) (2)). The Center will ordinarily approve a request for a shorter withdrawal period when the residue data are adequate and when no other human food safety concerns for the drug are evident.

Under 21 CFR 514.1(b)(7), applications are required to include a description of practicable methods for determining the quantity, if any, of the new animal drug in or on food, and any substance formed in or on food because of its use, and the proposed tolerance or withdrawal period or other use restrictions to ensure that the proposed use of the drug will be safe. For certain drug products, a tissue residue depletion study is not needed to ensure that residues of the test product will be consistent with the codified drug tolerance at the withdrawal time assigned to the reference product. These include but may not be limited to products for which a waiver of in vivo bioequivalence testing is granted, and products for which the assay method used in the blood level bioequivalence study is sensitive enough to measure blood levels of the drug for the entire withdrawal period assigned to the reference product. Other requests for waiver of the tissue residue study will be considered on a case-by-case basis.

CVM will not request that the assay methodology used to determine the withdrawal period for the generic product be more rigorous than the approved methodology used to determine the existing withdrawal period for the pioneer product. If an analytical method other than the approved method of analysis is used, the generic sponsor should provide data comparing the alternate method to the approved method.

APPENDIX: Confidence Bounds on the Logarithm Scale

We want to develop an expression for the confidence bound of the difference between the pharmacokinetic parameter for the test treatment and the reference treatment, expressed as a percentage of the reference treatment. This bound is derived from the 90% confidence interval of the difference between the mean of the test treatment and the mean of the reference treatment. This appendix addresses the case when the data analysis used to calculate the 90% confidence interval has been done with the natural log of the pharmacokinetic parameter as the dependent variable.

For purposes of this illustration we will use Area Under the Curve (AUC) as the pharmacokinetic parameter.

Notation and Distributional Assumptions:

Area under the Curve for Reference Treatment AUC_R (1)

Area under the Curve for Test Treatment AUC_T (2)

Natural log of AUC $LnAUC$ (3)

$LnAUC_T \sim N(\mu_T, \sigma^2)$ and $LnAUC_R \sim N(\mu_R, \sigma^2)$ (4)

$\overline{LnAUC}_T = \sum_{i=1}^n \frac{LnAUC_{iT}}{n}$ which estimates μ_T , similarly for μ_R (5)

$e^{(\overline{LnAUC}_T)}$ is the geometric mean of AUC_T to be denoted by $\dot{\mu}_T$, (6)
similarly for $\dot{\mu}_R$

Calculation of the Confidence Interval:

The 90% Confidence Interval of $(\mu_T - \mu_R)$ is denoted by (L, U) and is calculated from (7)

$$L = \left(\overline{\text{LnAUC}}_T - \overline{\text{LnAUC}}_R \right) + t_{n_A+n_B-2; .05} \times s \sqrt{\frac{1}{2} \left(\frac{1}{n_A} + \frac{1}{n_B} \right)}$$

$$U = \left(\overline{\text{LnAUC}}_T - \overline{\text{LnAUC}}_R \right) - t_{n_A+n_B-2; .05} \times s \sqrt{\frac{1}{2} \left(\frac{1}{n_A} + \frac{1}{n_B} \right)}$$

Manipulating This Expression Gives:

$$L < \mu_T - \mu_R < U \quad (8)$$

$$e^L < e^{\mu_T - \mu_R} < e^U \quad (9)$$

$$e^L < \frac{\dot{\mu}_T}{\dot{\mu}_R} < e^U \quad (10)$$

$$e^{L-1} < \frac{\dot{\mu}_T - 1}{\dot{\mu}_R} < e^{U-1} \quad (11)$$

$$e^{L-1} < \frac{\dot{\mu}_T - \dot{\mu}_R}{\dot{\mu}_R} < e^{U-1} \quad (12)$$

Expressed As A Percentage:

$$(e^L - 1) \times 100 < \left(\frac{\dot{\mu}_T - \dot{\mu}_R}{\dot{\mu}_R} \right) \times 100 < (e^U - 1) \times 100 \quad (13)$$

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

OCT 17 1990

Dear Sir or Madam:

This is the sixth in a series of policy letters regarding the implementation of the Generic Animal Drug and Patent Term Restoration Act (GADPTRA), which was signed into law on November 16, 1988.

