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



## I. PURPOSE

The purpose of this policy and procedure (P&P) document is to explain:

- What is early information (EI);
- What is not EI;
- What submissions can contain EI;
- What EI submissions will contain;
- Administrative processes for EI; and,
- Review process for EI.

This document applies to new animal drug review leading to a new animal drug application (NADA) or a supplemental NADA; and all technical sections submitted to an investigational new animal drug (INAD) file for all NADA projects.

This document does not apply to generic investigational new animal drug (JINAD) file submissions or abbreviated new animal drug applications (ANADA). However, it does apply to supplemental applications to approved ANADAs submitted under Section 512 (b)(1) of the Federal Food, Drug & Cosmetic Act (FD&C 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 Center for Veterinary Medicine (CVM) introduced the idea of EI as a re-

engineering 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 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.

The procedures outlined in this P&P do not require sponsors to submit EI, conduct specific studies, or submit specific information prior to the PSC other than what is required in 21 CFR 514.5(b).[2] To meet the goals of the EI process, we would like the sponsor to share with CVM the information they already have that informed their decisions in early drug development. Critical to this process is an open dialogue between the sponsor and CVM to discuss issues and work through questions with the goal of finding solutions and reaching agreement at the eventual PSC.

Project managers (PMs) and team leaders should discuss the EI process in communications with sponsors early in development. Office of New Animal Drug Evaluation (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 will typically submit EI to characterize the product, to support technical section proposals (e.g. proposed studies or study design), and/or to request feedback on whether it could satisfy technical section requirements. To be considered EI, the information would generally be submitted sometime before the first PSC or the relevant technical section-specific PSCs for that project. More information on the content of EI submissions is provided in Section VI. of this document.

The following are some examples of data and/or information that might be submitted as EI:

- Information proposed to fully or partially complete a technical section (see Section VI.C below);
- Information to support use of non-U.S. study sites or use of existing data from a foreign approval;

[1] ADUFA IV performance goals letter (page 8) https://www.fda.gov/media/116001/download
[2] See P&P 1243.3024 Scheduling Meetings

- 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;[3]
- 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);
- Information to explain what led the sponsor to make the decision to seek approval, including information such as 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 they want to discuss with CVM before opening an INAD. Meetings held under a General Correspondence file (GC Meeting) are intended to be high-level and targeted toward specific questions[4].
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 presubmission conference.[5]
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.[6]

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 CAN CONTAIN EARLY INFORMATION?

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

[3] See Guidance for Industry #185, Target Animal Safety for Veterinary Pharmaceutical Products https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cvm-gfi-185-vich-gl43-target-animal-safety-veterinary-pharmaceutical-products
[4] see Office Policy: Meetings with Outside Stakeholders under General Correspondence (GC) Files
[5] See P&P 1243.3024 Scheduling Meetings
[6] https://www.fda.gov/animal-veterinary/animals-intentional-genomic-alterations/vip-veterinary-innovation-program

1. The submission that opens an investigational file (i.e., INAD A-0000 submission)

2. INAD H submission

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

## VI. WHAT WILL THE SUBMISSION CONTAIN?

As described above in Section III, there are many different 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. And so, there is no standard format for an EI submission. The critical factor that will define 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)
- questions or specific issues the sponsor wants CVM to address, with supporting scientific information such as references to pages or articles in their submission to inform those questions or issues, as appropriate.
- well-organized data and/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 (Review Principles) 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 will be 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 the U.S. or outside 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 will allow 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 technical section 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.[7]

Summary pharmacokinetic (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 should 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
- 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 animal safety, user safety, or human food safety issues (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 from the requirement to prepare an EA for the NADA.

## VII. ADMINISTRATIVE PROCESSES FOR EARLY INFORMATION

### A. The General Process

[7] See SOP 1243.166.001, Clinical Pharmacology Team (HFV-166) Involvement and Communications during the Project Lifecycle

A submission identified by the sponsor in eSubmitter as containing EI is assigned to a primary reviewer (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)
- Information specific to a technical section is assigned to the division responsible for that technical section

The PR works with their team leader (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 should first contact the appropriate PM for that sponsor to determine if the PM had any communication with the sponsor about this submission. The review division will contact the sponsor to discuss the submission and determine the appropriate next step that facilitates an efficient review.

When it is determined the submission is EI, the PR sends consults,[8] as appropriate, based on the content of the submission. Due to a lack of established guidance for development of novel drugs and indications or use of novel study design and approaches, we expect many EI submissions will 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 reviewers (and their TLs) who receive consults, the PM and other experts involved in the discussions make up the project team.

