REQUIREMENTS FOR INVESTIGATIONAL NEW ANIMAL DRUG EXEMPTIONS

I. PURPOSE

This document explains:

- • the purpose of investigational new animal drug exemptions;
- • what a person must do to exempt unapproved new animal drugs for tests *in vitro* and in laboratory research animals;
- • when and what information a sponsor must submit to claim an exemption; and
- • the sponsor's responsibilities in maintaining an exemption.

NOTE: The requirements for establishing an (J)INAD file are separate from the requirements for sponsors seeking an investigational exemption. The investigational exemption legally allows people to ship unapproved new animal drugs in interstate commerce for investigational use.

II. WHAT IS AN INVESTIGATIONAL NEW ANIMAL DRUG EXEMPTION?

Statutory authority to exempt unapproved investigational new animal drugs from the requirements of an approved new animal drug application (NADA) or abbreviated new animal drug application (ANADA) is in section 512(j) of the Federal Food, Drug, and Cosmetic Act (the act). We often refer to this as an investigational exemption. This exemption makes it possible for unapproved new animal drugs to be shipped in interstate commerce for use by experts, qualified by scientific training and experience, to investigate their safety and effectiveness.

There are two sets of requirements for investigational exemptions. The regulations at 21 CFR part 511 include a set of requirements for exempting unapproved new animal drugs for tests *in vitro* and in laboratory research animals (21 CFR 511.1(a)) and a different set of requirements for unapproved new animal drugs used in clinical investigations (21 CFR 511.1(b)). These regulations allow sponsors to collect safety and effectiveness data needed to support the approval of new animal drug applications while at the same time protecting the public from unsafe residues of investigational new animal drugs in food.

III. EXEMPTION REQUIREMENTS FOR UNAPPROVED NEW ANIMAL DRUGS FOR TESTS *IN VITRO* AND IN LABORATORY RESEARCH ANIMALS

Unlike unapproved new animal drugs for clinical investigations, persons distributing unapproved new animal drugs for safety testing conducted in *vitro* or in laboratory research animals do not have to submit a notice to us before shipping such drugs in interstate commerce.[1]

In order to be exempt from sections 512(a) and 512(m) of the act, a new animal drug for in vitro and laboratory research animal testing:

- Must bear the following labeling before it is shipped or delivered to the investigator:[2]

CAUTION: Contains a new animal drug for investigational use only in laboratory research animals or for tests *in vitro*. Not for use in humans.

[1] We do request that a sponsor submit an NCIE if they are conducting safety studies using food-producing animals for which the sponsor intends to use the edible products from these animals as human food or animal feed. See P&P 1243.4066. A food-use authorization would be required (P&P 1243.4040).
[2] 21 CFR 511.1(a)(1)

- If it is a bulk substance for use in the manufacture of a new animal drug for investigational use, it must bear the following labeling statement:[3]

CAUTION: For manufacturing, processing, or repacking in preparation of a new animal drug limited by Federal law to investigational use.

In addition, the person distributing the new animal drug for this testing:

- Must use due diligence to assure that the person to whom the drug is sent is regularly engaged in conducting laboratory research and that the new animal drug is actually used for *in vitro* tests or for testing in animals used only for laboratory research.[4]

- Must maintain adequate records for each shipment and delivery of the new animal drug for two years after such shipment and delivery and must make such records available to us, upon request.[5]

A person **cannot** obtain an exemption for a new animal drug that is intended for *in vitro* use in the regular course of diagnosing or treating disease.[6]

It is not uncommon for a sponsor to submit a Notice of Claimed Investigational Exemption (NCIE) form (also called a drug shipment form) for a laboratory study (even though such a submission is not required by the regulations in 21 CFR part 511). See Appendix A for a general description of 511.1(a) and 511.1(b) studies. See Section IV for a description of an NCIE form and its contents.

IV. EXEMPTION REQUIREMENTS FOR NEW ANIMAL DRUGS FOR CLINICAL INVESTIGATION

For new animal drugs used in clinical investigations, the sponsor must establish an investigational new animal drug file ((J)INAD) and meet the requirements for an investigational exemption before shipping the drug in interstate commerce. An original (J)INAD will generally be established for each new chemical entity, species, combination, and dosage form.

