OFFICE OF NEW ANIMAL DRUG EVALUATION REVIEWER'S CHAPTER

SUBMISSION AND REVIEW OF EARLY INFORMATION (EI) TO PRESUBMISSION CONFERENCES AND PROTOCOL REVIEW

I. PURPOSE

This document defines and describes for Office of New Animal Drug Evaluation (ONADE) reviewers:

- what is and what is not early information (EI),
- what submissions can contain EI,
- what EI submissions contain, and
- the administrative and review processes for EI.

This document applies to new animal drug review leading to a new animal drug application (NADA) or supplemental NADA and all technical sections (TSs) submitted to an investigational new animal drug (INAD) file for all NADA projects. It does not apply to generic investigational new animal drug (JINAD) files or abbreviated new animal drug applications (ANADAs). However, it does apply to supplemental applications to approved ANADAs submitted under Section 512(b)(1) of the Federal Food, Drug & Cosmetic Act [i.e., "(b)(1) supplements that require safety or effectiveness data"].

II. BACKGROUND

As part of the negotiations for the reauthorization of the Animal Drug User Fee Act (ADUFA), the CVM introduced the idea of EI as a reengineering of the review process to provide new avenues for earlier exchange of information and dialogue between CVM and drug sponsors.[1] The goal of EI is to reach agreement regarding some or all of the investigational requirements for approval at a presubmission conference (PSC), and to move to protocol submission and concurrence more efficiently. To do that, we often need additional scientific background materials in advance for our review. Early submission of

[1] ADUFA IV performance goals letter (page 8) https://www.fda.gov/media/116001/download

scientific information may also allow us to agree to a development plan that best utilizes the existing data and information and to have more direct discussions with sponsors to identify the most efficient pathway for demonstrating that a new animal drug is safe and effective.

Project managers (PMs) and team leaders (TLs) should discuss the EI process in communications with sponsors early in development. ONADE staff may discuss submission of EI with sponsors in pre-investigational new animal drug (pre-INAD) meetings, portfolio overview meetings, or any other interaction with sponsors, as appropriate.

III. WHAT IS EARLY INFORMATION?

The ADUFA performance goals letter defines EI as "data and/or information which uniquely describes the general attributes of the new animal drug (e.g., the known characteristics of the drug that can impact safety, effectiveness and/or quality)". EI is further defined in this P&P as the review of data or large amounts of information warranting a 100-day review timeframe and submitted only in an INAD A or H submission. Sponsors typically submit EI to characterize the product, support TS proposals (e.g., proposed studies, study design), and/or request feedback on whether it could satisfy TS requirements. To be considered EI, the information is generally submitted sometime before the first PSC or the relevant TS-specific PSCs for that project (see Section VI for more information on the content of EI submissions). Examples of data and/or information that might be submitted as EI include:

- information proposed to fully or partially complete a TS (see section VI.C);
- information to support use of non-U.S. study sites or use of existing data from a foreign approval;
- information regarding validation of a proposed induced infection or laboratory model study;
- information on pharmacology/toxicology ("the pharm/tox package") prior to our review of the target animal safety protocols (see Guidance for Industry #185);
- information to support the use of innovative study designs (e.g., adaptive design, biomarkers, novel variables, animal model studies, custom-designed studies);
- information to support aspects of a protocol (e.g., specific numbers or populations of animals, specific endpoints or primary variable criteria); and
- information to explain what led the sponsor to make the decision to seek approval; for example, pilot laboratory or field studies that led them to the initial conclusions on the safety and effectiveness profile of the drug, in the context of their development plan.

IV. WHAT IS NOT EARLY INFORMATION?

EI is one of several pathways available for sponsors to interact with and get feedback from CVM early in drug development. While the pathways described below take place early in drug development, they are not EI, and they fall outside the scope of this P&P.

1. Pre-INAD: Sponsors may have relevant information to discuss with CVM prior to opening an INAD. Meetings held under a General Correspondence file (GC Meeting) are intended to be high-level and targeted toward specific questions (see Office Policy: Meetings with Outside Stakeholders under GC Files.