We are introducing two policy statements (refer to attachment) which address our continuing implementation of the new law. The policy statements are entitled as follows:

- 1) "Withdrawal Period for Generic Animal Drug Products"
- 2) "Eligibility of a New Salt or Ester of a Pioneer Animal Drug for an ANADA"

The first policy statement, "Withdrawal Period for Generic Animal Drug Products", is a revision of the policy statement entitled "Withdrawal Period for Generic Drugs" which was issued with our third policy letter dated August 2, 1989. The revised statement replaces the 8-2-89 statement.

We welcome comments and questions from all interested parties. If any changes are made, the revised policy statements will be placed on public display, and a notice of availability will be published in the FEDERAL REGISTER.

Comments on the policy statements may be submitted to:

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

We will continue to announce the availability of our policy statements regarding the new law.

Sincerely yours,

Richard H. Teske

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

Attachment

1) Withdrawal Period for Generic Animal Drug Products

A generic animal drug product will ordinarily be granted the same withdrawal period as the pioneer product if bioequivalence, using blood level data, is demonstrated. However, if the time for blood concentrations to decline to the limit of detection is longer for the generic product than the reference (pioneer) product, then a tissue residue study may be required.

If bioequivalence is demonstrated using pharmacological or clinical endpoint studies, then the generic sponsor must ordinarily collect tissue residue depletion data to establish the appropriate withdrawal period.

The withdrawal period established in the tissue residue study need not be the same as the withdrawal period for the pioneer drug. If the generic sponsor submits a tissue residue study, and the data indicate that the withdrawal period is longer than for the pioneer product, then the generic product will be given the longer withdrawal time. However, under an abbreviated new animal drug application (ANADA), a generic product will not be assigned a shorter withdrawal period than the pioneer product.

The sponsor may attempt to establish a shorter withdrawal period for the generic product by filing a supplement to the approved ANADA. The supplement will be a Category II supplement, as defined in CVM's policy on supplemental applications. For a Category II supplement, a re-evaluation of the safety (or efficacy) data in the parent application (i.e. pioneer NADA) may be required.

The generic sponsor should use the approved method of analysis in its tissue residue study, even if the approved method has changed since the original approval. If an analytical method other than the approved method of analysis is used, the generic sponsor must provide data comparing the alternate method to the approved method.

2) Eligibility of A New Salt or Ester of a Pioneer
Animal Drug for an ANADA

As part of the requirement of an abbreviated new animal drug application (ANADA), the generic sponsor must show that the active ingredient of the proposed generic product is the same as the active ingredient of the reference (pioneer) product. For salts and esters, the "same" active ingredient is interpreted to mean the same salt or ester form of the new animal drug in the finished animal drug product prior to its administration. A product that contains a different salt or ester form of the same drug in the finished animal drug product will be considered to contain a different active ingredient.

Because the Agency considers a different salt or ester to be a different active ingredient, suitability petitions seeking permission to file an ANADA for a different salt or ester from that of the pioneer product can not be approved, unless the petition seeks a change in one active ingredient in a combination product (or in a feed use combination) and the different salt or ester is previously approved or is not a new animal drug as defined by the Federal Food, Drug, and Cosmetic Act. An ANADA seeking approval of a different salt or ester in a product that contains a single new animal drug will not be accepted.



March 20, 1991

Dear Sir or Madam:

This is the seventh in a series of policy letters regarding the implementation of the Generic Animal Drug and Patent Term Restoration Act (GADPTRA), which was signed into law on November 16, 1988.

