OFFICE OF NEW ANIMAL DRUG EVALUATION REVIEWER'S CHAPTER

NOTICE OF CLAIMED INVESTIGATIONAL EXEMPTION (NCIE)

I. PURPOSE

This document describes:

- an NCIE;
- the types of studies that require sponsors to submit NCIEs, and when NCIEs are not required;
- how to correct errors or omissions in an NCIE;
- when we should receive an NCIE relative to the shipment of a new animal drug;
- the notification process if a sponsor is importing a new animal drug for use in clinical studies; and
- how we review and use the information in an NCIE.

II. DEFINITION OF AN NCIE

An NCIE, also known as a drug shipment notice, is a written notification to FDA under their investigational new animal drug (INAD) file of a sponsor's intent to ship an investigational new animal drug, including animal feed containing or bearing a new animal drug, and animal biotechnology products[1] (including animals containing intentional genomic alterations (IGAs), and animal cell- and tissue-based products (ACTPs)) for use in clinical investigations intended to support approval of a new animal drug. The INAD regulations for clinical studies (21 CFR 511.1(b)) describe the information that must be submitted in an NCIE. An NCIE is coded as a B submission in the Submission Tracking and Reporting System (STARS).

[1] For additional information about reviewing shipping information for animal biotechnology products, see DABCT SOP 1243.106.001 or the appropriate DABCT Team Leader (TL).

III. STUDIES FOR WHICH AN NICE IS REQUIRED

Studies that fall under 21 CFR 511.1(b), new animal drugs for clinical investigation in animals, require the submission of an NCIE. If a study meets any criteria below, then the study is considered a clinical investigation and an NCIE is required. This requirement pertains to domestic and international shipments, including shipment from one foreign site to another, and both the importation and exportation of investigational drugs for use in clinical studies intended to support approval in the United States. This requirement also applies to shipment of approved products being used as the investigational drug.

An NCIE may be needed before the collection of real-world data or evidence from approved drugs, depending on the specific situation. Consult with ONADE's Policy Team, as needed, to address questions about NCIE requirements in these cases.

A. Animal Studies Conducted for the Effectiveness Technical Section under an INAD or in a New Animal Drug Application (NADA).[2]

NCIEs are required for effectiveness studies conducted to support dosage characterization, or to establish substantial evidence of effectiveness or reasonable expectation of effectiveness if pursuing conditional approval. These studies may include, but are not limited to:

- field studies;
- laboratory studies;
- bioequivalence studies (excluding dissolution studies); and
- *in vitro* studies.

B. Other Studies in Client-Owned Companion Animals

NCIEs are required for any study(ies) conducted in client-owned companion animals under an INAD file (e.g., pilot study in pet dogs). While pets are generally considered client-owned animals, not all client-owned animals are pets. Working and racing horses and dogs are generally considered client-owned animals. For the purpose of NCIEs, the incorporation of shelter-housed animals or purpose-bought animals into field effectiveness studies generally follow the same recommendations as client-owned animals.

C. Other Studies in Animals Whose Products Will Enter the Food Supply

NCIEs are required for all studies under any investigational file (including generic investigational new animal drug (JINAD) files) in food-producing animals when the products from these animals are intended for human food use.[3]

[2] All pivotal effectiveness studies require NCIEs. NCIEs may also be required for pilot effectiveness studies. Some pilot effectiveness studies are covered by Sections III-B, III-C and III-D of this P&P. The target animal division determines when NCIEs are needed for other pilot studies.

[3] An investigational food-use authorization must be granted before edible products from treated food-producing animals may be used as human food (21 CFR 511.1(b)(5)).

D. Other Studies Conducted with an IGA or ACTP

NCIEs are required for all shipments under an INAD of an IGA or ACTP.

IV. STUDIES AND SHIPMENTS FOR WHICH AN NICE IS NOT REQUIRED

Below are examples of when NCIEs are not required:

- approved drug used as a control in a clinical study;
- an exploratory or early effectiveness study, conducted in laboratory animals and in a laboratory setting, that is not intended to support dosage characterization or any label statement. In general, if an INAD is not established or needed to conduct the study (e.g., laboratory studies in early product development, laboratory studies where the sponsor has not determined the final molecule) and the study is not intended to support approval of a specific product (e.g., dosing, labeling, etc.), then NCIEs are not required. These studies may be considered under 21 CFR 511.1(a) - tests in vitro and in laboratory research animals;
- shipment of the investigational drug to an intermediary site, such as a Contract Research Organization (CRO) (an NCIE will be required for the shipment from the intermediary site to the site conducting the study);
- shipment of the active pharmaceutical ingredient (API) to the site where the investigational drug will be manufactured; and
- studies to support generic drugs (JINAD), with one exception. CVM has updated the policy on NCIEs regarding bioequivalence studies to support generic new animal drug approvals. Generic drug sponsors are no longer required to submit NCIEs for bioequivalence or any other studies intended to support approval, except when an investigational food-use authorization is requested, as outlined in Section III.C.

V. IMPORTING AN INVESTIGATIONAL DRUG FOR CONDUCTING CLINICAL INVESTIGATIONS

If a sponsor is importing the investigational drug directly to the site conducting the clinical investigations, they only need to submit an NCIE.

If a sponsor is importing an investigational drug to an intermediary, then 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 shipment to the site conducting the clinical investigations. A notification of import should include the following:

- name and 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;
- 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 drug (see P&P 1243.4065 for the appropriate labeling statement).

If you receive a notification of import, then review the information following the principles described in Section VIII to determine whether a response to the sponsor is needed; if not, then file the submission with no reply (FNR).

