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OFFICE OF NEW ANIMAL DRUG EVALUATION REVIEWER'S CHAPTER

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**REQUIREMENTS FOR INVESTIGATIONAL NEW ANIMAL DRUG EXEMPTIONS**

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**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 an investigational new animal drug (INAD) file or generic investigational new animal drug (JINAD) file are separate from the requirements for sponsors seeking an investigational exemption. The investigational exemption legally allows people to ship investigational new animal drugs in interstate commerce for investigational use.

**II. WHAT IS AN INVESTIGATIONAL NEW ANIMAL DRUG EXEMPTION?**

Statutory authority to exempt 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 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.

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.

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, consult your team leader and the ONADE Policy Team.

### **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 do not have to submit a notice to us before shipping such drugs in interstate commerce.<sup>1</sup>

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:<sup>2</sup>

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

- 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:<sup>3</sup>

**CAUTION<sup>4</sup>: 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.<sup>5</sup>

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<sup>1</sup> 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).

<sup>2</sup> 21 CFR 511.1(a)(1)

<sup>3</sup> 21 CFR 201.122(b)

<sup>4</sup> This is a labeling statement for a drug substance, and is included for informational purposes only.

<sup>5</sup> 21 CFR 511.1(a)(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.<sup>6</sup>

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 act.<sup>7</sup>

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 Section II for a general description of 511.1(a) and 511.1(b) studies. See P&P 1243.4066 for a description of an NCIE shipment notice and its contents.

#### IV. EXEMPTION REQUIREMENTS FOR INADS FOR CLINICAL INVESTIGATIONS

For investigational 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 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 act, an NCIE must be submitted to the (J)INAD before each shipment of investigational new animal drug.<sup>8</sup> The NCIE must be signed by the sponsor or by an agent acting on behalf of the sponsor.<sup>9</sup> Sometimes a sponsor will ask to establish a (J)INAD file for their investigational new animal drug without including an NCIE with the submission, however, the exemption is not in effect until an NCIE is submitted<sup>10</sup> and the requirements below are met:

1. The label of the new animal drug must bear the statements:<sup>11</sup>

**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:<sup>12</sup>

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<sup>6</sup> 21 CFR 511.1(a)(3)

<sup>7</sup> 21 CFR 511.1(a)(4)

<sup>8</sup> See P&P 1243.4066 Notice of Claimed Investigational Exemption (NCIE)

<sup>9</sup> 21 CFR 511.1(b)

<sup>10</sup> 21 CFR 511.1(b)(4)

<sup>11</sup> 21 CFR 511.1(b)(1)

<sup>12</sup> 21 CFR 201.122(b)

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**CAUTION<sup>13</sup>: 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.<sup>14</sup>
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.<sup>15</sup>
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.<sup>16</sup>

**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.<sup>17</sup>
2. Assure that the investigation is monitored by a person qualified by scientific training and experience to evaluate information obtained from the investigation.<sup>18</sup> 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).<sup>19</sup>
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.<sup>20</sup>

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<sup>13</sup> This is a labeling statement for a drug substance, and is included for informational purposes only.

<sup>14</sup> 21 CFR 511.1(b)(1)

<sup>15</sup> 21 CFR 511.1(b)(2)

<sup>16</sup> 21 CFR 511.1(b)(3)

<sup>17</sup> 21 CFR 511.1(b)(6)

<sup>18</sup> 21 CFR 511.1(b)(8)(ii)

<sup>19</sup> 21 CFR 511.1(b)(8)(ii)

<sup>20</sup> 21 CFR 511.1(b)(10)

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## 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.<sup>21</sup>
2. Maintain the following information for at least two years:<sup>22</sup>
  - 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.<sup>23</sup>

## 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.<sup>24</sup>
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.<sup>25</sup>
  - b. Furnish adequate and timely reports of the investigation to the sponsor.<sup>26</sup>
  - 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.<sup>27</sup>

## D. Prohibited Activities

A sponsor shall not:

1. Unduly prolong distribution of the new animal drug for investigational use.<sup>28</sup>
2. Represent the new animal drug as being safe or effective for the purposes for which it is being investigated.<sup>29</sup> (This requirement is not intended to restrict the full exchange of scientific information).

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<sup>21</sup> 21 CFR 511.1(b)(8)(i)

<sup>22</sup> 21 CFR 511.1(b)(3)

<sup>23</sup> 21 CFR 511.1(b)(3) and (b)(8)(i)

<sup>24</sup> 21 CFR 511.1(b)(7)(i)

<sup>25</sup> 21 CFR 511.1(b)(7)(ii)

<sup>26</sup> 21 CFR 511.1(b)(7)(iii)

<sup>27</sup> 21 CFR 511.1(b)(7)(ii)

<sup>28</sup> 21 CFR 511.1(b)(8)(iii)

<sup>29</sup> 21 CFR 511.1(b)(8)(iv)

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.<sup>30</sup>

#### E. Contract Research Organizations

A sponsor may transfer any or all of its obligations to a CRO.<sup>31</sup> 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).<sup>32,33</sup>

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.<sup>34</sup> If all obligations are transferred, a general statement to that effect is acceptable.<sup>35</sup> Any obligation not covered by the written description shall be deemed not to have been transferred.<sup>36</sup>

A CRO that assumes any obligation(s) of a sponsor shall comply with the specific regulations applicable to the obligation(s) assumed.<sup>37</sup>

#### 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 before they ship the drug as per the requirements for clinical investigations described above.<sup>38</sup>

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. They should notify us of the import in a "G" submission under the INAD and notify us of the shipment from the entity to the scientific institution conducting the clinical investigations in an NCIE. The "G" notification of import 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;

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<sup>30</sup> 21 CFR 511.1(b)(8)(v)

<sup>31</sup> 21 CFR 511.1(f)(2)

<sup>32</sup> 21 CFR 511.1(f)(1)

<sup>33</sup> 21 CFR 510.3(e)

<sup>34</sup> 21 CFR 511.1(f)(2)

<sup>35</sup> 21 CFR 511.1(f)(2)

<sup>36</sup> 21 CFR 511.1(f)(2)

<sup>37</sup> 21 CFR 511.1(f)(3)

<sup>38</sup> See P&P 1243.4066

- 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.<sup>39</sup> If you send a letter to the sponsor, include a copy of the letter in the administrative file.

## 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 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

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<sup>39</sup> 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

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.

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.