We are introducing four policy statements (refer to attachment) which address our continuing implementation of the new law. The policy statements are entitled as follows:

- 1) "Guidance for Analytical Methods for ANADA's"
- 2) "Hybrid Applications"
- 3) "ANADA's, NADA's and Supplemental Approvals for Subtherapeutic Antibiotics"
- 4) "Waivers of *In Vivo* Bioequivalence Studies for Topical Products"

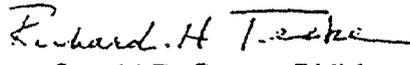
We welcome comments and questions from all interested parties. If any changes are made, the revised policy statements will be placed on public display, and a notice of availability will be published in the FEDERAL REGISTER.

Comments on the policy statements may be submitted to:

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5600 Fishers Lane
Rockville, MD 20857

We will continue to announce the availability of our policy statements regarding the new law.

Sincerely yours,


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

Attachment

1) GUIDANCE FOR ANALYTICAL METHODS FOR ANADA's

Sponsors of abbreviated new animal drug applications (ANADA's) should discuss any questions or problems concerning analytical methodology with CVM before undertaking pivotal bioequivalence or residue studies. Early discussion of the issues relevant to analytical methods can lead to the solution of any actual or potential analytical problems which could invalidate the animal drug studies.

The purpose of this guidance is to outline technical items that should be addressed when developing and validating analytical methods for bioequivalence studies for generic animal drugs. Details on the requirements for analytical methods are specified in the "Guideline for the Approval of a Method of Analysis for Residues," available from CVM's Industry Information Staff.

The guidance presented here is not intended to specify the techniques that should be used in developing or validating analytical methods. Rather, the guidance is intended to characterize the type of information needed to validate analytical methods. The technology used to develop an analytical method and the tests and experiments used to establish the performance characteristics of the analytical method are the decision of the drug sponsor.

In general, there are six important aspects that should be addressed in assessing method performance:

1. The concentration range of the analyte, or any designated metabolite, and demonstration of linearity over the concentration range. This range can be determined by conducting recovery studies using the sample and method.
2. The limit of detection (LOD). This is the minimum level of the marker drug in the target matrix that can be discriminated from background to some level of statistical confidence. The 95% confidence level is typically used.
3. The limit of quantitation (LOQ). This is the minimum level of marker drug in the target matrix that can be quantitated to some level of statistical confidence. The 95% confidence level is typically used.

4. Accuracy: This is usually determined at various drug concentrations in the target matrix within the concentration range of the method. "Accuracy" is also referred to as "recovery."

5. Specificity: This is an estimate of the extent to which the method responds only to the drug of interest. Specificity should also assess interferences that may be caused by potential degradation products and/or the matrix, e.g. tissue, feed, blood, and urine.

6. Reproducibility: This is an estimate of precision. This is usually expressed as a coefficient of variation or relative standard deviation.

FDA reviewers will evaluate the data on the above six items to establish whether the proposed method is scientifically sound and is appropriate for the intended measurement. Items 1 through 6 above should be the basic elements in a validation plan for analytical methods that are either newly developed or are newly modified versions of existing methods.

If existing methods which have been previously satisfactorily validated are to be used verbatim, then quality assurance procedures should be established to assure that the method is operating in a state of control every time the method is used in a study. In this case, the FDA reviewer would typically verify that a quality assurance (QA) procedure has been developed and is part of the operational instructions for the method. Good quality assurance procedures do not have to be elaborate or complicated. The core of a quality assurance plan is the types of control samples, materials and techniques that are used to assess that the method is performing satisfactorily. The purpose of the controls is to show that the equipment and reagents are performing as intended, and that the method is responding acceptably to the analyte and is free of interferences. All validated methods should have a quality assurance assessment as part of the standard operating procedures (SOP's) for the method application.