2. Other ONADE Meetings (OO) under the INAD (Z): Sponsors may want to discuss certain aspects of drug development with CVM after they've opened the INAD, but before they are ready for the PSC (see P&P 1243.3024).

3. Pre-investigational development (PID): As part of the Veterinary Innovation Program (VIP), qualifying sponsors may work with CVM prior to determining the precise product and indication that will be the subject of the NADA (see SOP 1243.106.013).

If you have questions about the most appropriate pathway for early interactions with a sponsor, contact the PM. EI and the other forms of early interaction listed above are not mutually exclusive. The recommended pathway for a specific project may take advantage of all these tools, depending on where the sponsor is in development, what feedback they want from CVM before the PSC and the type and amount of data and/or information needed for CVM to provide that feedback.

V. WHAT SUBMISSION TYPES CAN CONTAIN EARLY INFORMATION?

Submission types we receive that may contain EI are the following:

1. submission to open an investigational file (i.e., INAD A-0000 submission); and

2. the INAD H (either OT or MS or OT sub class codes) submission.[2]

Sponsors sometimes include EI in a meeting request (Z submission) rather than an A 0000 or H followed by a meeting request. If any review team member identifies that a sponsor included EI in a meeting request, the primary reviewer (PR) assigned to that meeting request asks the sponsor to submit the EI in an H submission (MS subclass code) and resubmit the meeting request, with the EI removed, in a new Z submission. The PR voids the initial Z submission containing the EI.

VI. WHAT WILL THE SUBMISSION CONTAIN?

As described in Section III, there are multiple reasons a sponsor might submit EI, so the contents of the EI submission will vary depending on the sponsor's goals and expectations, as well as the stage of development of their proposed drug. As such, there is no standard format for an EI submission. The critical factor that defines what an EI submission contains is the sponsor's specific reason for submitting it. However, the EI submission should generally include:

- the sponsor's goals for submitting the EI and their expectations for the outcome of CVM's review;

- a brief summary of the submission (if appropriate);

- a table of contents (if appropriate);

[2] See P&P 1243.4092 H Submission Preceding a Meeting or Protocol for more information on this type of H submission.

- questions or specific issues the sponsor wants CVM to address, with supporting scientific information (e.g., references to pages or articles in their submission to inform those questions or issues, as appropriate); and

- well-organized data or information relevant to the goals of the submission.

When looking at the submission, the sponsor should have tied together all of the information in the EI submission in a thorough, cohesive manner with overarching conclusions that explain how the EI impacts their future development objectives. The EI submission should not simply be a compilation of available information or a list of references. The sponsor should explain why they are submitting the EI and how the information provided relates to or supports that purpose. See section VIII.A for how to work with the sponsor if this information is not clearly presented in the submission. Although CVM understands that not all of the specific details for a future development plan is available in these early stages, identification of issues, background and targeted product characteristics as early as possible helps CVM understand the scope of the project and the questions/issues raised in the EI submission.

If the EI submission includes information obtained from published literature, the sponsor should submit the entire article(s), translated into English as needed. The sponsor should include their rationale for including the articles and explain how the articles support their conclusions or development plan proposals. It is not sufficient to simply include articles and let CVM interpret their relevance for the proposed development plan. If the EI submission includes studies conducted by or on behalf of the sponsor, the sponsor should include the final study report(s) with tables and figures and typically should not contain raw data unless requested by CVM.

Below are examples of information that we can encourage sponsors provide as EI if we think it could facilitate the review and approval process if submitted in early stages. (Note: this is not a checklist but can serve as examples of the types of information that, if available, could facilitate the goals of EI):

A. Drug and Product Characteristics

Drug class and basic mechanism of action; established name and physico-chemical properties of the active pharmaceutical ingredient(s) (e.g., solubility, chemical structure, octanol-water partition coefficient, adsorption/mobility, etc.); potential excipients and their purpose in the formulation, dosage form and type of formulation (e.g., immediate vs. modified release); intended packaging (e.g., single- or multi-dose). Identifying if the product is a nanomaterial and/or will it be produced by recombinant DNA technology (e.g., by genetically engineered microorganisms)? Understanding physico-chemical properties of a drug is useful for preparing for discussions on formulation and environmental issues and for early prediction of the in vivo drug performance.

