DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

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:

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) 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.

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 (GADPTRA) 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.