[3] 21 CFR 201.122(b)
[4] 21 CFR 511.1(a)(2)
[5] 21 CFR 511.1(a)(3)
[6] 21 CFR 511.1(a)(4)

The sponsor of a (J)INAD may be an individual or entity who plans to submit an application for approval (i.e., (A)NADA) following the completion of the investigation. The NCIE form submitted to the (J)INAD file must be signed by the sponsor or by an agent acting on behalf of the sponsor.[7] Sometimes a sponsor will ask to establish a (J)INAD file for their investigational new animal drug without including an NCIE form with the submission. The exemption does not apply until an NCIE form is submitted.[8]

In order to exempt a new animal drug for clinical investigational use from sections 512(a) and 512(m) of the act, we must have from the sponsor of the investigation the signed NCIE form in triplicate, or a signed statement containing the following information listed below.[9] Note that we must have this information from the sponsor before each shipment of the new animal drug.[10]

(1) The identity of the new animal drug.

(2) Copies of all labeling and other pertinent information to be supplied to the investigators.

(3) The name and address of each investigator.

(4) The approximate number of animals to be treated and the number of control animals. If this information is not available, the amount of new animal drug to be shipped must be provided.

(5) If the new animal drug is given to food-producing animals, also include[11]:

- A commitment that edible products from investigational animals will not be used for food without prior authorization from us;
- Approximate dates of the beginning and end of the experiment or series of experiments; and

[7] 21 CFR 511.1(b)
[8] 21 CFR 511.1(b)(4)
[9] The NCIE form (Form 3458) can be found on the FDA internet website (www.fda.gov/cvm/default.html) on the Forms page. The sponsor may also submit the form electronically from the form page site.
[10] 21 CFR 511.1(b)(4)
[11] See P&P 1243.4040 Investigational Food-Use Authorizations: The Role of the Primary (AA) Review Division (this P&P is currently under beta test until March 2009).

- The maximum daily dose(s) to be administered to a given species, the size of animal, maximum duration of administration, method(s) of administration, and proposed withdrawal time, if any.

(6) A statement containing the name and address of the contract research organization (CRO) (if any) to which the sponsor has transferred any obligation(s) for the conduct of the clinical investigation, identification of the study or studies involved, and a listing of the obligation(s) transferred.

Furthermore, the requirements below must also be met for an investigational new animal drug to qualify for the exemption:

(1) The label of the new animal drug must bear the statements:[12]

CAUTION: Contains a new animal drug for use only in investigational animals in clinical trials. Not for use in humans. Edible products of investigational animals are not to be used for food unless authorization has been granted by the U.S. Food and Drug Administration or by the U.S. Department of Agriculture.

If it is a bulk substance for use in the manufacture of a new animal drug for investigational use, it must bear the following labeling statement:[13]

CAUTION: For manufacturing, processing, or repacking in preparation of a new animal drug limited by Federal law to investigational use.

(2) If the product container is too small to accommodate a label with sufficient space to bear the caution statements, the statements may be included on the carton label and other labeling on or within the package from which the new animal drug will be dispensed.[14]

(3) The person distributing the new animal drug will use due diligence to assure that it will actually be used for tests in animals and is not used in humans.[15]

[12] 21 CFR 511.1(b)(1)
[13] 21 CFR 201.122(b)
[14] 21 CFR 511.1(b)(1)
[15] 21 CFR 511.1(b)(2)

(4) The person distributing the new animal drug will maintain adequate records for each shipment of the new animal drug for a period of two years after such shipments and make such records available to us, upon request.[16]

V. RESPONSIBILITIES OF THE (J)INAD SPONSOR

In order to maintain an exemption, a sponsor must:

A. General

(1) Upon a written request from us, submit any information with respect to the investigation, which may affect a determination on whether there are grounds for terminating the investigational exemption in the interest of the public health.[17]

(2) Assure that the investigation is monitored by a person qualified by scientific training and experience to evaluate information obtained from the investigation.[18] The monitoring of investigations should be conducted according to acceptable procedures, such as those described in "Guidance for Industry #58, Good Target Animal Study Practices: Clinical Investigators and Monitors," May 1997; VICH GL9; as well as the requirements of 21 CFR parts 58 and 558.

