#227

Chemistry, Manufacturing, and Controls (CMC) Technical Section Filing Strategies

Guidance for Industry

Draft Guidance

This guidance document is being distributed for comment purposes only.

This version of the guidance replaces the version made available September 2015 entitled "Two-Phased Chemistry, Manufacturing and Controls Technical Sections." This revision provides recommendations for submission of the individual components of the CMC technical section: a drug substance component, a drug product component, and a sterile process validation component for sterile drug products. This revision also includes additional strategies for sponsors to obtain CVM input on certain types of information prior to submission of the CMC technical section.

Submit comments on this draft guidance by the dated provided in the *Federal Register* notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with docket number FDA-2014-D-1492.

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

Additional copies of this draft guidance document may be requested from the Policy and Regulations Staff, Center for Veterinary Medicine, Food and Drug Administration, 7500 Standish Place, Rockville MD 20855, and may be viewed on the Internet at https://www.fda.gov/animal-veterinary, https://www.fda.gov/regulatory-information/search-fda-guidance-documents, or http://www.regulations.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Veterinary Medicine (CVM)
September 2024

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Chemistry, Manufacturing, and Controls (CMC) Technical Section Filing Strategies

Draft Guidance for Industry

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. Introduction

This guidance provides recommendations to sponsors submitting chemistry, manufacturing, and controls (CMC) data submissions. There are several mechanisms to receive input from the Center for Veterinary Medicine (CVM) prior to submission of the CMC technical section, as well as various approaches to submitting the CMC technical section itself. For review efficiency, CVM prefers that full CMC information be provided in a single technical section submission. However, there may be instances when submission of the individual components of the technical section (drug product, drug substance, and facility sterile process validation (SPV) information for sterile drug products) could reduce the overall time to complete a technical section, and therefore drug approval. This guidance describes the options for soliciting early input from CVM and the process for submission of components of the CMC technical section.

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.

In general, FDA's guidance documents 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 guidances means that something is suggested or recommended, but not required.

II. Background

A complete New Animal Drug Application (NADA) or Abbreviated New Animal Drug Application (ANADA) must include the CMC information identified in 21 CFR 514.1(b)(4) and (5). To facilitate the approval of NADAs or ANADAs, CVM 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]

Submissions are made using eSubmitter[2] and this guidance includes some information about what selections to make or information to include in the eSubmitter templates, depending on the submission strategy chosen.

III. Content of the Components of the CMC Technical Section

The content provided to address each of the components of the CMC technical section will be the same regardless of filing strategy.

A. Drug Substance Component

Drug substance information may be provided directly or as a reference to a Type II master file.[3] For sterile drug substances, we recommend providing the sterile process validation information in a Type V master file.

B. Drug Product Component

The drug product component includes all information necessary to assess the CMC of the drug product. There are additional questions in the eSubmitter template about how the drug product manufacturer ensures the quality of the drug substance, including questions about the properties of the drug substance, the specifications to which the drug product manufacturer holds the drug substance, and the methods used by the drug product manufacturer to perform those tests. For sterile drug products, there are also product-specific sterile process validation questions in the eSubmitter template about topics such as filtration, container-closure integrity, preservative effectiveness, pyrogen or endotoxin testing, sterility testing, and bioburden testing.

C. Facility Sterile Process Validation Component

Facility sterile process validation information may be provided directly or as a reference to a Type V master file. This component will include information that supports sterile processing at the facility, such as process simulations (media fills), component preparation, closure preparation, closure-related thermal qualification of the cycle, closure-related microbial efficacy of the cycle, container preparation, microbial monitoring of the environment, steam in place, moist steam sterilization of equipment, equipment-related thermal qualification of the cycle, equipment-related microbial efficacy of the cycle, and single use disposable (SUD) equipment. There will be

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[1] For details of the administrative (A)NADA process, refer to GFI #132, "Administrative Applications and the Phased Review Process," (May 2018).

