REQUIREMENTS FOR INVESTIGATIONAL NEW ANIMAL DRUG EXEMPTIONS

I. PURPOSE

This document explains:

- the purpose of investigational new animal drug exemptions;
- 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 (generic) investigational new animal drug ((J)INAD) files are separate from the requirements for sponsors seeking an investigational exemption.

II. WHAT IS AN INVESTIGATIONAL NEW ANIMAL DRUG EXEMPTION?

Statutory authority to exempt investigational new animal drugs from the requirements of an approved (abbreviated) new animal drug application ((A)NADA) is in section 512(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and our implementing regulations are in 21 CFR Part 511. We often refer to this as an investigational exemption. This exemption allows for investigational 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.[1]

There are two sets of requirements for investigational exemptions. 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. The investigational exemption legally allows people to ship investigational new animal drugs in interstate commerce for

[1] Under 21 CFR 201.122(b), a bulk substance for use in the manufacture of new animal drug for investigational use must bear the following labeling statement: **CAUTION: For manufacturing, processing, or repacking in preparation of a new animal drug limited by Federal law to investigational use.** We note that the requirements of 21 CFR Part 511 do not apply to these shipments.

investigational use. 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 (e.g., nonclinical laboratory study), then the sponsor must comply with the requirements of 21 CFR 511.1(a). Examples of "511.1(a)" studies include *in vitro* safety studies, target animal safety, human food safety, and blood-level bioequivalence studies 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 study is a clinical study (we consider these to be studies whose purpose is to collect effectiveness information, a study in client-owned animals, and/or animals whose products will enter the food supply), 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, consult your team leader and the ONADE Policy Team.

Note: Specific questions about labeling of intentional genomic alterations (IGSs), and animal cell and tissue based products (ACTPs), as investigational drugs should be directed to an ONADE project manager.

III. EXEMPTION REQUIREMENTS FOR INAD STUDIES PERFORMED *IN VITRO* OR IN LABORATORY RESEARCH ANIMALS

Unlike investigational new animal drugs for clinical investigations, persons distributing investigational new animal drugs for safety testing conducted *in vitro* or in laboratory research animals (e.g., nonclinical laboratory studies) that will not have any edible products used for food do not have to submit a notice to us before shipping such drugs in interstate commerce.[2] In order to be exempt from sections 512(a) and 512(m) of the FD&C 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 (21 CFR 511.1(a)(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:

- 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 (21 CFR 511.1(a)(2)); and

- 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 (21 CFR 511.1(a)(3)).

[2] 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). An investigational food-use authorization would also be required (see P&P 1243.4040).

A new animal drug that is intended for in vitro use in the regular course of diagnosing or treating disease is not exempt from 512(a) and 512(m) of the FD&C Act (21 CFR 511.1(a)(4)).

It is not uncommon for a sponsor to submit a Notice of Claimed Investigational Exemption (NCIE) form (also called a drug shipment notice) for a nonclinical laboratory study, even though such a submission is not required by the regulations in 21 CFR part 511. See Section II for a general description of 511.1(a) and 511.1(b) studies. See P&P 1243.4066 for NCIE procedures.

IV. EXEMPTION REQUIREMENTS FOR INADS FOR CLINICAL INVESTIGATIONS

For investigational new animal drugs used in clinical investigations, the sponsor must establish an investigational file ((J)INAD) and meet the requirements for an investigational exemption before shipping the drug in interstate commerce. An original (J)INAD is generally established for each new chemical entity, species, combination, and dosage form. The (J)INAD sponsor may be an individual or entity who plans to submit an application for approval (i.e., (A)NADA) following the completion of the investigation. In order to exempt a new animal drug for clinical investigational use from sections 512(a) and 512(m) of the FD&C Act, an NCIE must be submitted to the (J)INAD before each shipment of the investigational new animal drug (see P&P 1243.4066). The NCIE must be signed by the sponsor or by an agent acting on behalf of the sponsor (21 CFR 511.1(b)). The request to establish a (J)INAD file for an investigational new animal drug precedes an NCIE submission, and the exemption is not in effect until an NCIE is submitted (21 CFR 511.1(b)(4)) and the requirements below are met.

