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;
- what information a sponsor must submit to claim an exemption; and
- the sponsor's responsibilities.

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

II. WHAT IS AN INVESTIGATIONAL NEW ANIMAL DRUG EXEMPTION?

Our (FDA, CVM, ONADE) 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 and a different set of requirements for unapproved new animal drugs used in clinical investigations. These regulations allow sponsors to obtain 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 *in vitro* and laboratory research animal testing do not have to submit a notice to us before shipping such drugs in interstate commerce.

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:[1]

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

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

[1] 21 CFR 511.1(a)(1)

- Must use due diligence to assure that the consignee 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.[2]

- 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.[3]

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.[4]

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.

The sponsor of a (J)INAD may be an individual or entity with 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.[5] Sometimes a sponsor will ask to establish a (J)INAD file for their investigational new animal drug without including

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

an NCIE form with the submission. The exemption does not apply until an NCIE form is submitted.[6]

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, before the sponsor can ship the drug in interstate commerce:[7,8]

(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[9]:

- 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
- 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)

[6] 21 CFR 511.1(b)(4)
[7] 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.
[8] 21 CFR 511.1(b)(4)
[9] 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).

for the conduct of the clinical investigation, identification of the study or studies involved, and a listing of the obligation(s) transferred.

By regulation, we must have this information from the sponsor before each shipment of the new animal drug.

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

(1) The labeling of the new animal drug must bear the statements:[10]

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.

(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.

(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.[11]

(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.[12]

[10] 21 CFR 511.1(b)(1)
[11] 21 CFR 511.1(b)(2)
[12] 21 CFR 511.1(b)(3)

V. RESPONSIBILITIES OF THE (J)INAD SPONSOR

The INAD regulations (21 CFR part 511) impose certain responsibilities on the sponsor of a (J)INAD. A summary of those responsibilities is included below.

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.[13]

(2) Assure that the investigation is monitored by a person qualified by scientific training and experience to evaluate information obtained from the investigation.[14] 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).[15]

(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.[16]

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.[17]

(2) Maintain the following information for at least two years:[18]

[13] 21 CFR 511.1(b)(6)
[14] 21 CFR 511.1(b)(8)(ii)
[15] 21 CFR 511.1(b)(8)(ii)
[16] 21 CFR 511.1(b)(10)
[17] 21 CFR 511.1(b)(8)(i)
[18] 21 CFR 511.1(b)(3)

(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.[19]

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.[20]

(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. [21]

(b) Furnish adequate and timely reports of the investigation to the sponsor.[22]

(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.[23]

D. Prohibited Activities:

A sponsor shall not:

(1) Unduly prolong distribution of the new animal drug for investigational use.[24]

(2) Represent the new animal drug as being safe or effective for the purposes for which it is being investigated.[25] (This requirement is not intended to restrict the full exchange of scientific information).

[19] 21 CFR 511.1(b)(3) and (b)(8)(i)
[20] 21 CFR 511.1(b)(7)(i)
[21] 21 CFR 511.1(b)(7)(ii)
[22] 21 CFR 511.1(b)(7)(iii)
[23] 21 CFR 511.1(b)(7)(ii)
[24] 21 CFR 511.1(b)(8)(iii)

(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.[26]

E. Contract Research Organizations

A sponsor may transfer any or all of its obligations to a CRO.[27] A CRO is a person 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).[28]

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.[29] If all obligations are transferred, a general statement to that effect is acceptable.[30] Any obligation not covered by the written description shall be deemed not to have been transferred.[31]

A CRO that assumes any obligation(s) of a sponsor shall comply with the specific regulations applicable to the obligation(s) assumed.[32]

VI. IMPORTING INVESTIGATIONAL NEW ANIMAL DRUGS

Under 21 CFR 511.1(b)(9), if a sponsor plans to import an investigational new animal drug and it is not being shipped directly to the scientific institution conducting the clinical investigations, the sponsor should notify us of the shipment before it occurs. While the NCIE form lists import as an option under the type of shipment field, the form is not intended to be used for the situation described above. However, sponsors do sometimes use the NCIE form in that manner. If you receive such a notice, review it.[33] Determine if a response letter is needed or if the submission can be filed without

[25] 21 CFR 511.1(b)(8)(iv)
[26] 21 CFR 511.1(b)(8)(v)
[27] 21 CFR 511.1(f)(2)
[28] 21 CFR 511.1(f)(1)
[29] 21 CFR 511.1(f)(2)
[30] 21 CFR 511.1(f)(2)
[31] 21 CFR 511.1(f)(2)
[32] 21 CFR 511.1(f)(3)
[33] For purposes of this document, "you" refers to the primary reviewer.

reply.[34] If you send a letter to the sponsor, include a copy of the letter in the administrative file.

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

VII. REFERENCES

Statutes

Federal Food, Drug, and Cosmetic Act

§ 512(a)

§ 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 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

[34] See P&P 1243.3010 Format and Style Conventions for Letters.

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.)

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.

APPENDIX 1. "511.1(A)" STUDY VS. "511.1(B)" STUDY

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.