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

[3] CVM accepts references to both Veterinary Master Files and Drug Master Files. For a description of the content of different types of master files, see GFI #57, "Preparation and Submission of Veterinary Master Files," (January 1995).

additional questions about the drug product manufacturing process to provide a linkage between the overall validation done at the facility and how the drug product fits into that validation.

IV. Requesting CVM Input Prior to Submission of the CMC Technical Section

Discussions with CVM about the strategy to generate content, particularly for complex or new approaches, prior to the submission of a CMC technical section may result in fewer incomplete comments on that information during CVM's review of the CMC technical section. The following are some of the mechanisms that can be used to solicit input from CVM.

A. Meeting Requests

Meetings with CVM may be requested to discuss specific questions related to the CMC technical section submission.[4,5] Following the meeting, CVM will provide a Memorandum of Conference summarizing the discussion and documenting the responses to any specific questions posed by the sponsor. For input provided by CVM in response to a meeting request, the meeting submission number should be referenced in the CMC technical section.

B. Protocols and Supporting Data

Protocols may be submitted to gain formal concurrence from CVM on the design of a variety of studies, including method validations, stability studies, and approaches to sterile process validation.[6] Protocol submissions should not include supporting data, but where data are necessary for assessment of the protocol, supporting data may be submitted in an H submission[7] prior to submission of the protocol. Any protocol submissions should be referenced in the CMC technical section.

V. Filing Strategies for the CMC Technical Section

The CMC technical section may be submitted in an application or to an investigational file. If submitted to an investigational file, there are multiple filing strategies available. Sponsors submitting their CMC technical section as part of a non-administrative (A)NADA-A-0000 should submit a complete CMC technical section. When using the (J)INAD file phased-review process, sponsors may submit either a complete CMC technical section or the individual components of the CMC technical section. Figure 1 illustrates the various filing strategies available for the CMC technical section and includes how a response to an incomplete letter, if required, should generally be submitted. A sponsor may also submit CMC information in a

[4] For information on meetings, see CVM Program Policy and Procedures (P&P) Manual 1243.3024 Scheduling and Holding Meetings with Outside Parties (September 2023).