B. Intended Conditions of Use

Indication, route of administration, dose, frequency, duration, target animal species, and class. Examples of important points for CVM to consider: does the indication reflect the clinical scenario; can the proposed indication be diagnosed, and treatment outcome be evaluated under actual conditions in the hands of the end user?

Understanding the proposed indication and conditions of use is critical for CVM to agree on a product development plan.

C. Information Proposed to Fully or Partially Complete a Technical Section (e.g., Existing Drug Approvals and Investigational Uses (United States (U.S.) or Foreign)

Is the drug already approved or under investigation (within or outside the U.S.) as an animal drug, human drug, food additive, etc.? If it is approved for animals, is it the same indication and dosage regimen? Is there a concurrent project in progress or planned elsewhere (i.e., is this intended to be a global approval, and if so, will the development plan/study designs be similar)? Sponsors may be motivated to pursue a particular approval because they plan to leverage existing data or information. Providing this as EI before the PSC allows CVM to discuss the proposed development plan fully, including options for addressing any gaps identified. While CVM cannot make a determination if existing data satisfies TS requirements under EI, if the sponsor submits sufficient information about the existing data early, we can work with them to identify gaps or provide other feedback to help them hone their development plan.

EI about plans for global development can facilitate coordination between CVM and foreign regulatory agencies and provide an opportunity to discuss if existing data can be used to support or partially support FDA approval. For additional information on the use of foreign data, see P&P 1243.4068.

D. Pharmacokinetic (PK) Data

Basic PK characteristics (e.g., absorption, distribution, metabolism, excretion), pharmacodynamic characteristics, fed/fasted information, etc. (see SOP 1243.166.001). Summary PK data (tables or plots) should include individual values rather than means because the studies typically have only a few animals. The sponsor should state if they want CVM to verify their PK analysis (e.g., fed/fasted data) and include the following data in the submission:

- individual animal data in XML format with columns for the animal ID, dose, sex, time of sample collection, prandial state (if applicable), and drug concentrations;
- analytical method report; and
- 10-20% representative chromatograms.

E. Effectiveness Data

Pilot or proof-of-concept work to suggest the product will have the desired effect in the target animal.

F. Safety Characteristics

Any known safety issues for animals, users, or human food (known toxicity, risks, antimicrobial activity); summary of pharmacovigilance data, reported adverse drug events (ADEs) (if available); any concerns with excipients, etc.

G. Environmental Profile

Known data, information, or characteristics related to environmental effects/toxicity to aquatic and terrestrial organisms, environmental fate (e.g., degradation/persistence, excretion/metabolism, etc.). If known, indicate intent to prepare an environmental assessment (EA) or claim a categorical exclusion (CE) from the requirement to prepare an EA for the NADA.

VII. ADMINISTRATIVE PROCESSES FOR EARLY INFORMATION

A submission identified by the sponsor in eSubmitter as containing EI is assigned to a PR in the appropriate division or team based on the intended purpose and content using current processes.

For example:

- a general overview of the drug is assigned to the appropriate target animal division (TAD); or
- TS-specific information is assigned to the division responsible for that TS.

The PR works with their TL to verify if the submission is EI. If the primary review division does not believe a submission identified by the sponsor as EI is actually EI, the review division first contacts the appropriate PM for that sponsor to determine if the PM had any communication with the sponsor about this submission. The review division contacts the sponsor to discuss the submission and determine the appropriate next step to facilitate an efficient review.

