OFFICE OF NEW ANIMAL DRUG EVALUATION REVIEWER'S CHAPTER

NOTICE OF CLAIMED INVESTIGATIONAL EXEMPTION (NCIE)

I. Purpose 1
II. What is an NCIE and for what studies are they appropriate? 1
III. How we use NCIEs 2
IV. Timing for submission of an NCIE 3
V. How do we review an NCIE? 3
VI. Final actions 4
VII. References 4
VIII. Version history 4
Appendix: Information to include in notice of claimed investigational exemption (NCIE) 6

I. PURPOSE

This document:

- Describes an NCIE
- Describes the types of studies that require sponsors to submit NCIEs
- Specifies what information should be included in the NCIE
- Identifies when we should receive an NCIE relative to the shipment of a new animal drug for investigational use
- Describes how we use the information in an NCIE
- Describes how we review an NCIE submission

II. WHAT IS AN NCIE AND FOR WHAT STUDIES ARE THEY APPROPRIATE?

An NCIE, also known as a drug shipment notice, is a written notification to FDA of a sponsor's intent to ship an investigational new animal drug (INAD), including animal feed containing or bearing a new animal drug, for use in clinical investigations intended to support approval of a new animal drug. The INAD regulations (21 CFR 511.1(b)(4) for clinical studies describe the requirements for submitting an NCIE. An NCIE is coded as a B submission in STARS (Submission Tracking and Reporting System).

We require NCIEs for clinical investigations in animals, including but not limited to studies in the target species, laboratory studies, field studies, bioequivalence studies (excluding dissolution studies) and *in vitro* studies. This requirement includes;

- the importation of investigational new animal drugs shipped directly to researchers responsible for clinical investigational use in animals[1]
- shipment from an entity receiving an import to the scientific institution conducting the clinical investigations (we should be notified of the import in an INAD "G" submission as outlined in P&P 1243.4065)
- exportation of investigational new animal drugs for use in clinical studies intended to support approval of a new animal drug in the United States
- nonclinical laboratory study(ies) under any investigational file (including generic investigational new animal drug (JINAD) file) for the purpose of evaluating safety in food-producing animals when the edible products from these animals are intended for human food or animal feed use[2]
- studies conducted in client-owned companion animals

Sponsors are not required to submit NCIEs for non-clinical studies. Sometimes we receive NCIEs for drug shipment for studies such as *in vitro* trials where animals are not used and in other non-clinical studies. See section V for information on reviewing such NCIEs. Sponsors submit NCIEs in eSubmitter, however, in rare cases, refer to the Appendix for information that should be provided by the sponsor when submitted in paper.

CVM has updated the policy on NCIEs regarding bioequivalence studies for generic new animal drug approvals. Generic sponsors will no longer be required to submit NCIEs for bioequivalence or any other studies intended to support approval. The only exception will be in instances when an investigational food-use authorization is issued to conduct tissue residue depletion studies.

III. HOW WE USE AN NCIE

The NCIE provides us with information primarily about clinical investigation studies in animals. NCIEs are used by the target animal review divisions for a variety of purposes including to:

- keep track of how much drug is shipped, where and when,
- be informed when studies start,
- initiate Bioresearch Monitoring (BIMO) requests,
- monitor whether the sponsor unduly prolongs investigation or distribution, or engages in commercial distribution, or test marketing of the investigational new animal drug
- monitor activity under the investigational exemption
- monitor investigational food-use authorizations,

[1] See 21 CFR 511.1(b)(9) and P&P 1243.4065, Requirements for Investigational New Animal Drug Exemptions
[2] In such cases, an investigational food-use authorization is required (P&P 1243.4040)

- monitor movement of investigational animals with intentional genomic alterations (IGAs) or products derived from animals with IGAs, and
- be aware of studies conducted in client-owned animals.

IV. TIMING FOR SUBMISSION OF AN NCIE

As stated in 21 CFR 511.1(b)(4), the INAD regulations require that sponsors submit the NCIE prior to shipment of the investigational new animal drug. The regulations require submission of the NCIE prior to and not concurrent with or after shipment.

V. HOW DO WE REVIEW AN NCIE?

NCIEs are submitted to CVM electronically using FDA's e-submitter tool or in rare circumstances under a cover letter in paper. An NCIE is coded as a "B" submission in STARS. Review any NCIE that you receive from the sponsor, regardless of whether it was required to be submitted.

