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Guidance for Industry

Two-Phased Chemistry, Manufacturing, and Controls (CMC) Technical Sections

Submit comments on this guidance at any time. Submit electronic comments on the guidance to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852. All comments should be identified with the Docket No. FDA-2014-D-1492.

For further information regarding this document, contact Heather Longstaff, Center for Veterinary Medicine (HFV-145), Food and Drug Administration, 7500 Standish Place, Rockville, MD 20855, 240-402-0651, e-mail: heather.longstaff@fda.hhs.gov.

Additional copies of this guidance document may be requested from the Policy and Regulations Staff (HFV-6), Center for Veterinary Medicine, Food and Drug Administration, 7519 Standish Place, Rockville, MD 20855, and may be viewed on the Internet at either http://www.fda.gov/AnimalVeterinary/default.htm or http://www.regulations.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
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Two-Phased Chemistry, Manufacturing, and Controls (CMC) Technical Sections

I. INTRODUCTION

This guidance provides recommendations to sponsors submitting chemistry, manufacturing, and controls (CMC) data submissions. For review efficiency, the Center for Veterinary Medicine (CVM) prefers that CMC information be submitted in a single technical section. However, there may be instances when a two-phased technical submission process is more beneficial to improve the overall time to drug approval. Sponsors may submit the phased CMC technical section as a single technical section or a two-phased technical section. This guidance describes the use of the two-phased technical section submission process.

This guidance does not provide recommendations on the specific CMC information that should be submitted to comply with 21 CFR §§ 514.1(b)(4) and (5). A sponsor should consider all relevant FDA guidance documents for recommendations on the information that should be submitted to support drug approval.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidance means that something is suggested or recommended, but not required.

II. WHAT IS A TWO-PHASED CMC TECHNICAL SECTION

A complete New Animal Drug Application (NADA) or Abbreviated New Animal Drug Application (ANADA) must include information identified in 21 CFR §§ 514.1(b)(4) and (5). In order to facilitate the approval of NADAs or ANADAs, CVM now accepts major data submissions for individual sections of an NADA or ANADA (technical sections) under the Investigational New Animal Drug (INAD) or Generic Investigational New Animal Drug (JINAD) file. The CMC technical section is considered one of the major data submissions.[1]

[1] For details of the administrative (A)NADA process, refer to GFI #132: The Administrative New Animal Drug Application Process.

Traditionally, sponsors submit complete CMC information in one submission, under either the (J)INAD or the (A)NADA process. Some CMC information, as described below, may be available for review prior to submitting a single traditional CMC technical section. In such instances and with CVM's concurrence, sponsors may submit the CMC data using a two-phased submission process.

The two-phased process allows the submission of two separate CMC submissions, each with its own review clock, and each including complete appropriate CMC information that is available for review at the time of submission. The two submissions may both be submitted to the (J)INAD, or the first submission may be submitted to the (J)INAD and the second to the (A)NADA after transition of the (J)INAD to the (A)NADA.

III. PROCESS FOR THE TWO-PHASED CMC TECHNICAL SECTION

A. Recommended Communications

CVM recommends that sponsors contact the Division of Manufacturing Technologies (HFV-140) prior to using the two-phased submission process in order to obtain concurrence of the sponsor's approach to submitting the CMC technical section(s). A sponsor may also contact CVM regarding the first phase, to discuss or seek clarification on any deficiencies prior to submitting the second phase.

B. How to Submit Two-Phased Submissions in eSubmitter

Sponsors may submit two-phased submissions in paper or preferably through eSubmitter.[2] If sponsors elect to use eSubmitter, all of the questions in the CMC template must be answered in both phases. When submitting the first phase, any questions in the eSubmitter templates that ask for information that will be submitted in the second phase may be answered with "To be submitted in Phase II." When submitting the second phase, any questions that were addressed in the first phase may be answered with a reference to the first phased submission.

IV. FIRST PHASED SUBMISSION

CVM has identified several components of the CMC technical section that sponsors may complete early in the development process and therefore are available to submit to CVM in the first phase of the two-phased submission process. For example, a second-party or master file holder often prepares a master file containing CMC information for the drug substance, which may be available for review prior to the submission of a referencing data submission. If a sponsor references the master file in the first phase, the master file holder may have time to address any deficiencies and CVM may schedule cGMP inspections without significantly impacting the overall time to approval for the (A)NADA.

[2] eSubmitter can be located at: http://www.fda.gov/ForIndustry/FDAeSubmitter/default.htm

A. What to Include

The following items may be appropriate for inclusion in the first phased submission:

- all master file references, e.g., Type II for drug substances and Type V for sterile process validation information,
- drug substance CMC information,
- analytical methods and validations, and
- other items as discussed and agreed upon with CVM.