(3) Promptly investigate and report to us and to all investigators any findings associated with the use of the new animal drug that may suggest significant hazard(s) pertinent to the safety of the new animal drug (e.g., adverse events, unexpected mortality, or hazard(s) to humans and the environment).[19]

(4) Submit either an environmental assessment pursuant to 21 CFR 25.40 or a claim for categorical exclusion under 21 CFR 25.30 or 25.33.[20]

B. Recordkeeping

(1) Retain reports received from investigators for two years after the discontinuation of the investigation or approval of a new animal drug application.[21]

[16] 21 CFR 511.1(b)(3)
[17] 21 CFR 511.1(b)(6)
[18] 21 CFR 511.1(b)(8)(ii)
[19] 21 CFR 511.1(b)(8)(ii)
[20] 21 CFR 511.1(b)(10)

(2) Maintain the following information for at least two years:[22]

(a) Names and addresses of the investigators (individuals or organizations) to whom the drug was shipped.

(b) Date, quantity, and batch or code mark for each drug shipment or delivery.

(3) Make such records and reports available to us for inspection and copying, upon request.[23]

C. Selection of Investigators

(1) Assure that the new animal drug is shipped only to experts qualified by scientific training and experience to evaluate the safety and/or effectiveness of new animal drugs.[24]

(2) Assure that the investigators:

(a) Maintain complete records of the receipt and disposition of each shipment or delivery of the investigational new animal drug. [25]

(b) Furnish adequate and timely reports of the investigation to the sponsor.[26]

(c) Maintain complete copies of all records of the investigation for two years after the discontinuation of the investigation or approval of a new animal drug application.[27]

D. Prohibited Activities:

A sponsor shall not:

(1) Unduly prolong distribution of the new animal drug for investigational use.[28]

[21] 21 CFR 511.1(b)(8)(i)
[22] 21 CFR 511.1(b)(3)
[23] 21 CFR 511.1(b)(3) and (b)(8)(i)
[24] 21 CFR 511.1(b)(7)(i)
[25] 21 CFR 511.1(b)(7)(ii)
[26] 21 CFR 511.1(b)(7)(iii)
[27] 21 CFR 511.1(b)(7)(ii)

(2) Represent the new animal drug as being safe or effective for the purposes for which it is being investigated.[29] (This requirement is not intended to restrict the full exchange of scientific information).

(3) Commercially distribute or test-market the new animal drug prior to approval of the (A)NADA pursuant to Section 512(c) of the act.[30]

E. Contract Research Organizations

A sponsor may transfer any or all of its obligations to a CRO.[31] A CRO is an individual, partnership, corporation, or association that assumes, as an independent contractor with the sponsor, one or more of the obligations of a sponsor (e.g., protocol design, selection or monitoring of investigations, evaluation of reports, and preparation of materials to be submitted to us).[32, 33]

If a sponsor chooses to transfer certain obligations to a CRO, the sponsor must document such transfer in writing and, if not all obligations are transferred, describe each of the obligations being assumed.[34] If all obligations are transferred, a general statement to that effect is acceptable.[35] Any obligation not covered by the written description shall be deemed not to have been transferred.[36]

A CRO that assumes any obligation(s) of a sponsor shall comply with the specific regulations applicable to the obligation(s) assumed.[37]

VI. IMPORTING INVESTIGATIONAL NEW ANIMAL DRUGS

If a sponsor plans to import an investigational new animal drug and ship it directly to a scientific institution conducting clinical investigations, the sponsor must notify us using the NCIE form before they ship the drug.[38]

[28] 21 CFR 511.1(b)(8)(iii)
[29] 21 CFR 511.1(b)(8)(iv)
[30] 21 CFR 511.1(b)(8)(v)
[31] 21 CFR 511.1(f)(2)
[32] 21 CFR 511.1(f)(1)
[33] 21 CFR 510.3(e)
[34] 21 CFR 511.1(f)(2)
[35] 21 CFR 511.1(f)(2)
[36] 21 CFR 511.1(f)(2)
[37] 21 CFR 511.1(f)(3)

