Completeness Assessment for Type II Active Pharmaceutical Ingredient Drug Master Files to Be Referenced in ANDAs

Current Thinking

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Docket for Public Comments

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Draft Guidance for Industry on Initial Completeness Assessments for Type II API DMFs Under GDUFA

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Docket ID: FDA-2012-D-1010 **Agency:** Food and Drug Administration
Parent Agency: Department of Health and Human Services

Public Comments Received

- Total seven documents were received in the Docket, submitted by Industrial Groups, Pharmaceutical Companies and individuals, domestically and internationally.
- Comments on both the general requirement and procedures, and the checklist items.
- Comments include requests of addition or removal of certain items, and more for clarifications
- Comments overlap with some inquiries received through DMFOGD email account, forwarded from ASKGDUFA and DRUGINFO, received at GPhA Conference, GDUFA Conference and CDER Small Business Webinar.

Addressing Public Comments

- The comments received have been consolidated into a summary table.
- Proposed revisions and the rationale for such proposals have been evaluated.
- The actions to address these comments have been proposed.
- The revision draft of the CA guidance has been submitted to the GDUFA policy group for review.
- Multiple avenues are taken to clarify Agency's current thinking with regard to Completeness Assessment.

Notification to ANDA applicant who references the incomplete DMF

- If the DMF is found complete, FDA will post the DMF number on a public available list on FDA's website to indicate that the DMF is available for reference by generic drug applicants.
- If the DMF is determined to be incomplete, the findings and comments will be complied in an Incomplete Letter to the DMF holder explaining why the DMF was found incomplete.
- If the DMF is determined to be incomplete and is referenced by a generic submission which is authorized to rely on the DMF, the generic submission applicant will be notified with the initial CA status of the DMF.

#1. Subject of the DMF is a single drug substance produced by one manufacturing process.

For purposes of facility self-identification and payment of fees, GDUFA defines API differently from the way this has been defined historically.

Sec. 744A. Definitions.
(2) The term ‘active pharmaceutical ingredient’ means—

(A) a substance, or a mixture when the substance is unstable or cannot be transported on its own, intended
  (i) to be used as a component of a drug; and
  (ii) to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the human body; or
(B) a substance intended for final crystallization, purification, or salt formation, or any combination of those activities, to become a substance or mixture described in subparagraph (A).

Please refer to GUDFA Q&A guidance for the agency’s interpretation of GDUFA definitions.

About manufacturing process:

- Limited to one drug substance while multiple manufacturing sites for a single drug substance is permitted when the same process is utilized in each of those sites.
- Limited to one manufacturing process while certain process alternatives/changes may be permissible with sufficient supportive information provided. e.g.:
  - Validated reprocess/rework procedures
  - Micronization leading to different particle sizes
  - Addition of a stabilizing antioxidant for stability purpose
  - Minor process variation that is the same chemical transformation with little risk to the impurity profile

- Separate DMF should be filed for:
  - Different salt form
  - Different synthetic route
  - Significant process alternation resulting in different impurity profile and requiring different control strategy

#2. For previously submitted DMFs, the DMF holder needs to submit a complete update

- The large number of amendments since the original submission or last complete update make it difficult to determine the current state of the information in the DMF.
- Five years since the DMF has received a complete update, or more than 5 amendments to the DMF are the good guide to determine the necessity for submission of a complete update.
- All changes must be reported as amendments. Annual Reports are **NOT** to be used to report changes in the DMF
- The complete update should reflect the current status of the process and not require reference to any previous submission for information. The DMF holder is encouraged to submit the update in ECTD format which will convert this DMF to electronic format going forward.
- The requirement for complete update does not apply to the DMF if the entire DMF is in ECTD format which can always present the DMF in its current state..
- Clearly state “complete update” in the cover letter when a complete update is submitted.

