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

I. PURPOSE

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

- What early information (EI) is;
- What submissions can contain EI;
- What EI submissions will look like;
- Administrative processes for EI; and,
- Review process for EI.

This document applies to pioneer drug review leading to a new animal drug application (NADA) or a Supplemental NADA; and all technical sections for all NADA projects.

This document does not apply to generic investigational new animal drug (JINADs) 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 and Cosmetic Act (i.e., these are "(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 III), CVM introduced the idea of early information 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 early information is to reach agreement regarding some or all of the investigational requirements for approval at a 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 presubmission conference 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 presubmission conference.

Project managers and team leaders should discuss the EI process in communications with sponsors early in development. All Office of New Animal Drug Evaluation (ONADE) staff should discuss submission of early information 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 III 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).

There are many other reasons to submit EI. The following are some additional examples of different types of EI:

- Information to support the appropriateness of a novel indication and preliminary discussion about the unique questions the sponsor may need to address with this type of indication;
- Information to support use of non-U.S. study sites or use of existing effectiveness data from a foreign approval;
- Discussion on use of literature in support of new animal drug development;
- Information regarding validation of a proposed induced infection or laboratory model study;

[1] ADUFA III performance goals letter (page 11)
http://www.fda.gov/downloads/ForIndustry/UserFees/AnimalDrugUserFeeActADUFA/UCM343226.pdf

[2] See P&P 1243.3024

- 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 protocol-specific information (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.

To be considered EI for the purposes of the procedures outlined in this document, the information would generally be submitted sometime prior to the first PSC for that project. More information on the content of EI submissions is provided in Section V. of this document.

IV. WHAT SUBMISSIONS CAN CONTAIN EARLY INFORMATION

Sponsors may choose to submit EI in the following ways:

A. General correspondence (GC) file [pre-INAD]:[4]

This could be a request for review or a request for a meeting. Note: In eSubmitter, the first submission to the GC must be the A-0000. If a sponsor just wants our review and informal discussions, we can review it under the A-0000. If a sponsor wants a pre-INAD meeting, a second submission is required to request the Z. For paper submissions, the first submission to the GC may be a Z-0000, and therefore a second submission would not be required.

EI submitted prior to establishment of the INAD should be for high level discussions or a request for non-binding comment in the very early stages of development (e.g., to discuss potential indications, strategies for novel pathways, or for CVM to provide early input on potential roadblocks to drug development, etc. Discussions with sponsors that rely on review of data or significant amounts of information should occur under the INAD).

1. INAD A-0000 submission
2. Presubmission conferences (PSC) (Z submission, scope PS):

   PSC meetings containing EI will be scheduled either approximately 30 or 100-days after receipt of the materials (see section VI for more details).

[3] See Guidance for Industry #185 Target Animal Safety for Veterinary Pharmaceutical products http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM052464.pdf

[4] When the sponsor opens the INAD, the eSubmitter template will ask them to provide the numbers for any related files, including General Correspondence files.

3. Non-PSC meetings (Z submission, scope OO)

   If the sponsor wants to meet with CVM to discuss a small amount of information, then a Z submission, OO meeting would be appropriate. Some examples would be to discuss adaptive design or discrete questions about a drug development plan. This type of meeting would be scheduled as soon as possible and is not subject to the PSC meeting timeframes of either 30 or 100 days

4. H Submission prior to a PSC

   The H submission can be prior to the first PSC or any additional PSC to discuss any of the technical sections. There should be approximately 100 days from submission to the date of the PSC.

V. WHAT WILL THE SUBMISSION LOOK LIKE?

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; therefore, there is no standard format for an EI submission. The critical factor that will define what an EI submission looks like is the sponsor's specific reason for submitting it.

However, the EI submission should generally include:

- a cover letter or other document that identifies 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)
- any questions or specific issues the sponsor wants CVM to address
- well-organized data and/or information relevant to the goals of the submission

Sponsors should tie 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 an unorganized collection of available information without context for review. 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.

Depending on the administrative path for submitting EI, discussions at this stage may or may not be binding on the sponsor or CVM. However, these discussions may be helpful to both CVM and the sponsor to help understand the project and identify and work to solve potential obstacles.

Examples of information that could facilitate the review and approval process if submitted in early stages include the following (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. extended or delayed release); intended packaging (e.g., single- or multi-dose). Is the product 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 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. Existing drug approvals and investigational uses (US or foreign).