Upon receipt of the NCIE, determine if the sponsor has submitted either a claim for a categorical exclusion or an environmental assessment for the INAD or JINAD file.[3] If the sponsor has not submitted either a CE or an EA, discuss with your team leader and/or one of the Environmental Team leaders, then the sponsor should be contacted and reminded under 21 CFR 511.1(b)(10) they must submit one of these in order to maintain an investigational new animal drug exemption.[4] Proposed boilerplate language to request a CE or EA from a sponsor for investigational use is available in P&P 1243.7220 Section III.A.2.

Check the submission and shipment dates to determine if the sponsor submitted the NCIE prior to shipment. When we find that sponsors have not submitted the required NCIEs, or if they submitted NCIEs after the initiation of investigations, inform your team leader and discuss whether to contact the sponsor to remind them of their responsibilities under the 21 CFR 511.1(b)(4) for submitting NCIEs prior to shipment of new animal drugs for investigational use. Record these communications in either the review summary field in STARS or the review documentation you prepare for the NCIE. For subsequent occurrences (either in the same (J)INAD file or across multiple (J)INAD files for that sponsor), discuss with your team leader the need to send an acknowledgment letter to the sponsor that they must submit their NCIEs prior to shipment of investigational new animal drugs.[5]

In your review of an NCIE, check for completeness and accuracy and compare it to the regulations (21 CFR 511.1(b)). Confirm that the use of the drug outlined in the NCIE is consistent with the proposed indications of use and target animals and any other limitations of the (J)INAD file. It may be appropriate to compare the NCIE with previous information and reviews in the (J)INAD file, such as:

- A-0000 submission

[3] This information may be found in different STARS submission types (e.g., A, G, O, E, etc.). Beginning in January of 2009, this would be found in X submissions.
[4] P&P 1243.4065, Requirements for Investigational New Animal Drug Exemptions
[5] See P&P 1243.4065.

- Investigational food-use authorizations
- Protocols
- Other submissions to the (J)INAD file

If you detect errors in a sponsor's NCIE (i.e., information required by 21 CFR 511.1(b)(4) is missing, or information in the NCIE contradicts information contained in the (J)INAD file), contact the sponsor to request the corrections, and record these communications in the review documentation. If necessary, request an amendment or a revised NCIE (a new B submission) to correct significant errors. For subsequent incorrect submissions (either in the same (J)INAD file or across multiple (J)INAD files for that sponsor), discuss with your team leader the need to send an acknowledgment letter to the sponsor requesting corrective action.

VI. FINAL ACTIONS

Appropriate final actions for NCIEs include:[6]

- submission filed with NO review documentation; no letter sent (FNR)
- submission filed with review documentation; no letter sent (FNR w/memo)
- submission reviewed; letter sent (acknowledgment letter)

In most instances, you may use the FNR final action for NCIEs. Use the FNR w/memo final action where your division or team procedures dictate, or to document communications between you and sponsors for correction of errors detected in NCIEs. Though used infrequently, issuing an acknowledgment letter to sponsors who repeatedly submit incorrect NCIEs may be warranted.

VII. REFERENCES

CVM Program Policies and Procedure Manual

1243.3030 – Completing Final Action Packages for Submission Tracking and Reporting System (STARS) Submissions

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

1243.4065 – Requirements for Investigational New Animal Drug Exemptions

1243.7220 – Processing Environmental Impact Submissions for New Animal Drugs

VIII. VERSION HISTORY

March 31, 2009 – Original version

[6] P&P 1243.3030, Completing Final Action Packages for STARS Submissions

April 3, 2009 – Revised to clarify that when nonclinical laboratory safety studies use food-producing animals and the sponsor intends to use the edible products for human food or animal feed a food-use authorization is required.

May 28, 2010 – The document has been rearranged and the information has been updated to reflect current ONADE processes.

October 9, 2014 – The document has been updated to reflect the electronic process.

October 5, 2016 – Updated categorical exclusion and environmental assessment information in Section V. and updated the format.

July 18, 2017 – Updated to add clarity to the process and to put document into current format.