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 review of the EI. Any member of the project team can suggest an internal meeting to discuss the EI if it will facilitate review. A meeting will be set up by the PR, 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. Because the specific information needed depends on the submission goals and because sponsors generate this information in different ways and at different times, reviewers need to be flexible and strive toward open communication with the sponsor. Ultimately, the goal of the 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 technical section (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,

[8] See P&P 1243.3200, Routing a Request to Obtain a Consulting Review of a STARS Submission

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, information in the EI submission 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 technical sections
- How early studies can be used to identify gaps the sponsor will need to address in the development plan.

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

- 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, or the submission is poorly organized or does not contain the sponsor's interpretation of submitted information, the PR should contact the sponsor to discuss the expectations for review of the information. Depending on the issue and the review stage, potential options would be to request an amendment, document the conversation with the sponsor, or review the information commensurate with the quality of the submission.
- Because EI is intended to help decrease the time to approval, the PR should work with the sponsor to determine the best path forward in keeping with this principle (e.g., amending the submission to provide clarifying information). Note: we cannot refuse to review[9] the original submission to the INAD, e.g., the A-0000 submission.
- The project team should meet to discuss the EI, as needed. It is important that all reviewers have a common understanding of the context of the review and that all reviewers are working together to ensure a coordinated approach. The PR should ensure 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

[9] See P&P 1243.2050 for information on the Refuse to Review process

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 should discuss whether this updated information could be submitted as a minor amendment[10] to the current submission. Also consider if an informal conversation with the sponsor would be appropriate. Reviewers should document any informal conversations in their reviews. Obtaining updated information may be particularly useful before having a PSC because knowing the most current information will facilitate a successful meeting. This process is not intended to have sponsors submit significant amounts of new information as a minor amendment.

Any of the information reviewed in the context of EI may later be determined to be pivotal in support of a technical section. 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 technical section 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 should:

- Be prepared in accordance with the P&P on reviews and submission summaries.[11]
- Utilize the ONADE Review Template.
- Provide a brief and succinct summary of the purpose of the submission, what was included in the submission and specific requests or questions from the sponsor. The information should not be described in detail, nor should large sections of the submission be copied verbatim from the sponsor's submission.
- Answer questions posed by the sponsor, if any, and describe any early insight from CVM on the information submitted.
- Discuss important findings that contributed to answering the sponsor's questions or to general recommendations being made by the reviewer for the development plan.

[10] See P&P 1243.3026 for additional information on amendments.
[11] See P&P 1243.3009 Format and Style Conventions for Reviews and Submission Summaries

- Summarize key points that may impact protocol design or the requirements for technical sections, 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.
    - Need for additional information to address the sponsor's questions (note that where possible this information should be 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 technical section submission.
        - For example, if a sponsor wants feedback on whether foreign studies may satisfy approval requirements for a technical section, we can give them feedback and recommendations from our review of the final study report(s), protocol(s) or study summaries submitted with EI; however, before we could accept that data as pivotal, it would have to resubmitted with the appropriate raw data in the technical section.
- Summarize discussions with the sponsor and any internal meetings

## 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 will select 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.

Because formal regulatory agreements on the number or types of studies required for approval are made only in a PSC, 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 a submission that contained EI, the reviewer will note in the STARS Review Summary field that the submission contained EI. This will make it easier for future reviewers to identify the submission(s) that contained the EI. For additional on closing out submission refer to P&P 1243.3030 Final Action Packages.

The following final actions are expected to be the most commonly used for the specific submission types used for EI.

- 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 additional information on opening an INAD, see P&P 1243.4000.

- 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)[12].
- 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, you will need to 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 will allow for the following benefits to occur with their protocol (E) submissions. You can search the STARS Review Summary field to see if EI has been submitted for the INAD. Refer to P&P 1243.4060 for more information on the review of protocols.

### 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, should determine if the short justifications submitted with the protocol are consistent with this guidance. If the information submitted with the protocol is not appropriate for this pathway, the PR will work with the sponsor to correctly submit the justification information in an H submission (see below).

[12] See P&P 1243.3025 Preparing Meeting Documents

### 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 should contact the sponsor and work with them to void the protocol submission and resubmit it at the appropriate time.

For projects where the sponsor has not submitted EI, reviewers should follow current policy that allows discretion on the timing of H submissions containing data or information to support a study protocol.

## XI. REFERENCES

CVM Guidance for Industry

185, Target Animal Safety for Veterinary Pharmaceutical Products

Program Policy and Procedure Manual

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 – Amending and Resetting the Clock on Submission Tracking and Reporting System (STARS) 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 New Animal Drug (INAD) File

1243.4060 – Review of Protocols

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

## 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.