Is the drug approved (US or outside US) as an animal drug, human drug, food additive, etc. If 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 etc.be similar)?

Early information about global development can facilitate coordination between CVM and foreign regulatory agencies and provide an opportunity to see if existing data can be used to support or partially support FDA approval.

D. Pharmacokinetic (PK) data:

basic PK characteristics (absorption, distribution, metabolism, excretion), pharmacodynamic characteristics, fed/fasted information, etc.

E. Early 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.

If the EI submission includes information obtained from published literature, the sponsor should submit the entire article(s), translated into English as needed. It is not sufficient to simply include articles and let CVM interpret their relevance for the proposed development plan. The sponsor should include their rationale for including the articles and explain how the articles support their conclusions or development plan proposals.

For sponsor-conducted studies the EI submission should include the final study report(s) with tables and figures and should not contain raw data. Summary tables with individual animal data should be provided for PK studies and may be needed for other studies depending on the issue the sponsor wants our input on.

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 to the current submission. It may be an amendment or it may simply be an informal conversation so we have the most up-to-date information. This may be particularly useful prior to a PSC where 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.

VI. ADMINISTRATIVE PROCESSES FOR EARLY INFORMATION

A. The general process

A submission identified 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, e.g.:

- 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
- First PSC is assigned to a Project Manager (PM)

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 (unless the PM is also the PR) to determine if the PM had any communication with the sponsor about this submission. The review division can then contact the sponsor to discuss the submission and determine the appropriate next step that facilitates an efficient review.

Representatives from all technical sections[5], scientific specialists (e.g., biostatistics), and science advisors need access to EI when it is submitted so they can provide their expertise and/or potentially use EI to inform each of the technical sections. The role of the science advisors and biostatistics experts is to see if the project may benefit from their specialized areas of scientific expertise, particularly those areas involving novel study design, pharmacokinetics and risk-analysis. Depending on the nature of the EI submission, other experts from across the Center can be consulted on an as- needed basis.

For each EI submission, the PR uses the EI Outlook template to notify the potential members of the project team that an EI submission has been received. The PR sends the email to:

- The PM (unless the PM is also the PR)
- TLs representing the technical sections for this project
- Any other expertise needed based on the nature of the EI

Note, the Outlook template is pre-populated with the following recipients:[6]

- Biostatistics TLs
- Pharmacology TL
- Environmental Safety TL
- ONADE science advisors

[5] The technical sections for a companion animal drug include target animal safety, effectiveness, chemistry, manufacturing, and controls and environmental impact. The technical sections for a food animal drug include target animal safety, effectiveness, chemistry, manufacturing, and controls, environmental impact and human food safety.

[6] The Outlook template is populated with names of people involved in tracking EI submissions who are not involved in the consultation process (Deputy Office Director and the Directors of the Division of Production Drugs (HFV-120) and Division of Human Food Safety (HFV-150)).

The email includes the submission identifier and a general description of the sponsor's goal for the EI submission and the general types of data/information included.

The TLs receiving the email look at the submitted EI to determine if they need a consult, and, if yes, reply to the email within 5 days requesting a consult from the PR and identifying the name of the reviewer who should receive the consult.

The science advisors look at the submitted EI to determine if they have expertise appropriate for that project, and, if yes, contact the PR to discuss next steps for the project. The science advisor team will work with the PR and the project team but does not generally require a formal consulting review.

The PM documents that EI has been submitted for this project.[7]

The PR sends consults as requested or as needed. The reviewers (and their TLs) who receive consults, the PM and any science advisors involved 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.

The PR, TL and/or PM should make appropriate modifications to the general administrative process, as needed, to make the review efficient, e.g., sending a single email notification for a single drug that has multiple INAD submission for different species.

B. Determining the appropriate lead time for a PSC

PSCs should, by default, be considered a standard PSC (meetings scheduled approximately 30-45 days after receipt of the request). If a standard PSC request (Z submission) includes submission of EI that provides an extensive amount of background data/information (for example, full reports from several pilot studies) or unique questions that require several internal discussions (for example, unique/novel product, novel endpoints, etc.) on the drug, the project team may determine it needs to be categorized as a 100-day PSC. Prior to making a final determination, the PR should have a conversation with the sponsor to clarify submission and meeting expectations.