When it is determined the submission is EI, the PR sends any appropriate consults (per P&P 1243.3200) based on the content of the submission. Due to a lack of established guidance for the development of novel drugs and indications or use of novel study design and approaches, we expect many EI submissions to involve science/policy issues that may benefit from specialized areas of expertise. PRs are encouraged to contact the ONADE Science Policy TL and the ONADE Policy TL on submissions that may represent these areas of drug development. The project team is made up of reviewers (and their TLs) who receive consults, the PM, and other experts involved in the discussions.

Based on the complexity of the issues in the EI and the number of consulting reviewers involved, one or more internal meetings may be appropriate to coordinate EI review. Any project team member can suggest an internal meeting to discuss the EI if it will facilitate review. Then, the PR sets up a meeting, as needed, with the timing defined by the complexity of the issues to be discussed.

VIII. REVIEW PROCESSES FOR EARLY INFORMATION

A. Review Principles

The key to reaching successful outcomes is flexibility in communication between CVM and the sponsor during the review timeframe. The specific information needed depends on the submission goals and sponsors generate this information in different ways and at different times, so reviewers need to be flexible and strive toward open communication with the sponsor. Ultimately, the goal of EI review is to allow us to make informed decisions to help guide sponsors in their drug development.

Because work done by sponsors early in development may not meet rigorous scientific standards, the information submitted may not be as thorough or complete as information submitted to a TS (P submission). EI may provide partial information or information that suggests or proposes a direction to take. Rely on your scientific expertise, knowledge of the regulatory requirements, and the context from the sponsor explaining why they submitted the EI to answer questions and provide direction.

While binding agreements are not made in a review prepared for an A or H submission, EI submission information may provide the background that enables us to make binding agreements in a PSC that takes place after review of the EI submission. We can also use EI to facilitate reaching protocol concurrence if a sponsor submits EI to, for example, support study design elements early in protocol development.

When looking at the EI submission, reviewers should consider:

- the information broadly rather than focusing on specific details that may have low impact/risk on the overall objective;
- any information already known about the proposed drug;
- whether the provided information/approach has the potential to satisfy part or all the approval requirements for particular TSs; and
- how early studies can be used to identify gaps the sponsor will need to address in the development plan.

Upon receipt, reviewers assess the submission organization, content, and purpose.

- Is the submission intended to seek CVM's input on the sponsor's development plan? Or is the goal of the submission to seek CVM's input on a specific question or questions?
- If the intent of the EI submission is not clearly identified, the submission is poorly organized, or the submission does not contain the sponsor's interpretation of submitted information, the PR contacts the sponsor to discuss the expectations for review of the information. Depending on the issue and the review stage, potential options are to request an amendment, document the conversation with the sponsor, or review the information commensurate with the submission quality.
- Because EI is intended to help decrease the time to approval, the PR works with the sponsor to determine the best path forward in keeping with this principle (e.g., amending the submission to provide clarifying information). Note: per P&P 1243.2050, we cannot refuse to review the original submission to the INAD, e.g., the A-0000 submission.
- The project team meets to discuss the EI, as needed. It is important that all reviewers have a common understanding of the review context and that all reviewers work together to ensure a coordinated approach. The PR ensures that the review is guided by the goal or questions stated in the EI submission.

- The review period is an opportunity to interact with the sponsor with the goal of getting issues addressed in real time rather than in the time period between the PSC and protocol submissions. These interactions may include discussions on issues uncovered during review of the EI that can be resolved before the PSC. Open communication during the EI review will keep the project moving forward.

- If additional relevant information becomes available during the review of the EI submission (e.g., results from recently completed pilot studies, foreign ADEs), the sponsor and the reviewer discuss whether this updated information could be submitted as a minor amendment to the current submission (per 1243.3026). Also consider if an informal conversation with the sponsor is appropriate. Reviewers document informal conversations in their reviews. Obtaining the most current information may be particularly useful before having a PSC to facilitate a successful meeting. This process is not intended to have sponsors submit significant amounts of new information as a minor amendment.

Any information reviewed in the context of EI may later be determined to be pivotal in support of a TS. For example, CVM may determine that the EI fills a gap or can address a question that turns up during development. At that time, CVM may request the EI be resubmitted under the TS with the appropriate raw data. Studies that inform the design of pivotal studies do not need to be resubmitted in the P submission and if they are submitted and reviewed in the EI submission (e.g., fed/fasted PK studies, dose finding, and preliminary safety studies).

