GENERAL REVIEW AND ENFORCEMENT POLICIES

NON-ROUTINE INVESTIGATIONAL NEW ANIMAL DRUGS

1. Purpose:

This guide identifies recommended approaches for dealing with nonroutine situations involving the use of investigational new animal drugs.

2. Special Requests for Use of Unapproved Substances:

CVM occasionally receives requests from private practitioners, zoo veterinarians, etc., wishing to obtain investigational drugs, unapproved drugs, or chemical substances for use in treating animals in special situations. These requests should be handled as follows:

a. Each situation will be judged on its own merits and resolved on a case-by-case basis by the office of New Animal Drug Evaluation (HFV-100).

b. When a request is restricted to a single occurrence for emergency treatment to save an animal's life, the Center may allow shipment under specified conditions.

(1) There shall be a record of notification to the Center of the information specified by 21 CFR 511.1(b)(4). The shipper shall keep a record of the shipment and the practitioner a record of receipt and disposition of the drug for two years and make them available for FDA inspection.

(2) For requests involving exotic animals in zoos where a drug may be needed but the situation may not be life threatening, permission may be considered for multiple shipments, if indicated, under the same controls, i.e., submissions to FDA and retention of records.

c. The following additional information is obtained/considered prior to granting an Investigational Exemption for use of unapproved substances under above item #2:

(1) Drug source (domestic or import)?

(2) Species of animals?

(3) What are the stated conditions of emergency, if applicable?

(4) Is there a sound medical basis or scientific rationale to merit investigational use of the drug? Is the disease condition(s) identified? What are the critical criteria/ method(s) for diagnosis?

(5) Is there a protocol or adequate information and/or instructions for investigational use, i.e.:

(a) Clearly stated objective and proper criteria for selection of test subject(s).

(b) Is there a commitment to maintain and provide availability of records to asses the results of treatment?

(c) Is there an approved NDA (human) for the drug?

(d) Is there an approved NDA or NADA for a different dosage form of the drug?

(e) Is there an approved NDA or NADA for another drug with similar pharmacological action? If so, does it eliminate the need for the requested (Emergency) Investigational Exemption?

If the above issues are satisfactorily addressed, an INAD file is established and an Investigational Exemption is granted.

3. Requests from Research Institutions:

University or other institutional research involving INADs is subject to 21 CFR Part 511. The investigational notices must be submitted on a trial by trial or experiment by experiment basis if subject to 21 CFR 511.1(b). It is important to clearly distinguish between laboratory research under 511.1(a) and clinical work under 511.1(b). Each experimental activity must be properly classified. Research under paragraph (a) may be conducted without prior notice to FDA. Clinical work under paragraph (b) must be subject to a notice of claimed investigational exemption. While the regulations are interpreted as expecting all such data to be submitted eventually to FDA as part of an NADA submission, the Center recognizes that universities and some other institutions do not ordinarily submit NADAs even though they may be the sponsor of an INAD exemption. See paragraph 6 below for further explanation.

4. Identification of INAD Sponsor:

On many occasions drug companies are asked to ship investigational drugs under

circumstances where the company has no desire to sponsor the trials, yet wishes to supply the compounds as a research service. The drug company, if they agree to hold the INAD, would be subject to the requirements of the regulations, including having to monitor the studies. However, companies normally only supply and do not want to conduct any monitoring. An option for dealing with this situation is as follows:

a. If the drug company does not want the monitoring responsibility, they must have the individual wishing to conduct the trial be the sponsor of the INAD. The regulations provide for either the person shipping the drug or the person causing the shipment to act as a sponsor. If the investigator is also sponsor of the INAD, he/she is responsible for complying with all the requirements of the sponsor identified in 21 CFR 511.

b. The company must assure that any drug shipped bears the labeling statement specified by the regulation.