December 20, 2018 – Updated to reflect CVM policy change on NCIEs for abbreviated (generic) new animal drugs

May 14, 2021 – Updated language to current terminology and also to reflect the electronic process

APPENDIX: INFORMATION TO INCLUDE IN NOTICE OF CLAIMED INVESTIGATIONAL EXEMPTION (NCIE)

A. Submission Information

Date:
Document Type (INAD or JINAD):
Document Number:

B. Firm Information

Are you a US company? (Yes/No)
Firm Name:
Address Line 1:
Address Line 2:
City:
State, Province, or Territory:
Post Office or Zip Code:
Country:
Telephone number:
Fax number:
D&B D-U-N-S Number:

C. U.S. Agent or U.S.-based Employee Information (to be completed if the firm is not a U.S. company)

Contact Name:
Occupation Title:
Email Address:
Firm Name:
Address Line 1:
Address Line 2:
City:
State, Province, or Territory:
Post Office or Zip Code:
Country:
Telephone number:
Fax number:
D&B D-U-N-S Number:

D. Responsible Official Information (to be completed if the firm is a U.S. company)

Contact Name:
Occupation Title:
Email Address:
Firm Name:
Address Line 1:
Address Line 2:
City:
State, Province, or Territory:
Post Office or Zip Code:
Country:
Telephone number:
Fax number:

Is this an amendment to pending information that was previously submitted to CVM?(Yes/No)
If Yes, provide the submission number and identify the amended information. If No, provide the rest of the information requested below.

E. General Information

Study/ Trial ID:
Drug Shipment Number:
Is this Notice of Claimed Investigational Exemption (NCIE) in relation to: (Shipment/Receipt)
Is this an IMPORT? (Yes/No)
Is this going directly to an investigator or institution where the research will be conducted? (Yes/No)
Type of Shipment: (Initial, Supplemental, or Corrected)
If Supplemental, Reason for Supplemental:
If Corrected, Instructions for Corrected:

F. Product Description

Does the drug product have a USP monograph? (Yes/No)
Product Established Name (list all active pharmaceutical ingredients):
Proprietary Name, if available:
Concentration/Strengths:
Proposed Indication(s) for Use:
Proposed Dose & Duration:
Dosage form:
Route of Administration:

G. Type and Number of Animals

Common Animal Name:
Production Class (if applicable):
Size and Type of Animals:
Approximate Number of Animals in this study/ trial:
Treated:
Control:
Total:

What is the maximum duration of drug treatment per animal?

What is the maximum daily dosage?

Proposed use:

H. Shipment or Receipt Information

Date of Drug Shipment or Receipt:
Total Quantity (Weight or Volume) and Concentration of Drug(s) Shipped or Received:

Type of Study/ Trial:

Is this Study or Trial intended to support a technical section or (A)NADA submission? (Yes/No)

I. Investigational Information

Investigator Name:
Occupation Title:
Email Address:
Address Line 1:
Address Line 2:
City:
State, Province, or Territory:
Post Office or Zip Code:
Country:
Telephone Number:

J. Study/Trial Information

Approximate date(s) of study/ trial:
Start:
Finish:

Was a Protocol for the study/ trial previously submitted to CVM? (Yes/No)
If Yes, provide CVM Submission Number:

Location of Study/ Trial Information:
Firm Name:
Address Line 1:

Address Line 2:
City:
State, Province, or Territory:
Post Office or Zip Code:
Country:
Telephone Number:
Fax Number:

K. Study Monitor Information

Study Monitor Name:
Occupation Title:
Email address:
Address Line 1:
Address Line 2:
City:
State, Province, or Territory:
Post Office or Zip Code:
Country:
Telephone Number:

L. CRO Information

Was a contract research organization (CRO) used? (Yes/No)
If Yes, enter CRO information below
CRO Name:
Address Line 1:
Address Line 2:
City:
State, Province, or Territory:
Post Office or Zip Code:
Country:
Telephone Number:
Fax Number:
D&B D-U-N-S Number:
Description of obligations transferred to CRO:

M. Animals Intended for Use in Food

Are animals intended for use as human food? (Yes/No)
Do you have a food use authorization? (Yes/No)
    If Yes, provide the CVM Submission Number:
Has a food use authorization request been submitted? (Yes/No)
    If Yes, provide the Correspondence Date:
NOTIFICATION WAIVER: A waiver of requirements for notification of the date and place of slaughter, following the required withdrawal period had been granted by the FDA (Yes/No)
    If Yes, provide the CVM Submission Number:

N. Investigational New Animal Drug Labeling

Please select the labeling text that will be used on your investigational new animal drug:

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

New animal drugs for clinical investigation: 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.

New animal drugs for EXPORT: Caution. Contains a new animal drug for use only in investigational clinical trials. Not for use in humans. Edible products from animals used for investigation are not to be used for food in any manner contrary to the requirements of the country in which the clinical trials are to be conducted.

O. Comments

If you have additional comments that you would like to include in this submission, please add them below.