B. Review Documentation

The EI review:

- is prepared in accordance with the P&P on reviews and submission summaries (per P&P 1243.3009);

- utilizes the ONADE review template;

- provides a brief and succinct summary of the submission purpose and contents and any specific sponsor requests or questions. The information should not be described in detail, nor should large sections of the submission be copied verbatim from the sponsor's submission;

- answers questions posed by the sponsor, if any, and describe any early insight from CVM on the information submitted;

- discusses important findings that contributed to answering the sponsor's questions or to the reviewer's recommendations for the development plan;

- summarizes discussions with the sponsor and any internal meetings; and

- summarizes key points that may impact protocol design or the TS requirements, including but not limited to:

    - potential gaps in the development plan;

    - potential roadblocks, questions, and other issues the sponsor can address prior to or at the PSC;

- the need for additional information to address the sponsor's questions (note: where possible, this information is discussed with the sponsor during the review and requested as minor amendments, as needed);
- study reports submitted as EI that may also need to be submitted as pivotal in the eventual TS submission.
    - E.g., if a sponsor wants feedback on whether foreign studies may satisfy approval requirements for a TS, we can provide feedback and recommendations from our review of the final study report(s), protocol(s) or study summary(ies) submitted with EI. However, before we could accept that data as pivotal, it would have to resubmitted with the appropriate raw data in the TS.

IX. FINAL ACTION

All available final action codes for A and H submissions are acceptable to use for A and H submissions that contain EI. The PR selects the most appropriate final action code for the submission based on the nature of the EI submission and the shared expectations of the sponsor and the project team.

Formal regulatory agreements on the number or types of studies required for approval are made only in a PSC, so use the following boilerplate language in any correspondence where the development plan is discussed outside of a PSC.

"The comments in this letter reflect CVM's current thinking based on the information you provided as early information. These points are non-binding to both you and CVM. An official memorandum of conference and binding agreements on the development plan are issued only during a formal presubmission conference."

When closing out an EI submission, the reviewer notes in the STARS Review Summary field that the submission contained EI. This makes it easier for future reviewers to identify the EI submission(s). For additional on closing out submission, refer to P&P 1243.3030. The following final actions are expected to be the most commonly used for the specific submission types used for EI.

A. INAD A-0000 Submission

Send an Opening an INAD (A-0000) acknowledgement letter. Transmit written responses to the specific questions asked by sponsors, if any, and provide recommendations to the sponsor based on our review of the EI included in the submission. For information on opening an INAD, see P&P 1243.4000.

B. INAD H Submissions

Send an acknowledgement letter. Transmit written responses to the specific questions asked by sponsors, if any, and provide recommendations to the sponsor based on our review of the EI in the submission.

A sponsor may request that a meeting (Z submission) be held after submission of the A-0000 or H submission to either discuss the EI submission or discuss aspects of the development plan that rely on the EI. In these situations, consider if it will be more

efficient to share feedback on our review of the EI in the meeting instead of in the A-0000 or H submission letter. In these cases:

- if the EI was submitted in the A-0000, send the standard Opening an INAD acknowledgement letter and inform the sponsor that feedback on the EI will be provided at the meeting and in the memorandum of conference (MOC) per P&P 1243.3025; or

- if the EI was submitted in an H submission, use the final action "File No Reply with a memo (FNR with memo)". Because no letter will be sent to the sponsor for the submission, inform the sponsor by phone or email that CVM feedback will be provided at the meeting and in the MOC.

X. PROCESSES AVAILABLE TO SPONSORS BASED ON THE SUBMISSION OF EARLY INFORMATION

If a sponsor utilizes the processes defined in this P&P and has submitted an A or H submission that included EI, CVM allows for the following benefits to occur with their protocol (E) submissions. Search the STARS Review Summary field to see if EI has been submitted for the INAD. Refer to P&P 1243.4060 for details on protocol review.