2) HYBRID APPLICATIONS

Section 512(n)(3) of the act provides for suitability petitions which may be filed to request permission to submit an abbreviated new animal drug application (ANADA) for certain changes in the listed (pioneer) animal drug. The suitability petition can be approved only if the proposed changes do not require investigations other than bioequivalence or tissue residue for approval of the new product. However, an applicant may wish to make a modification in an approved animal drug, which would require investigations beyond bioequivalence and tissue residue studies. For example, an applicant may wish to obtain approval of a new indication for a listed animal drug.

Following the approval of an ANADA, the holder of the approved ANADA may seek approval of a supplemental application that contains reports of clinical investigations needed for approval of the new indication. Because such a supplement would require the review of data, FDA would treat it as a submission under section 512(b)(1) of the act.

An applicant may also wish to seek approval of, for example, a new dosage form of a listed animal drug that requires the review of investigations. The statute could be interpreted to require such an applicant to first obtain approval of an ANADA for the listed animal drug's approved dosage form, and then file a 512(b)(1) supplement to the approved ANADA containing clinical data to obtain approval of the new dosage form. If the applicant did not first obtain an ANADA for the approved dosage form, the applicant could be required to submit a full new animal drug application (NADA) under section 512(b)(1) of the act for the new dosage form and duplicate the basic safety and effectiveness studies conducted on the listed animal drug. FDA has concluded that such an interpretation would be inconsistent with the legislative purposes of the 1988 Amendments because it would serve as a disincentive to innovation and would require needless duplication of research.

FDA believes that a more consistent, less burdensome interpretation of the 1988 Amendments is to allow a generic applicant to submit a 512(b)(1) application for a change in an already approved animal drug that requires the submission and review of investigations conducted by or for the applicant, without first obtaining approval

of an ANADA for a duplicate of the listed animal drug. Therefore, FDA proposes to accept applications for changes requiring the review of investigations conducted by or for the applicant, including changes in dosage form, strength, route of administration, and active ingredients (in a combination product), as well as new indications and new species. These applications will be known as "hybrid" applications. Like similar supplements to approved ANADA's, these applications will rely on the approval of the listed animal drug, together with the data needed to support the change. The applicant will thus be relying on the approval of the listed animal drug only to the extent that such reliance would be allowed under section 512(n) of the act: to establish the safety and effectiveness of the underlying animal drug. FDA notes, however, that it will not accept such an application for an animal drug that differs from the listed animal drug only in that its extent of absorption is significantly less than that of the listed animal drug.

An application that relies in part on the approval of a listed animal drug, is, for this purpose, considered an application described in section 512(b)(2) and must make a certification as to any relevant patents that claim the listed animal drug. In addition, the date of submission and effective approval of these applications may, under section 512(c)(2)(D), be delayed to give effect to any patent or period of exclusivity accorded the listed animal drug.

Because these hybrid applications will be reviewed in part as applications under section 512(b)(1) of the act, they will be subject to the statutory and regulatory requirements applicable to such applications, including the patent submission requirements of sections 512(b)(1) and (c)(3) of the act, and may be eligible for 3 years of exclusivity under sections 512(c)(2)(F)(ii) and (iii) of the act.

The exact requirements for a hybrid application will depend upon the proposed new animal drug product in question. However, in general, the hybrid application may include a bioequivalence study, tissue residue study, and the additional studies the Center deems necessary for approval of the innovative product.

All applicants should consult with CVM to determine the types of studies required for approval of the hybrid application. The general content and format described for the ANADA in the second generic policy letter (dated June 7, 1989) can be used for submission of the hybrid application. However, the environmental assessment should follow the requirements for the 512(b)(1) supplemental application.

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3) ANADA'S, NADA'S AND SUPPLEMENTAL APPROVALS FOR SUBTHERAPEUTIC ANTIBIOTICS

Background

FDA regulation 21 CFR 558.15 provides that new animal drug applications (NADAs) for the subtherapeutic use of antimicrobials in animal feed would not be approved after specified dates in 1973 unless specific data were submitted to resolve questions concerning transferable resistance. FDA has, since 1973, not approved NADAs for subtherapeutic use of drugs containing penicillin or the tetracyclines, including combinations* containing those drugs. This restriction has applied both to original NADAs and those filed under the Drug Effectiveness Study Implementation (DESI) program. These drugs are the subject of notices of opportunity for hearing (NOOHs), published in 1977, on FDA's proposal to withdraw their approvals.

