NOTICE OF CLAIMED INVESTIGATIONAL EXEMPTION (NCIE)

I. PURPOSE

This document:

- Describes an NCIE
- Describes the types of studies for which we require NCIEs
- Identifies when we should receive an NCIE (21 CFR 511.1(b)(4)) relative to the shipment of a new animal drug for investigational use
- Describes the procedures to follow if an NCIE is not received at an appropriate time
- Describes how we review an NCIE submission
- Describes when and how we document our review of an NCIE, and how we address errors in an NCIE in our review documentation

II. WHAT IS AN NCIE?

An NCIE (FORM FDA 3458), also known as a drug shipment notice, is a written notification to FDA of a sponsor's intent to ship an unapproved new animal drug (including animal feed containing or bearing a new animal drug) for use in investigations intended to be conducted to support approval of new animal drugs or

animal feeds. The investigational new animal drug (INAD) regulations (21 CFR 511.1(b)(4)) describe the requirements for submitting an NCIE.

We require NCIEs for all clinical (i.e., effectiveness) studies including laboratory studies conducted to evaluate effectiveness (21 CFR 511.1(b)(4)). This includes the importation of unapproved new animal drugs directly to researchers responsible for conducting effectiveness studies.[1] It also includes exportation of unapproved new animal drugs for use in clinical investigations. In addition, we request that a sponsor submit an NCIE if they are conducting a nonclinical laboratory study(ies) for the purpose of evaluating safety in food-producing animals and they intend to use the edible products from these animals for human food or animal feed.[2]

III. WHEN SHOULD WE RECEIVE AN NCIE?

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

When we find that sponsors have not submitted 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 the review documentation. For subsequent occurrences (either in the same (J)INAD or across multiple (J)INADs for that sponsor), discuss with your team leader the need to send an acknowledgment letter to the sponsor requesting that they submit their NCIEs prior to shipment of new animal drugs.[3]

IV. HOW DO WE REVIEW AN NCIE?

Follow division/team procedures for assigning review responsibilities of an NCIE.

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[1] See 21 CFR 511.1(b)(9) and P&P 1243.4065, Requirements for Investigational New Animal Drug Exemptions

[2] In such cases, a food-use authorization is required (P&P 1243.4040).

[3] Note that if a sponsor fails to comply with the conditions for an investigational exemption under 21 CFR 511, we may terminate the exemption. See P&P 1243.4065.

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 (J)INAD. If neither one is found in 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]

Check the submission and shipment dates to determine if the sponsor submitted the NCIE prior to shipment. If the NCIE was submitted prior to shipment, use P&P 1243.3020 for reviewing the NCIE within your STARS queue.

In your review of an NCIE, check for completeness and accuracy and compare it to the regulations (21 CFR 511.1(b)).

Compare the NCIE against applicable items in the (J)INAD file for consistency with the file:

- A-0000 submission
- Food use authorizations
- Protocols
- 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 the Bioresearch Monitoring program.

V. REVIEW DOCUMENTATION AND CORRECTION OF ERRORS

Appropriate final actions for NCIEs include:[5]

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

[4] P&P 1243.4065, Requirements for Investigational New Animal Drug Exemptions
[5] P&P 1243.3030, Completing Final Action Packages for STARS Submissions

- submission reviewed; letter sent (acknowledgment letter)

In most instances, reviewers use the FNR final action for NCIEs. Reviewers use the FNR w/memo final action where division/team procedures dictate, or to document communications between CVM 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.

The first time we 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 or across multiple (J)INADs for that sponsor), discuss with your team leader the need to send an acknowledgment letter to the sponsor requesting corrective action.

VI. 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

VII. 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.