1. The label of the investigational new animal drug must bear the statements (21 CFR 511.1(b)(1)):

   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 (21 CFR 511.1(b)(1)).

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 (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 (21 CFR 511.1(b)(3)).

5. If a sponsor is importing an investigational drug to an intermediary, the sponsor must notify us of the shipment in a notification of import (G submission) under the INAD file, followed by an NCIE (B submission) for the shipment to the site conducting the clinical investigations (see P&P 1243.4066).

V. RESPONSIBILITIES OF THE (J)INAD SPONSOR

In order to maintain an exemption, a sponsor must do the following.

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 (21 CFR 511.1(b)(6)).

2. Assure that the investigation is monitored by a person qualified by scientific training and experience to evaluate information obtained from the investigation (21 CFR 511.1(b)(8)(ii)). The monitoring of investigations should be conducted according to acceptable procedures described in 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/or the environment) (21 CFR 511.1(b)(8)(ii)).

4. Submit either an environmental assessment pursuant to 21 CFR 25.40 or a claim for categorical exclusion (CE) under 21 CFR 25.30 or 25.33 (21 CFR 511.1(b)(10)).

B. Recordkeeping

Retain reports received from investigators for two years after the discontinuation of the investigation or approval of a new animal drug application (21 CFR 511.1(b)(8)(i)).

1. Maintain the following information for at least two years (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.

2. Make such records and reports available to us for inspection and copying, upon request (21 CFR 511.1(b)(3) and (b)(8)(i)).

3. See Appendix 1 for a schedule of INAD record keeping requirements.

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 (21 CFR 511.1(b)(7)(i)).

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 CFR 511.1(b)(7)(ii)).

b. Furnish adequate and timely reports of the investigation to the sponsor (21 CFR 511.1(b)(7)(iii)).

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 (21 CFR 511.1(b)(7)(ii)).

D. Prohibited Activities

A sponsor shall not:

1. Unduly prolong distribution of the new animal drug for investigational use (21 CFR 511.1(b)(8)(iii)).

2. Represent the new animal drug as being safe or effective for the purposes for which it is being investigated (21 CFR 511.1(b)(8)(iv)). (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 (21 CFR 511.1(b)(8)(v)).

E. Contract Research Organizations

A sponsor may transfer any or all of its obligations to a contract research organization (CRO) (21 CFR 511.1(f)(2)). 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) (21 CFR 511.1(f)(1) and 21 CFR 510.3(e)).

If a sponsor transfers any investigational responsibilities to a CRO, the sponsor must notify CVM of such transfer in writing (21 CFR 511.1(f)(2)). The sponsor may include this information in an NCIE if known at the time an NCIE is submitted. Alternatively, the sponsor may provide this information in a G submission to the INAD. The sponsor should describe each of the obligations being assumed by the CRO. Any obligation not included in the written description shall be considered not to have been transferred.

A CRO that assumes any obligation(s) of a sponsor shall comply with the specific regulations applicable to the obligation(s) assumed (21 CFR 511.1(f)(3)).

VI. 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 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 514 – New Animal Drug Applications

§ 514.80, Records and reports concerning experience with approved new animal drugs

Part 558 – New Animal Drugs for Use in Animal Feeds

CVM Program Policy and Procedures Manual – ONADE Reviewer's Chapter

1243.3010 – Format and Style Conventions for Letters

1243.4040 – Investigational Food-Use Authorizations: The Role of the Target Animal Division Reviewer

1243.4066 – Notice of Claimed Investigational Exemption (NCIE)

VII. 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.

July 1, 2014 – Revised to further clarify the two types of exemptions and what studies are in category.

July 11, 2017 – Revised to further define the process and reformatted to current format.

August 1, 2018 – Revised to remove references to a Guidance for Industry #58 that is no longer in use. It was removed from section V. A. 2. and from the list of references.

June 2, 2021 – Quality system review was completed, and no substantive updates were required. Minor revisions made to update titles in the reference section and some formatting updates.