ANADAs

Drugs for subtherapeutic use that contain penicillin and the tetracyclines that have been approved for safety and effectiveness are eligible to be, and are, "listed" drugs under the Generic Animal Drug and Patent Term Restoration Act (GADPTR) of 1988. A drug that was subject to the DESI review is "approved for safety and effectiveness" if FDA, based upon its review of, for example, a DESI-conforming supplemental application, has approved the application. Listed drugs can be the subject of abbreviated new animal drug applications (ANADAs) unless FDA has issued a notice of hearing (NOH) concerning such drugs. Because NOHs have not been issued for drugs providing for subtherapeutic use of penicillin and the tetracyclines, ANADAs for those drugs that have been approved for safety and effectiveness can be submitted and approved under the 1988 Act starting January 1, 1991.

NADA's

FDA will continue to refuse to approve original applications for drugs providing for subtherapeutic use of penicillin and the tetracyclines, pending resolution of the resistance transfer issues.

Supplemental Applications

Consistent with the provisions of 21 CFR 558.15, FDA has, since 1973, not approved supplemental applications for new uses of penicillin and tetracycline containing drugs for subtherapeutic use, although the agency has approved certain other kinds of supplemental applications for such drugs. "New uses" refers to new combinations, new indications and use in additional species.

FDA has concluded that 21 CFR 558.15 requires the agency to continue to refuse to approve supplemental applications (including supplements to NADA's, ANADA's, and hybrid applications) for new uses of penicillin- and tetracycline-containing drugs for subtherapeutic use, pending resolution of the resistance transfer issues.

However, FDA will continue to consider the following types of NADA or ANADA supplements for changes relating to the manufacture of drug products currently listed in 21 CFR 558.15:

- Bulk drug shipments
- Changes in:
 - repacking operations
 - containers -- size, style, material, type
 - equipment (for any operation in the manufacturing process)
 - batch sizes
 - analytical control procedures (for the new drug substance, raw materials, and finished dosage form)
 - manufacturing processes
 - new technology
 - new equipment
 - revision of procedures
 - record keeping
 - reprocessing/reworking
 - raw materials/specifications
 - product storage requirements
 - new drug substance synthesis or fermentation
- Addition of alternate sources of the new drug substance
- Addition of alternate manufacturing, packaging, labeling and testing facilities
- Export of product as approved
- Updating/revision of analytical methods for the release of the finished drug product

Supplemental NADA's or ANADA's for drug products subject to 21 CFR 558.15 will also continue to be considered for the following:

- change in Type A medicated article concentration
- new therapeutic uses for less than 14 days duration of use.
- new combination products which include oxytetracycline at 75-80 mg/head/day for liver abscesses in cattle

GADPTRA permits a generic applicant to petition for certain changes from the listed drug it is proposing to copy, i.e. for a different dosage form, route of administration, strength or substitution of an active ingredient in a combination drug (including substitution in a feed-mixed combination). FDA has concluded that, if it permits generic sponsors to make any of the aforementioned changes in drugs containing penicillin or tetracycline for subtherapeutic use, it will also permit the sponsors of the "listed" drugs to submit supplemental applications for the same changes.

*New combinations have not been allowed, with the exception of new combination products which include oxytetracycline at 75-80 mg/head/day for liver abscesses in cattle.

4) WAIVERS OF *IN VIVO* BIOEQUIVALENCE STUDIES FOR TOPICAL PRODUCTS

CVM will consider requests for waivers of *in vivo* bioequivalence studies for abbreviated new animal drug applications (ANADA's) for topically applied products intended for local therapeutic effects in non-food animals. Waivers will be considered for all dosage forms of topicals, including dermatologic, ophthalmic, and otic preparations.