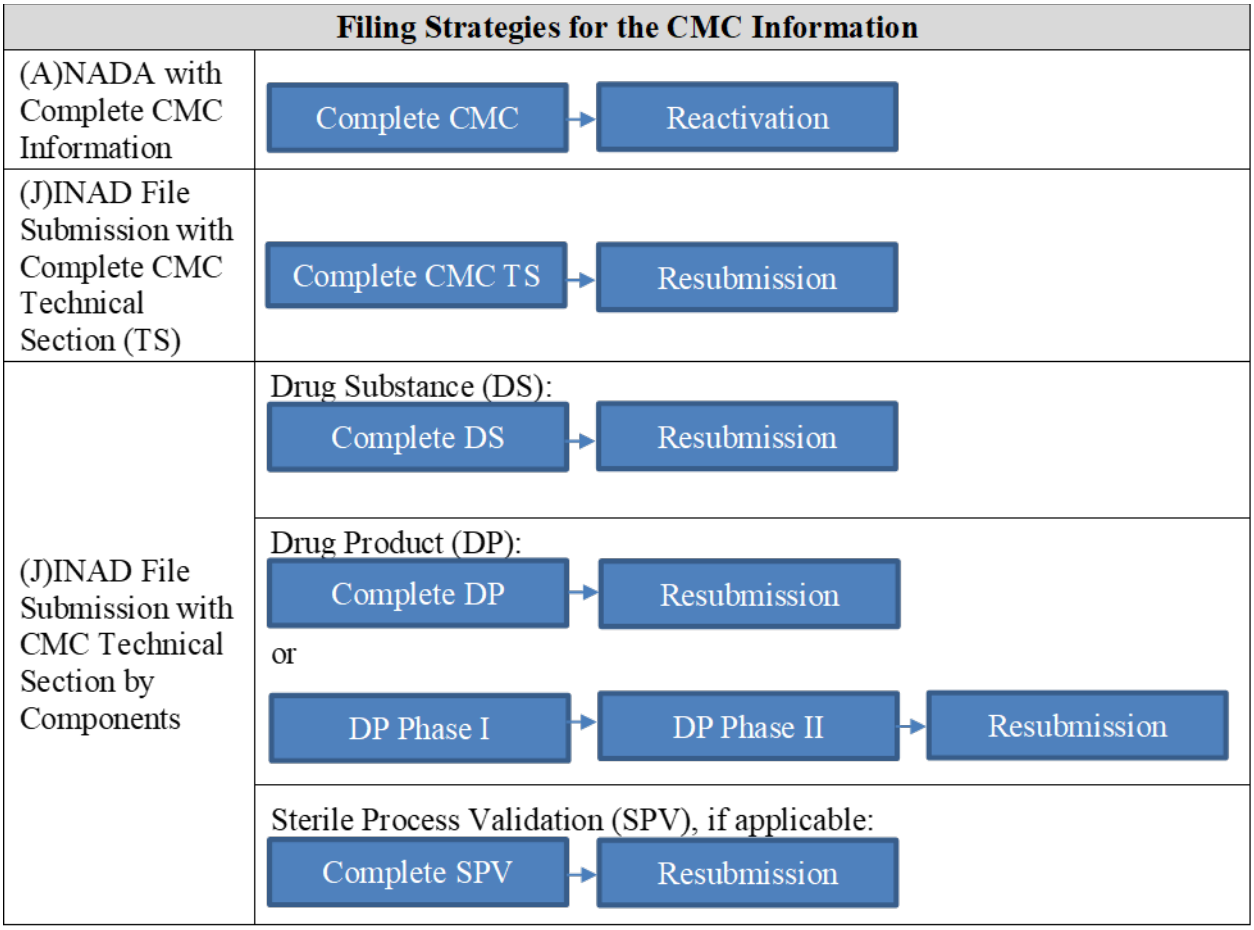
[5] See CVM P&P Manual 1243.2200 Submission and Review of Early Information (EI) to Presubmission Conferences and Protocol Review (September 2023).

[6] For information on protocols, see CVM P&P Manual 1243.4060 Review of Protocols (April 2021).

[7] For information on "H" submissions, see CVM P&P Manual 1243.4092 H Submissions Preceding Meetings and Protocols (November 2023).

(J)INAD file using the phased-review process and may address any deficiencies that may be issued in an incomplete letter after review of the technical section by submitting the response as part of the (A)NADA-A-0000.

Figure 1. Filing Strategies for the CMC information, including a response in the event of incomplete comments on the initial submission. A response to an (A)NADA is called a reactivation and a response to a (J)INAD file submission is called a resubmission.



A. (A)NADA or (J)INAD File Submission with Complete CMC Technical Section

Traditionally, sponsors submit complete CMC information in one submission, under either the (J)INAD file or the (A)NADA. This submission includes the drug product information, drug substance information, and facility sterile process validation information, if applicable for the drug product. Sponsors receive one CVM response to the submission, either a technical section complete letter for a (J)INAD file, an approval letter for an (A)NADA, or an incomplete letter. For incomplete letters, a reactivation/resubmission is submitted that includes the responses to all incomplete items.

B. (J)INAD File Submission with CMC Technical Section Components

Another filing option for the CMC technical section is to separate the complete CMC technical section into individual components that are submitted in parallel to one another. The recommended ways to split the CMC technical section are described in the sections below.