February 14, 2022- Removed section about Importing Investigational Drugs and transferred that information to P&P 1243.4066 Notice of Claimed Investigational Exemption (NCIE). Updated description of 511.1(b) studies. Added information about labeling requirements for IGAs and ACTPs. Added Appendix for INAD Record Keeping Requirements.

July 14, 2022 – Quality systems review for minor formatting updates.

January 26, 2024 – Revised section V. E. to remove the language that said the sponsor must send us information on transferring responsibilities to a CRO in a G submission. It now states the sponsor can notify us they are transferring obligations to a CRO in an NCIE or G submission. Updated to put into the new P&P template. To bring all office quality system documentation into compliance with the FDA Visual Identity Program approved fonts, ONADE has adopted Arial 11-point font. The font of this document was changed from Verdana 10-point font to Arial 11-point font.

March 13, 2024 – Revised section II. Moved the information that 21 CFR Part 511 does not apply to shipments of bulk substance for use in the manufacture of new animal drug for investigational use and information on the labeling statement such a shipment must bear to a footnote. Also, reorganized some of the information in section II.

APPENDIX 1. INAD RECORD KEEPING REQUIREMENTS

INAD record type	Sponsor	Facilities/Investigators
Other INAD documents not associated with a GCP or GLP study. For example: - Pilot studies - FUA and Cat Ex submissions and letters (current and superseded) - Archived data from when a sponsor took over an INAD from another organization - Other CVM correspondence (e.g., G, Z, Q, H submissions, emails with CVM*) *Depending on the nature of the specific correspondence, some routine correspondence with CVM may not fall under the record retention periods. However, sponsors may wish to retain all correspondence with CVM about the INAD, to ensure the file is complete.	21 CFR 511.1(b)(8)(i) applies: records should be kept for 2 years after either an NADA application is approved or after investigations have conclusively ended for the drug project. Note: - For inactive INADs that may be reactivated in the future, records must be maintained until 2 years after the date that an NADA has been approved or investigations have conclusively ended for the drug project. - For INADs where an approval for one indication has occurred but investigation continues on other indications: o Records associated with the approved indication must be kept for 2 years after the approval of that indication. o Records associated with the indications still under investigation must be kept for 2 years after investigations have conclusively ended for that indication or 2 years after approval of that indication.	21 CFR 511.1(b)(7)(ii) applies: records should be kept for 2 years after either an NADA is approved or after investigation stops. The research facility can send the raw data to the sponsor after the study concludes, as long as the research facility (or a third party) retains a copy that can be referenced/used during any inspections. This transfer of data to the sponsor can occur prior to submission to CVM. The research facility cannot release all control of the data to the sponsor until the drug is approved. Raw data cannot be transferred to the sponsor for copying then returned to the research facility – this would be releasing control of the data. If a study being conducted is terminated before concluding then the records, or copies of the records, need to be kept either at the research facility or third party for 2 years past the termination of the study. The incomplete raw data can be sent to the sponsor as noted above.

INAD record type	Sponsor	Facilities/Investigators
GCP Final Study Reports, Study data and other records	21 CFR 514.80(e) applies: keep study records for 5 years after date of submission Note: If the NADA is not approved and/or investigations are ongoing for more than 5 years after the study conclusion, then these records should be kept per 21 CFR 511(b)(8)(i) for 2 years after either an NADA application is approved or investigations have conclusively ended for the drug project.	Same as above
GLP Final Study Reports, Study data and other records	21 CFR 58.195 applies: either the test facility or the sponsor should keep study records for at least 5 years after the date the study is submitted to the FDA. Note: If the NADA is not approved and/or investigations are ongoing for more than 5 years after the study conclusion, then these records should be kept per 21 CFR 511(b)(8)(i) for 2 years after either an NADA application is approved or investigations have conclusively ended for the drug project.	Same as above
Records related to shipments of the investigational new animal drug. For example: - drug shipments - import notices	21 CFR 511.1(b)(3) applies- records should be kept for 2 years after shipment and delivery	21 CFR 511.1(b)(3) applies: records should be kept for 2 years after shipment and delivery