The proposed generic product must be the same as the pioneer product in concentration and identity of active ingredients, as well as in dosage form (i.e., pioneer ointment and generic ointment, pioneer cream and generic cream).

The inactive ingredients should be the same in the pioneer and generic products whenever possible. However, certain differences in the inactive ingredients may be allowed in the formulation of the generic product being considered for a waiver. The specifics of the allowable changes will depend upon the drug product in question.

The request for waiver of the *in vivo* bioequivalence study may be filed in the INAD or the ANADA. The request for waiver should provide information about the differences in the pioneer and generic product formulations and a justification for granting the waiver.

To request a change in dosage form for topical products (e.g.,—pioneer ointment and generic cream), a suitability petition (as described in 21 CFR 10.30) must be filed. For a change in dosage form for a topical product, an *in vivo* bioequivalence study will ordinarily be required.



JUL 23 1991

Dear Sir or Madam:

This is the eighth in a series of policy letters regarding the implementation of the Generic Animal Drug and Patent Term Restoration Act (GADPTRA), which was signed into law on November 16, 1988.

The purpose of this letter is to announce the Center for Veterinary Medicine's policy with regard to the generic copying of certain drugs that were subject to review under the Drug Efficacy Study Implementation (DESI) program. Briefly, the policy is that CVM will not permit copying of a DESI-reviewed drug product unless that product has been "DESI-finalized," i.e., the Agency has approved the drug product for effectiveness and its labeling complies with the conditions of that approval.

In connection with this policy determination, the agency is removing certain "nonfinalized" DESI-reviewed New Animal Drug Applications (NADA's) from the list of drug products that are eligible for copying under GADPTRA, and is placing the NADA's in a separate list. The change will be reflected in an upcoming 1991 monthly supplement to FDA Approved Animal Drug Products (the Green Book").

The DESI Program

Under the DESI program, NADA's approved prior to October 10, 1962 were reviewed to determine the drugs' effectiveness for labeled claims. (Drugs whose applications had become effective prior to that date had been reviewed only for safety.) Some of the DESI-reviewed drugs were found to be effective for one or more indications; typically, however, the DESI review required labeling changes for those drugs. Other drugs were found to be less than effective; in most cases, sponsors of products containing those drugs were required to submit additional data to establish the effectiveness of their drug products.

Some sponsors complied with the requirements of the DESI notices, and DESI-approved claims for such drug products are codified in 21 CFR parts 520 et seq as documentation of FDA's approval for effectiveness. However, other sponsors did not comply; although approvals of many of the affected NADA's have been withdrawn, final action has not yet been taken on approximately 34 NADA's. Some of these nonfinalized drugs were rated effective for certain claims, but their sponsors have not submitted revised labeling to comply with the notice. Other drugs were rated less than effective for all claims. The nonfinalized NADA's and the change in the Green Book listings are the subjects of this policy letter.

The GADPTRA List

Under GADPTRA, FDA "lists" a drug product, i.e., the drug product is eligible for copying, if that drug product has been approved both for safety and effectiveness. CVM has tentatively concluded that a DESI-reviewed NADA may not be listed unless FDA has approved the drug product for effectiveness, i.e., the sponsor has complied fully with the DESI requirements and that compliance is reflected in the approved NADA. Thus, even if the DESI review concluded that the drug product was effective for one or more

indications, the drug may not be listed until the sponsor has made any required changes (e.g., in labeling) and those changes have become the subject of an approved supplemental NADA.