Note: If it is a drug in a bulk package intended for processing, repacking or use in the manufacture of another drug, we should NOT be receiving a notification of import OR an NCIE. Once the drug is repacked or used in the manufacture of a new animal drug that will be used in a clinical investigation, an NCIE must be provided when that investigational new animal drug is shipped to the clinical investigation location/site.

VI. 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 drug, not concurrent with or after shipment.

VII. 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 divisions for a variety of purposes, including to:

- keep track of how much drug is shipped, where, and when;
- receive timely information on when studies start;
- initiate Bioresearch Monitoring (BIMO) requests;
- monitor activity under the investigational exemption;
- monitor investigational food-use authorizations;
- know what obligations the sponsor has transferred to a CRO;
- monitor movement of investigational animals with IGAs or products derived from animals with IGAs; and
- maintain current, accurate knowledge of studies conducted in client-owned animals.

VIII. HOW WE REVIEW AN NCIE

NCIEs are submitted to CVM electronically using eSubmitter or, rarely, under a cover letter in paper. NCIEs are coded as B submissions in STARS. Review any NCIE received from the sponsor, regardless of whether it was required as described above.

Upon NCIE receipt, determine whether the sponsor has submitted either a claim for a categorical exclusion (CE) or an environmental assessment (EA) for the intended investigational use (X submission). If the sponsor has not submitted either a CE or an EA,

then discuss with your TL and/or an Environmental Team TL and contact the sponsor to remind them that, under 21 CFR 511.1(b)(10), they must submit one of these to maintain an INAD exemption (see P&P 1243.4065). Proposed boilerplate language to request a CE or EA from a sponsor for investigational use is in P&P 1243.7220, Section III.A.2.

Check the submission and shipment dates to determine whether the sponsor submitted the NCIE prior to shipment. If sponsors have not submitted the required NCIEs or if they submitted NCIEs after the initiation of investigations, then discuss with your TL whether to contact the sponsor to remind them of their responsibilities under 21 CFR 511.1(b)(4) for submitting NCIEs prior to shipment of new animal drugs for investigational use. Record any communications with the sponsor in the review summary field in STARS and/or 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 TL whether to send an acknowledgment letter to the sponsor reminding them that they must submit their NCIEs prior to shipment of investigational drug.

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;
- investigational food-use authorizations;
- protocols; or
- 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), then contact the sponsor to request corrections and record these communications in the review. Request an amendment or a revised NCIE to correct significant errors if needed (see Section X). For subsequent incorrect submissions (either in the same (J)INAD file or across multiple files for that sponsor), discuss with your TL whether to send an acknowledgment letter to the sponsor requesting corrective action.

If the NCIE included information on transferal of obligations to a CRO and you have any concerns, speak with your team leader. If necessary, contact the sponsor for clarification or to address the issue(s). It may be appropriate to document the concerns and discussions in the administrative record.[4]

IX. FINAL ACTIONS

Appropriate final actions for NCIEs include:

- submission filed with no review documentation; no letter sent (FNR);
- submission filed with review documentation; no letter sent (FNR/MEMO); and

[4] Note that transferal of obligations can also be submitted by the sponsor as a G submission. Follow the process in section VIII for discussion and documentation of any concerns.

- submission reviewed; letter sent (ACK).

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

X. CORRECTING NICE OMISSIONS AND ERRORS

If an investigational drug was shipped without an NCIE being submitted, then as soon as we or the sponsor identify the omission, the sponsor must submit an NCIE reflecting the actual shipping date.

If we or the sponsor identify an error in an NCIE currently under review, then, depending on the extent of the error, the sponsor can amend the submission or submit a new NCIE. If they submit a new NCIE, then we will void the original.

If we or the sponsor identify an error in an NCIE that has been closed out, then the sponsor must submit the correction in a new NCIE (B submission) referencing the original B submission number. In that case, the reviewer specifies in the review documentation that the NCIE is a correction of a previously completed NCIE (e.g., “This NCIE is to correct XXX of B-0028.”)

XI. REFERENCES

CVM Program Policies and Procedure Manual – ONADE Reviewer’s Chapter

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

XII. 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.

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.

February 16, 2022 – Revised structure and criteria describing when an NCIE is and is not required. Moved information for importing investigational drugs for clinical studies from P&P 1243.4065 to this P&P. Updated language for correcting NCIE errors and omissions. Removed Appendix containing outdated list of required information for NCIE submissions. Updated section on corrections to NCIEs to indicate those submissions should be B submissions.

May 25, 2022 – Revised Sections III and IV to clarify language for which studies do/do not require NCIEs, including international shipments and pilot work. Second-level headers were updated to follow the current formatting expectations of A, B, C instead of 1, 2, 3.

July 5, 2022 – Revised Sections III and IV to clarify language for which studies do/do not require NCIEs. Added information about NCIEs reviewed by DABCT. Minor formatting updates for consistency with P&P formatting.

August 4, 2022 – Clarified expectations for early studies and international shipping (Section III)

February 22, 2023 – Updated to fix heading 2 errors and updated the TOC.

January 26, 2024 – Updated to include information that sponsors sometimes include information on transferring obligations to a CRO in their NCIE to section VII. Also added information on reviewing that transfer of obligation information to section VIII and noted that the sponsor may notify us of the transfer of obligations in the NCIE or a G submission. Updated 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 V to remove the citation to 21 CFR 201.122 because it pertains to bulk drug substances intended for further processing, repacking, or use in the manufacture of another drug. Also, added a statement to the section that clarifies that for a drug in a bulk package (as described in 21 CFR 201.122) we should not receive an NCIE or an import notification.