CVM recommends a reference to one drug or veterinary master file (DMF or VMF) for each active pharmaceutical ingredient (API). CVM may not accept multiple master file references for an API in the first phase and, therefore, may refuse to file or review.[3] A sponsor can submit multiple references in a technical section; however CVM usually discourages this practice since it decreases the likelihood of a single cycle review.

Each component submitted in the first phase should be complete; however, if a sponsor would like to use an alternate strategy this should be discussed with CVM prior to submission of the first phase. With respect to analytical controls, each individual analytical method and its corresponding validation package is considered to be a complete component, such that any or all of the methods may be submitted for review in the first phase (e.g., the assay method/validation could be submitted in the first phase and the impurity method/validation could be submitted in the second phase, or both methods/validations could be submitted together in either the first or second phase).

B. How Information from First Phase Relates to Second Phase

Upon review of the second phase, CVM assesses information received in the first phase in the context of the information in the second phase. This may result in comments on information previously found acceptable based on new or additional information provided in the second phase. For example, an impurity method/validation provided in the first phase may be re-evaluated during the second phase to ensure that the validation data support the proposed finished product specification for impurities that is provided in the second submission.

C. Review Outcomes

The sponsor receives a technical section incomplete letter following review of the first phased submission. There are two possible versions of the letter. The information in the first phased submission may be found acceptable, in which case a letter will be issued indicating that the submitted information is acceptable but the technical section remains incomplete. If the information in the first phased submission is found incomplete, the incomplete letter will contain CVM's comments. A sponsor should address any

[3] 21 CFR § 514.110 Reasons for refusing to file applications, see also, ADUFA III/AGDUFA II goals letters.

deficiency comments from the first phased submission in the second phased submission, along with any remaining information to complete the CMC technical section.

D. Review Clock

The review clock for a first phased submission is 180 days for an INAD, and 270 days for a JINAD.[4]

V. SECOND PHASED SUBMISSION

The second phased submission should not be submitted to the (J)INAD or the (A)NADA until the sponsor receives correspondence from CVM regarding the first phased submission.

A. What to Include

The second phased submission includes the remainder of the information necessary for a complete technical section that was not included in the first phased submission. If the second phased submission is missing information required for a complete technical section, CVM may refuse to file it in the (J)INAD or refuse to review the (A)NADA.[5]

Any responses to incomplete comments from the first phased submission are also included in this phase. All master files should also be referenced, regardless of whether master file references were provided in the first phased submission.

If the sponsor chooses to transition from the investigational phase to the application phase (file an (A)NADA) at the time of submission of the second phase, the technical section incomplete letter from the first phase should be included in the submission.

B. Review Outcomes

There are two possible outcomes following review of the second phased submission. The information in the second phased submission may be found acceptable, and a letter is issued indicating that the information is acceptable. If the second phase is part of a (J)INAD, the letter will indicate that and the technical section is complete. If the second phase is part of the (A)NADA, an approval letter will be issued when all of the sections are found complete. If the information in the second phased submission is incomplete, CVM will issue an incomplete letter. Sponsors should then submit responses to CVM comments as part of the reactivation to the second phased submission. As per the

[4] See ADUFA III/AGDUFA II goals letters, http://www.fda.gov/downloads/ForIndustry/UserFees/AnimalDrugUserFeeActADUFA/UCM343226.pdf, http://www.fda.gov/downloads/ForIndustry/UserFees/AnimalGenericDrugUserFeeActAGDUFA/UCM343235.pdf

[5] 21 CFR § 514.110 Reasons for refusing to file applications, see also, ADUFA III/AGDUFA II goals letters.

AGDUFA II/ADUFA III goals letter, this reactivation may be eligible for an abbreviated review clock at the discretion of CVM. [6]

C. Review Clock

The review clock for a second phased submission is 180 days for an INAD, and 270 days for a JINAD. [7]

[6] The ADUFA III goals letter stipulates that in order for INAD submissions/NADAs to be eligible for shorter reactivation times for the phased submissions, they must be submitted through the eSubmitter tool.
[7] See ADUFA III/AGDUFA II goals letters, http://www.fda.gov/downloads/ForIndustry/UserFees/AnimalDrugUserFeeActADUFA/UCM343226.pdf, http://www.fda.gov/downloads/ForIndustry/UserFees/AnimalGenericDrugUserFeeActAGDUFA/UCM343235.pdf