A. Protocols with Short Justifications

Sponsors can include short justifications that are limited in scope [e.g., no more than ten pages or no more than two (peer-reviewed) journal articles] in INAD E protocol submissions. The examples defining "limited in scope" were included in the ADUFA goals letter to give general guidance to sponsors on the amount of information that we would normally expect to see in a protocol submission.

The PR, in consultation with the TL, determines if the short justifications submitted with the protocol are consistent with this guidance. If the information submitted in the protocol is not appropriate for this pathway, the PR works with the sponsor to correctly submit the justification information in an H submission (see below).

B. Concurrent Submissions of Supporting Data and Protocols

Sponsors can submit a protocol E submission while an H submission with supporting data is under review as long as the protocol is submitted after the H has been in the review queue for at least 50 days. If the sponsor submits the protocol before the H submission has been in the review queue for 50 days, the PR contacts the sponsor and works with them to void the protocol submission and resubmit it at the appropriate time. For projects where the sponsor has not submitted EI, reviewers follow current policy that allows discretion on the timing of H submissions containing data or information to support a study protocol.

XI. REFERENCES

Guidance for Industry (GFI)

GFI #185, Target Animal Safety for Veterinary Pharmaceutical Products

CVM Program Policies and Procedure (P&P) Manual- ONADE Reviewer's Chapter

1243.2050 – Refuse to File and Refuse to Review

1243.3009 – Format and Style Conventions for Reviews and Submission Summaries

1243.3024 – Scheduling and Holding Meetings with Outside Parties

1243.3025 – Preparing Meeting Documentation (i.e., Memorandum of Conference, Acknowledgement Letter, Other Review Documentation)

1243.3026 – Assessing Submission Quality and Amending and Resetting the Clock on Submissions

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

1243.3200 - Routing a Request to Obtain a Consulting Review of a Submission Tracking and Reporting System (STARS) Submission

1243.4000 – Processing a Request to Open an Investigational (INAD) or Generic Investigational New Animal Drug (JINAD) File

1243.4060 – Review of Protocols

1243.4068 – Acceptability of Submissions Containing Foreign Data to Support Safety and Effectiveness

1243.4092 – H Submissions Preceding Meetings or Protocols

XII. VERSION HISTORY

April 1, 2014 – Original version

May 12, 2015- Revised to remove links to internal ONADE reference documents, reflect new roles for the pharmacology team leader, remove option to send EI in an email under the GC, and other minor wording change to add clarity to the process.

September 1, 2015 – Removed footnote that said, “If a submission appears to contain EI but the sponsor has not identified it as EI, CVM should review it as EI. CVM should also contact the sponsor to discuss the EI purpose and process.”

August 25, 2016 – Updated headings on all pages after page 1 and reformatted to current format.

August 15, 2018 – Revised to correct typographical errors and place in current format.

July 22, 2019 – Updated FDA.gov URL links to new directed links due to migration of new FDA.gov Website. No other updates needed

April 20, 2020 – Revised to eliminate the EI email notification, the General Correspondence file and Z submission type as options for submission of EI. Eliminated review times for EI of less than 100 days. Added additional information sponsors should submit with PK EI. Clarified that formal agreements can be made in PSC meetings that follow an EI submission.

June 22, 2020 – Updated to fix the heading on the second page to include the P&P number.

February 8, 2021 – Updated to describe how we will handle meeting requests containing EI, to remove the requirement that meetings are scheduled to take place at least 100 days after submission of EI, to add details about why a sponsor would be motivated to submit EI, to provide additional explanation of the “context” required to be provided in EI submissions, and to specifically address that EI may be submitted to support proposals that existing data or information fully or partially satisfies technical section requirements.

July 25, 2022 – Quality systems review for minor formatting updates.

September 29, 2023 – Revisions were made to include information about the new H submissions that may be received (i.e., those the precede a meeting or protocol) and reference the new P&P 1243.4092 that discusses that submission type. The format was updated to reflect the current office format.