The PR will work with the sponsor and the appropriate TLs to ensure PSCs are properly categorized and scheduled as either the standard PSC or the 100-day PSC. If a change from the standard PSC to the 100-day PSC is required, the PR will communicate the change to the sponsor and work with them to identify a suitable meeting date.

[7] Note in Section VIII, the PR also documents 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.

The PR will work with the project team to schedule pre-meetings prior to a 100-day PSC at the most appropriate time to incorporate findings from the EI review in discussions prior to the PSC.

VII. 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 make informed decisions to help guide sponsors in their drug development, and not to critique pilot studies, pre-INAD testing or published literature.

The intent of EI review is to work with sponsors to address issues or questions early to move the project more efficiently to agreements in a PSC and protocol concurrence. The review is not intended to provide binding agreements relative to a technical section, unless EI is submitted for review as part of the PSC request submission.

If any of the information reviewed in the context of EI is determined that it may be pivotal to support a technical section, it will need to be submitted as a data submission (P) to the technical section with the raw data and will be subjected to a more thorough review at that time. There may be instances where EI is not considered pivotal at the time it is initially reviewed but later in development CVM may determine that the EI fills a gap or can address a question that turns up later in development. At that time, CVM may request the EI be resubmitted under the technical section with the raw data.

Reviewers should consider:

- The information broadly rather than focusing on specific details that may have low impact/risk on the overall objective
- The information already known about the proposed drug
- Whether the provided information/approach could satisfy part or all the approval requirements for particular technical sections
- How early studies can be used to identify gaps needed to address the pivotal information required for approval

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

- Is the submission intended to seek CVM input on the sponsor's development plan? Or is the goal of the submission to seek CVM input on a specific question or questions?

- If the intent of the EI submission is not clearly identified, 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 refuse to review.

- Because EI is intended to help decrease time to approval, the PR should work with the sponsor to determine the best path forward keeping with this principle (e.g., amending the submission to correct deficiencies) and reserve refuse to review only for submissions that are not amenable to any other remediation.

- 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 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.

B. Review documentation

The EI reviews should:

- Follow 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 section of the submission be copied verbatim from the sponsor's submission.

- Answer questions posed by the sponsor 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 for the development plan.

- 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)
- If study reports submitted as EI may also need to be submitted as pivotal in the eventual technical section submission.
- For example, if a sponsor wants feedback on using foreign studies to satisfy approval requirements for a technical section, we can give them feedback 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 raw data in the technical section.
- EI studies that inform the design of pivotal studies do not need to be resubmitted in the technical section (e.g., fed/fasted, dose finding, and preliminary safety studies).

- Summarize discussions with the sponsor and any internal meetings

VIII. FINAL ACTION

All available final action codes for a specific EI submission type are acceptable to use. The PR should select the most appropriate final action code for each 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 should 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.

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

A. Submissions to a GC file

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

Include the following boilerplate language in the acknowledgement letter:

"To ensure the information provided in this submission is included in CVM's review of your Investigational New Animal Drug (INAD) file, reference the submission identifier (located at the top right of this letter) when you open your INAD file."

B. INAD A-0000

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

C. INAD Z submissions

Send an acknowledgement letter and MOC.[8]

D. INAD H submissions

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

However, if the H submission precedes a meeting with the sponsor (Z submission), the information from the H submission can be rolled into the final action for the Z submission. In this case, reviewers can use the final action "File No Reply with a memo (FNR with memo)" for the H and inform the sponsor that CVM feedback will be provided at the meeting and in an MOC.

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

If a sponsor utilizes the processes defined in this P&P, CVM will allow for the following benefits to occur with their protocol (E) submissions.

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 goal's 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 a stand-alone H submission.

The PR can contact the PM to confirm that EI has been submitted for this project and is eligible for this process.

[8] See P&P 1243.3025.

B. Concurrent submission 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.

The PR can contact the PM to confirm that EI has been submitted for this project and is eligible for this process.

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.

X. REFERENCES

CVM Guidance for Industry

185, Target Animal Safety for Veterinary Pharmaceutical Products

CVM Program Policy and Procedure Manual

1243.3024 – Scheduling and Holding Meetings with Outside Parties

1243.3025 – Preparing a Memorandum of Conference (MOC)

XI. 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.