The NADA's that are the subject of this letter were included in the Green Book list of drugs eligible for copying when the Agency first published the list. However, the Agency also stated at the time that it published the list that CVM was reviewing certain drugs approved prior to 1962 to determine whether any should be removed from the list [54 FR 6608 (February 13, 1989)]. Moreover, in our seventh GADPTRA policy letter (March 20, 1991), CVM stated that DESI-reviewed subtherapeutic drugs containing penicillin and the tetracyclines could be copied under GADPTRA only if they had been approved for effectiveness as well as safety [56 FR 15083 (April 15, 1991)].

Although the Agency is removing the nonfinalized drug products from the list of drugs that have been approved for safety and effectiveness, it will for convenience maintain a separate list of these NADA's in the Green Book. NADA's that are brought into compliance with the DESI review will be returned to the original list, and NADA's whose approvals are withdrawn will simply be removed from the supplemental list.

Conclusions

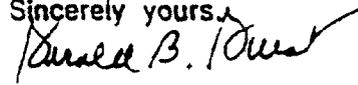
CVM recognizes that the policy decision announced in this letter will preclude approval of applications to copy the drug products in question, even though the pioneer sponsors may continue to market their products for the time being. Accordingly, the Center is taking action, as rapidly as its resources will allow, to withdraw approval of the pioneer NADA's whose sponsors do not comply with the applicable DESI requirements.

CVM acknowledges that it may not have identified all the pre-62 drugs that have not complied with the requirements of the DESI program. Similarly, there may be pre-62 NADA's that are not included in either the regular or supplemental lists in the Green Book and that will need to be reviewed for compliance with the DESI program. We welcome suggestions for corrections to either list, as well as comments and questions regarding the statement of policy contained in this letter.

If any changes are made in CVM policy on the nonfinalized DESI drugs, the revised statement will be placed on public display, and a notice of availability will be published in the FEDERAL REGISTER. Comments on any of the GADPTRA policy statements may be submitted to Docket Number 88N-0394, at the following address:
Dockets Management Branch, HFA-305, Park Building Room 1-23, Food and Drug Administration, 12420 Parklawn Drive, Rockville, MD 20857.

We will continue to announce the availability of future policy statements regarding implementation of GADPTRA.

Sincerely yours,


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

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JUN 27 1995

Food and Drug Adminis
Rockville MD 20857

Dear Sir/Madam:

This is the ninth in a series of policy letters regarding the implementation of the Generic Animal Drug and Patent Term Restoration Act (GADPTRA), which was signed into law on November 16, 1988.

We are introducing a revised policy statement (refer to the attachment) which addresses our continuing implementation of GADPTRA. The policy statement is entitled Environmental Review of Generic Animal Drugs.

The policy statement is a revision of the policy statement of the same title which was issued in our second policy letter dated June 7, 1989. The second policy letter required the submission of an environmental assessment (EA) for the finished and bulk manufacturing site(s) for the production of the product. The revised policy eliminates the routine requirement for an EA and requires the submission of a request for categorical exclusion under 21 CFR 25.24(d)(1) for an ANADA.

We welcome comments and questions on the policy statement from all interested parties. If any changes are made, the revised statement will be placed on public display, and a notice of its availability will be published in the *Federal Register*.

Comments on the policy statement should be addressed to:

Dockets Management Branch
Docket No. 88N 0394
HFA-305, Room 4-62
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

We will continue to announce the availability of future policy statements regarding the implementation of GADPTRA.

Sincerely yours,



Stephen Sundlof, D.V.M., Ph.D.
Director, Center for
Veterinary Medicine

Attachment

Environmental Review of Generic Animal Drugs

The National Environmental Policy Act (NEPA) requires that the Food and Drug Administration consider in its decision making, and disclose to the public, the environmental impacts that may be expected from proposed actions. The FDA's procedures for implementing NEPA are contained in 21 CFR Part 25. This discussion provides supplemental information specific to the Center's environmental policy regarding the implementation of the Generic Animal Drug and Patent Term Restoration Act (GAPTRA).