1. CMC Technical Section by Individual Component: Parallel Process for Drug Substance, Drug Product, and Facility Sterile Process Validation Components

When using the (J)INAD file phased-review process, the CMC technical section submission can be divided into three components: drug substance, drug product, and facility sterile process validation (if applicable for the drug product). Each component can be submitted separately and will have an independent review clock based on the date of submission of that individual component. Drug substance, drug product, and facility sterile process validation components may be submitted in parallel to each other (i.e., it is not necessary to wait for one component to be reviewed or found complete before submitting another component); however, CVM will cross-reference new information received in each CMC individual component in the context of the other CMC individual components to ensure all information is complete and consistent. Therefore, CVM recommends that the drug substance component be submitted prior to or concurrent with the drug product component. Information in the drug substance component is likely to impact the review of the drug product component (e.g., information related to impurities), so submission of the drug product component prior to submission of the drug substance component could result in an increased number of review cycles.

Once the CMC technical section has been submitted for an individual component, each subsequent submission for that component (i.e., a response to incomplete comments) should be sequential and only submitted following receipt of the letter from the previous submission. Responses to incomplete comments from multiple components should not be combined into a single submission.

2. CMC Technical Section by Individual Component: Sequential Process for Drug Product Component

Generally, the drug product component will be one complete submission. Depending on the drug product information a sponsor has ready for review, in certain circumstances it may be beneficial to divide the drug product information between two sequential submissions. For the drug product component only, there is an option to submit the information either in one complete component or in two sequential submissions, drug product Phase I and II, as depicted in Figure 1. The only routine situation where sponsors may submit the drug product component in two phases is for Type A medicated articles, where information specific to the Type A medicated article is submitted in Phase I and other information, such as the Type B and Type C

medicated feed studies or a medicated feed assay method transfer study, is submitted in Phase II. Submission of a Phase I drug product component for drug products other than Type A medicated articles without prior CVM concurrence is not acceptable and CVM may refuse to review the submission.[8,9] Any incomplete comments sent for the information in Phase I should be addressed in Phase II, along with the remaining information to complete the drug product component.

VI. Submission of the CMC Technical Section

A. Complete CMC Technical Section

When submitting a complete CMC technical section, select "Complete CMC Technical Section" for the submission type in eSubmitter. In situations where the sponsor is referencing another (J)INAD file, (A)NADA, or CDER product *in lieu* of submitting complete CMC information, the "Complete CMC Technical Section" option should still be selected in eSubmitter. The authorization to the referenced application or file can be uploaded there, along with the appropriate authorizations for any master files.

B. CMC Technical Section by Component

1. Drug Substance Component

To submit the drug substance component, select the submission type "Drug Substance." All questions in the drug substance CMC eSubmitter templates should be answered at the time of submission. The template will allow either submission of full information for the manufacture of the drug substance or a reference to a Type II master file.

In situations where the drug product includes multiple drug substances, separate drug substance components should be submitted for each individual drug substance. These submissions for different drug substances will be evaluated parallel to each other, as well as to the other components submitted. In order to expeditiously reach a technical section complete, and therefore approval, CVM recommends submitting the CMC technical section with a single supplier for each drug substance and adding additional drug substance suppliers post-approval through supplemental applications.[10]

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[8] As stated in the Animal Drug User Fee Amendments of 2023 Performance Goals Letter (at p. 3), "[w]ithin 60 days of receipt, FDA will refuse to review an INAD submission which is determined to be insufficient on its face or otherwise of unacceptable quality upon initial inspection using criteria and procedures similar to those found in 21 CFR 514.110." Submitting a Phase I drug product component for drug products other than Type A medicated articles without CVM's prior concurrence may render it so inadequate that we determine that the submission is not reviewable (see 21 CFR 514.110(b)(4)).

[9] For additional information on "refuse to review" (RTR), see CVM P&P Manual 1243.2050 Refuse to File and Refuse to Review (May 2023).

[10] See GFI #83, "Chemistry, Manufacturing, and Controls Changes to an Approved NADA or ANADA," (May 2007).