If a sponsor plans to ship an imported investigational new animal drug to an entity other than the scientific institution conducting the clinical investigations, then under 21 CFR 511.1(b)(9), the sponsor must notify us of the shipment before it occurs. The letter notifying us of such a shipment should include the following information:

- Name of drug;
- Proposed use of drug;
- Destination of the shipment (name and address);
- Name and address of distributor, broker or agent through whom the drug or drug substance is to be imported;
- Port of entry;
- Approximate date of drug or drug substance entry;
- Name and address of foreign manufacturer;
- Amount of drug or drug substance to be imported; and
- Which investigational labeling statement under 21 CFR 511.1 will be affixed to the investigational new animal drug or under 21 CFR 201.122 for a drug substance (see section III and IV of this document for the appropriate labeling statement).

If you receive such a notice, review it. Determine if you need to respond or if you can file the submission with no reply.[39] If you send a letter to the sponsor, include a copy of the letter in the administrative file. A sponsor should not use the NCIE form to notify us about shipments of imported investigational new animal drugs to an entity other than the scientific institution conducting the clinical investigations. Sometimes, however, sponsors do use the NCIE form for this situation. If you receive an NCIE form for this purpose, follow the procedures outlined at the beginning of this paragraph.

VII. REFERENCES

Statutes

Federal Food, Drug, and Cosmetic Act

§ 512(a)

[38] See P&P 1243.4066
[39] See P&P 1243.3010 Format and Style Conventions for Letters.

§ 512(j)

§ 512(m)

Code of Federal Regulations (Title 21)

Part 25 – Environmental Impact Considerations

§ 25.30, General

§ 25.33, Animal drugs

§ 25.40, Environmental assessments

Part 58 – Good Laboratory Practice for Nonclinical Studies

Part 201 – Labeling

§ 201.122, Drugs for processing, repacking, or manufacturing

Part 510 – New Animal Drugs

§ 510.3, Definitions and interpretations

Part 511 – New Animal Drugs for Investigational Use

Part 558 – New Animal Drugs for Use in Animal Feeds

CVM Program Policy and Procedures Manual

1243.3010 – Format and Style Conventions for Letters

1243.4040 – Investigational Food-Use Authorizations: The Role of the Primary (AA) Review Division

1243.4066 – Notice of Claimed Investigational Exemption (NCIE)

VIII. VERSION HISTORY

November 4, 2008 – Original version of 1243.4065. This original version replaces older policy and procedure documents. This document replaces P&Ps 1240.3000 New

Animal Drugs for Investigational Use, 1240.3025 Non-Routine Investigational New Animal Drugs, and 1240.3032 Requirements for Importation of Investigational New Animal Drugs.

February 18, 2009 – Revised to clarify the labeling statement required for bulk substances for use in the manufacture of new animal drugs for investigational use and to provide additional information on notices for imported investigational new animal drugs.

March 20, 2009 – Revised to correct minor grammatical errors and add appropriate legal citations.

April 3, 2009 – Revised to clarify that we request NCIEs for safety studies using food-producing animals when the sponsor intends to use the edible products for human food or animal feed and that NCIEs are not required for safety studies conducted in vitro or in laboratory research animals and included references to P&Ps on food-use and the NCIE.

APPENDIX 1. DIFFERENTIATING BETWEEN 511.1 STUDY TYPES

Whether a study is regulated under 21 CFR 511.1(a) or 21 CFR 511.1(b) depends on the primary intent of the study. If the purpose of a study is to collect safety information, then the sponsor must comply with the requirements of 21 CFR 511.1(a). Examples of a "511.1(a)" study include: target animal safety, human food safety, and a blood-level bioequivalence study to support an ANADA . Because these studies are conducted in a laboratory" (for our purposes, a "laboratory" could be a barn), they must also comply with the Good Laboratory Practice regulations, 21 CFR Part 58.

If the purpose of a study is to collect effectiveness information (e.g., a target animal effectiveness study), then the sponsor must comply with the requirements of 21 CFR 511.1(b).

If you are presented with a study that is not included as an example in this appendix, consult your team leader and the ONADE Policy Team.