Although 21 CFR 25.24(d)(1) provided a categorical exclusion from preparing an environmental assessment (EA) for certain previously approved animal drugs, CVM announced, in the second policy letter dated June 7, 1989, that it would require that applicants ordinarily provide as part of each abbreviated new animal drug application (ANADA), adequate information to objectively determine and verify the potential environmental impacts of the manufacture, but not the use, of the generic product. To meet this requirement, sponsors were required to organize the environmental information in the environmental assessment (EA) format that was provided as an attachment to the policy letter. The EA content and format, was based on the abbreviated EA formats for certain other classes of animal drugs contained in 21 CFR 25.31a(b)(4). The EA's are available for public review at the time of approval of ANADA's.

This cautious approach was taken because ANADA's were anticipated to usually provide for new bulk drug and final product manufacturing sites that are controlled by different sponsors than those described in the pioneer new animal drug applications. The EA requirement was designed to examine this difference in manufacturing sites. Information about potential environmental impacts from the use of the product was not required because introduction of the drug into the environment from its use as a generic generally would not alter the drug already present in the environment as a result of approval of a pioneer.

Since the June 7, 1989 policy letter, CVM has reviewed over 100 EAs for generic animal drug products. After reviewing the EAs, with few exceptions, the Center has prepared Findings of No Significant Impact (FONSI) for the manufacturing of the generic animal drug products. In those cases, where the EAs were inadequate, they were inadequate because of incorrect formatting or because of missing information for the applicable environmental requirements. On few occasions, the lack of information resulted in the sponsors going back to the Federal, State or local environmental offices that had responsibility for the site of manufacturing, correcting manufacturing processes to comply with the environmental requirements, and obtaining the proper documentation. In no case has CVM determined that a significant impact could result from the manufacturing of a generic animal drug product. Additionally, no mitigation of potential environmental impacts has been necessary.

Because CVM has not identified any significant environmental impacts from the manufacturing of generic animal drug products, the caution that CVM exercised is no longer necessary. Therefore, an EA will no longer routinely be required for ANADAs. Instead, CVM will categorically exclude ANADAs from preparation of an EA under 25.24(d)(1).

Categorical exclusions are provided for actions that do not individually or cumulatively have a significant effect on the human environment. Neither an environmental assessment nor an environment impact statement is required (see 40 CFR 1508.4) for such actions. As indicated above, since the June 7, 1989 policy letter, CVM has found no instance where significant environmental effects were expected as a result of the manufacture of a generic animal drug product. Therefore, a categorical exclusion is the more appropriate route for CVM to meet NEPA requirements for generic animal drug applications.

Categorical exclusions for certain new animal drug applications (NADAs) already exist under 21 CFR 25.24(d)(1). The categorical exclusion applies if the NADA meets the specified criteria that the drug product will not be administered at a higher dosage level, for a longer duration or for a different indication than were previously in effect. An ANADA is merely an abbreviated form of an NADA. Therefore, when an ANADA meets the specified criteria, the ANADA will usually qualify for a categorical exclusion under 21 CFR 25.24(d)(1).

Meeting the criteria for a categorical exclusion does not guarantee that an action will be categorically excluded. The categorical exclusion in 21 CFR 25.24(d)(1) already provides that if data establish that at the expected level of exposure the substance may be toxic to the environment, CVM will require an EA. Furthermore, under 21 CFR 25.23(b), if data establish that the proposed action may significantly affect the environment, CVM will require an EA.

CVM is revising its policy regarding the environmental requirement for ANADAs. An ANADA submitted for an animal drug product must ordinarily include a request for categorical exclusion from the preparation of an EA under 21 CFR 25.24(d)(1). The Center will review the request for categorical exclusion and determine whether the criteria listed for the exclusion are met. If the criteria are met, and the agency has no information available to it to establish that the proposed action may significantly affect the environment, the categorical exclusion will be granted. If the Center finds, or a sponsor determines, that the categorical exclusion does not apply, or information indicates that the proposed action may significantly affect the environment, then an EA will be required for the action.

cc: HFV-1