5. Obtaining Unformulated Drugs from Chemical Supply Houses:

A need may arise for a source of pure drug substance because of dosage form limitations on an approved formulated product. For example, a needed drug for an equine emergency may not be available in a suitable concentration or dosage form because it is approved only as a human or companion animal product. Since a chemical supply house is not authorized to ship the substance for drug use without FDA approval, an INAD exemption may be requested. If an emergency condition or special request exists, the proper procedure for responding to these requests is specified in paragraph 2 above except that all requests must be concurred in by the Director, Office of New Animal Drug Evaluation, or the Deputy Director for Therapeutic and Production Drug Review.

6. Appropriate Use of Laboratory Animal Exemption:

CVM Policy and Procedures Manual Guide 1240.3000 - "New Animal Drugs for Investigational Use" states that any species of animal may potentially be used in laboratory studies. This, however, must be their sole intended function. Questions arising as to the appropriate use of the laboratory animal exemption under 21 CFR 511.1(a) may be resolved as follows:

(1) 21 CFR 511.1(a) applies when pharmacologic, physiologic, or toxicity studies (including effectiveness models) are being conducted with the new animal drug. Although the animals under study are not ordinarily intended for food use, food use may be authorized on a case-by-case basis if toxicology and depletion data are adequate to determine that edible tissues are safe for food. If there is any expectation that laboratory animals may be slaughtered for food, every effort should be made to anticipate this, and the sponsor should be instructed to file the INAD request under 511.1(b).

(2) 21 CFR 511.1(b) applies if clinical studies on the treatment or prevention of a naturally occurring disease in the "laboratory" animal are proposed.

(3) Part 511 applies only if bonafide laboratory studies or clinical investigations are being done. An INAD exemption is inappropriate for routinely using drugs to treat disease outbreaks or to maintain health of the animal colony, herd, or flock. A veterinarian may obtain permission for limited use in an "emergency' situation as described under paragraph 2 (above).

Facilities which are engaged only in the raising of laboratory species for sale to other testing facilities are not ordinarily eligible to receive investigational drugs under 511.1(a) or (b).

7. Avoiding Undue Proliferation of INAD Files:

a. A new INAD file should be established when a new chemical entity is being investigated or when a new dosage form of an investigational or approved drug is proposed for study. However, as few separate files as necessary should be opened where early research is being proposed on a number of chemically similar analogues. Of course, a new file is also established on an individual sponsor basis regardless of the drug or form.

For administrative reasons a separate INAD file may also be established for individual species, although it is preferable to handle multiple species testing of the same drug dosage form in a single file. If this is not feasible in a particular case then it is advisable to handle all species of a similar class in one file, such as all food animal species. In no case should a separate file be established simply for investigating safety or effectiveness of different indications for the same drug, dosage form, or species.

b. INAD exemption notices are not required for 21 CFR 511.1(a) laboratory research. There may be instances where an INAD file may be established to permit the review of protocols or the import of investigational drugs.

c. Upon receipt of submissions regarding investigational drugs, the Division Director shall screen the information to determine whether it will generally meet NADE requirements for granting an investigational exemption.

In the event that the information is inadequate to justify an exemption, the submission shall be filed as General Correspondence and the sponsor notified. The GC file may be converted to an INAD file upon submission of adequate information to satisfy a 512(j) exemption.

d. The Document Control Section (DCU) shall not acknowledge a submission and assign an INAD number without the express approval and signature of the Division Director.

8. Food Safety Authorizations

There needs to be some control over the extension of investigations. This is possible only if some limits are placed on the numbers of animals treated and slaughtered for food. Leaving the authorization open-ended invites problems, such as, unduly prolonged investigations, and does not control how much drug is being used. Limits will be set to avoid unnecessary paperwork burdens.

a. The sponsor should be requested at the initiation of their investigations to provide an estimate of their needs which should be large enough to satisfy planned studies.

b. The sponsor should be advised that if withdrawal times are adjusted through the development of additional data, this can be accomplished within the initial number by a new authorization. This should eliminate repetitive requests for the same withdrawal time, but allow necessary adjustments.