#6. Contains Letters of Authorization for any DMFs referenced to support this DMF

- If a DMF (primary DMF) has referenced another DMF (secondary DMF) for intermediates, the primary DMF holder will need to provide the Letter of Authorization from the secondary DMF holder which authorizes the primary DMF holder to reference the secondary DMF for information.
- Not to be confused with the LOA given to the ANDA applicants
- For all DMF submissions, even if the DMF holder is the same company as the authorized party, Letters of Authorization must be submitted in two copies to the DMF itself.
- The copy of LOA should be located in the section 1.4.2. For more information please refer to the following FDA DMF page: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/default.htm

#8. Contains label with storage conditions and retest date

- A specified temperature storage condition based on the stability studies
- Actual numerical temperature ranges are preferable although using a USP terminology associated with a defined temperature limit or range such as "USP Controlled Room Temperature" would be acceptable.
- Retest date on both label and COA (FDA compliance policy 7356.002F, Chapter 56)
- Caution Statement: “Caution: for manufacturing, processing, or repacking”
- Prescription sign: Rx

#17, 20-24 on the Controls of Starting Materials

If API is a fermentation product:

Information required per #17, 20-24 are common for a synthetic process.

For a fermentation process, information pertaining to the quality and control of the following should be provided:

- Microorganism
- Cell bank system
- Media components

#17. The starting material should be clearly designated with appropriate justification.

Justification for designation of each starting material should be in agreement with the general principle outlined in ICH Q11. This can include information, if applicable, on:

- Name, address and contact information of the manufacturer(s) of each proposed starting material;
- A flow diagram and description outlining the synthetic route and conditions of each proposed starting material;
- Discussion on the impurities (including residual solvents and inorganic impurities), arising from the manufacturing process of each proposed starting material;
- The ability of analytical procedures to detect impurities in the starting material;
- The fate and purge of those impurities and their derivatives in subsequent processing steps;
- How the proposed specification for each starting material will contribute to the control strategy.

#35. Sterility assurance data is provided for sterile API

The full sterilization process validation and the method validation of sterility tests for the sterilized API should be provided, including, but not limited to:

- description of the specific sterilization processes for the bulk drug substance and all associated manufacturing equipment, components, and containers/closures
- description of sterile processing areas
- list of all filling lines/rooms/suites
- legible floor plans for sterile drug substance manufacturers
- description of environmental monitoring program for sterile products
- validation data for sterilization of bulk drug substance
- filter validation data if applicable
- validation data for the sterilization and depyrogenation of the final container/closure system
- validation data for the sterilization of all manufacturing equipment and components
- description of process simulation/media fill program and associated data from media fill runs
- container closure integrity testing report for final containers.

46~51. DS and impurity reference standards

For DS RS:

Qualification data on in-house primary reference standard includes spectroscopic characterization and quantification by mass balance; for compendial reference standard, the lot number and certificate are sufficient. Working reference standard should be qualified against the primary RS with identification tests and assay.

For Impurity RS:

Same principle above applies.

#54. Source, specification and representative COA for each material is provided.

- Primary contact material
- Functional secondary packaging component
- The specifications should include description and identification (and critical dimensions, with drawings where appropriate). Non-compendial methods (with validation) should be included where appropriate
- For non-functional secondary packaging components (e.g., those that neither provide additional protection nor serve to deliver the material), only a brief description should be provided.

#58. Stability Data is provided.

- Completeness Assessment does not specify how much stability data to be provided in the initial submission of a Type II API DMF
- Stability summary, conclusion, protocol, retest date and any available data should be provided to demonstrate a stability program is in place in order to meet the completeness assessment requirement
- Adequacy of the stability information will be evaluated during the scientific review when the DMF is referenced by an application with an LOA

Summary

- We appreciate the feedbacks/comments/suggestions received on the CA Guidance to enhance the DMF submission quality and review efficiency.

- We strive to communicate with the stake holders by answering individual inquiries, presenting at public meetings and publishing articles to clarify the current thinking with regard to the CA guidance.

- We are happy to see the uptrend of ECTD DMF submissions in the recent months, and continue encouraging the holders to submit and/or convert the entire DMF to ECTD.