OFFICE OF NEW ANIMAL DRUG EVALUATION REVIEWER'S CHAPTER

NOTICE OF CLAIMED INVESTIGATIONAL EXEMPTION (NCIE)

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 (i.e., effectiveness) studies intended to support substantial evidence of effectiveness, including but not limited to studies in the target species, laboratory studies, field studies, bioequivalence studies (excluding dissolution studies) and *in vitro* studies.[1] This requirement includes;

- the importation of investigational new animal drugs shipped directly to researchers responsible for clinical investigational use in animals.[2]

- exportation of investigational new animal drugs for use in clinical studies intended to support approval of a new animal drug in 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[3]

- 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. Refer to the Appendix for information that should be submitted by the sponsor in the NCIE when submitted in paper.

III. How we use NCIEs

The NCIE provides us with information primarily about studies conducted to support substantial evidence of effectiveness. 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 food use authorizations,
- monitor movement of genetically engineered animals or products derived from them, and
- be aware of studies conducted in client-owned animals.

[1] 21 CFR 514.4(a)
[2] See 21 CFR 511.1(b)(9) and P&P 1243.4065, Requirements for Investigational New Animal Drug Exemptions
[3] In such cases, a food-use authorization is required (P&P 1243.4040).

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 under a cover letter in paper. An NCIE is coded as a "B" submission in STARS. Upon receipt of the NCIE, determine if the sponsor has submitted either a claim for a categorical exclusion or an environmental assessment (X submission) for the INAD or JINAD file. If neither one is found in our STARS, contact the sponsor and remind them that under 21 CFR 511.1(b)(10) they must submit one of these in order to maintain an investigational exemption.[4] Review any NCIE that you receive from the sponsor, regardless of whether it was required to be submitted.

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, contact the sponsor via telephone or email 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 other information in the (J)INAD file, such as:

- A-0000 submission
- Food use authorizations
- Protocols

[4] P&P 1243.4065, Requirements for Investigational New Animal Drug Exemptions
[5] See P&P 1243.4065.

- Other submissions to the (J)INAD file
- Our reviews of these submissions

Apply other division or team specific procedures for review of NCIEs as required. For example, the division or team may use an NCIE as a prompt to request an inspection under our BIMO program.

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 via telephone or email to request the corrections, and record these communications in the review documentation. If necessary, request 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 Policy and Procedures Manual

1243.3030 – Completing Final Action Packages for STARS Submissions

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

1243.4065 – Requirements for Investigational New Animal Drug Exemptions

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

VIII. Version history

March 31, 2009 – Original version

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.

Appendix: Information to Include in Notice of Claimed Investigational Exemption (NCIE)

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

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:

U.S. Agent Information (to be completed if the firm is not a US 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:

Responsible Official Information (to be completed if the firm is a US 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:

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.

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:

Product Description

Established Name (list all active pharmaceutical ingredients):
Proprietary Name, if available:
Total Quantity (Weight or Volume) and Concentration of Drug(s) Shipped or Received:
Proposed Use:
Proposed Dose & Duration:
Dosage form:
Route of Administration:

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:

Shipment or Receipt Information

Date of Drug Shipment or Receipt:
Type of Study/ Trial:

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

Investigator 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:

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:

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:

CRO Information
Was a Contract Research Organization (CRO) used? (Yes/No)
    If Yes, enter CRO information below

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:
Description of obligations transferred to CRO:

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:

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.

Comments

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