2. Drug Product Component

The drug product component will generally be submitted as a complete drug product component. If the drug product component is being submitted in its entirety, select "Complete Drug Product" for the submission type in eSubmitter and answer all questions in the template.

If a sequential two-phased drug product approach is being used, CVM's expectation is that all questions in the drug product CMC eSubmitter template will be answered in one of the two phases. Within eSubmitter, the templates will allow you to submit without answering all questions, but if all questions are not answered by the time of the Phase II submission, CVM may refuse to review.

- If submitting the Phase I drug product submission, select "Drug Product Phase I" as the purpose of submission. 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 Phase II drug product submission, select "Drug Product Phase II" for the purpose of submission. Any questions that were fully addressed in Phase I may be answered with a reference to the first phased submission.

3. Facility Sterile Process Validation Component

To enter the facility sterile process validation (SPV) component, select the submission type "SPV." All questions in the SPV eSubmitter template should be answered at the time of submission. The template will allow either submission of full SPV information for the facility, or a reference to a Type V master file. Sponsors will also provide information identifying how the manufacturing process for the drug product falls within the processes used for SPV.

VII. Review Outcomes for the CMC Technical Section

The information provided in each CMC technical section component will be found acceptable or incomplete. There are a variety of outcomes and considerations depending on the filing strategy used.

A. Information is Found Acceptable

If the component is found acceptable, the type of letter sent will be determined by the overall status of the CMC technical section. For a complete CMC technical section submitted to a (J)INAD file, a technical section complete letter will be sent. For CMC technical sections submitted as components, prior to the last submission where all components have been found acceptable, components with acceptable information will result in a letter that indicates the information is acceptable, but the technical section remains incomplete. Once all components have been found complete, CVM will issue a

technical section complete letter under the component submission with the latest due date. Note that for CMC technical sections submitted by component, information that has been found acceptable in one component may be reassessed in the context of information submitted in another component. As an example of this, a detailed evaluation of the synthetic route of the drug substance under the drug substance component could impact the assessment of the drug product impurity specifications, even if those specifications have previously been found acceptable during review of the drug product component.

For CMC information submitted as part of a non-administrative (A)NADA, the Division of Manufacturing Technologies will convey that the CMC information is acceptable to the Target Animal Division (TAD). The TAD will send the appropriate letter to the sponsor based on the status of all content in the submission.

B. Information is Found Incomplete

If the information is found incomplete, an incomplete letter will be sent. For CMC technical section components, other than a drug product component Phase I, or a complete CMC technical section, the initial submission should be referenced in the response. If the information was submitted in a CMC technical section drug product component Phase I, the incomplete comments should be addressed in the Phase II submission. Responses to incomplete comments for all CMC technical section submissions other than drug product component Phase I are eligible for shortened review time (SRT) when appropriate.[11] For all submissions, the incomplete letter will include CVM's comments.

VIII. Review Clock[12]

A. (J)INAD File Phased-Review Process

The review time for phased CMC technical section submissions under the (J)INAD file phased-review process, which includes both complete CMC technical sections and CMC technical section components, is 180 days. For resubmissions offered SRT, the review time is 60 days.

B. (A)NADA Process

ANADA submissions have a 240-day review clock and reactivations offered SRT have a 120-day review clock. NADA submissions have a 180-day review clock and reactivations offered SRT have a 135-day review clock.

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[11] See CVM P&P Manual 1243.3060 Implementing Shortened Review Times for New Animal Drug Application (NADA) Reactivations and Investigational New Animal Drug (INAD) file Resubmisson using eSubmitter (March 2022) and CVM P&P Manual 1243.3070 Implementing Shortened Review Times for Abbreviated New Animal Drug Applications (ANADA) Reactivations and Generic Investigational New Animal Drug (JINAD) Resubmission (March 2022).

[12] The review times noted are as of the 2023 reauthorization of ADUFA V/AGDUFA IV.