Regulatory Review Process for Type II Secondary DMFs

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Purpose

This presentation will discuss the risk-based regulatory review process for the acceptance of Type II secondary DMFs for the adequacy of Type II primary DMFs supporting Abbreviated New Drug Applications (ANDAs) and some regulatory aspects of secondary DMFs.

Objective

- Many Type II drug master files (DMFs) refer to a secondary Type II DMF in support of their submissions
- What are secondary DMFs and how do they impact the review of primary DMFs
- The scope and role of a secondary DMF (starting material, intermediate, or an API) is a significant factor in evaluating their acceptance for a primary DMF
- Several case studies will be presented with different scopes and roles of secondary DMFs and the risk-based review approach in their evaluation
- Regulatory aspects of secondary DMFs will be discussed.

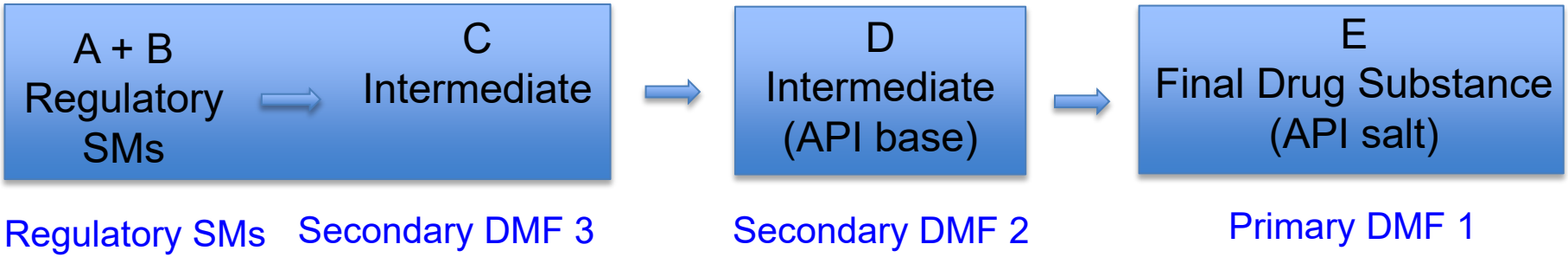
What are secondary DMFs and how do they impact the review of primary DMFs

- Secondary DMFs are DMFs referenced by a primary DMF for the process of its final drug substance synthesis
- A secondary DMF could be for a starting material, intermediate, or API
- There could be more than one secondary DMF associated with a primary DMF
- When there is a secondary DMF(s) associated with a primary DMF, the manufacturing process of the primary DMF drug substance is evaluated based on the information presented in all the DMFs (primary and secondary) including facilities

What are secondary DMFs and how do they impact the review of primary DMFs

- Assessment of control of process impurities in the primary DMF drug substance is based on the overall control strategy of impurities presented in both primary and secondary DMFs
- If the secondary DMF is referenced for a starting material, it should be justified based on ICH Q11 guidance
- All the manufacturing facilities of the secondary DMFs, starting from the regulatory starting materials, require cGMP compliant per ICH Q7

What are secondary DMFs and how do they impact the review of primary DMFs



- The regulatory SMs for the manufacturing process of the final drug substance E are A and B
- Manufacturing process presented in secondary DMFs 2 and 3 also considered part of manufacturing process of final drug substance E
- Manufacturing facility of intermediate D in secondary DMF 2 is also considered as API manufacturing facility
- All the API manufacturing and intermediate facilities should have sufficient information provided by the applicant for FDA inspection

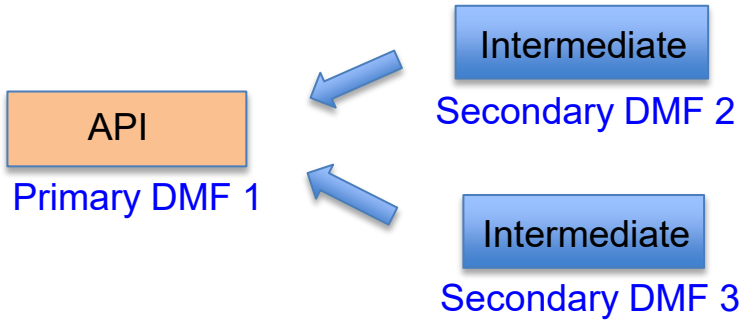
What are secondary DMFs and how do they impact the review of primary DMFs

Secondary DMF	Primary DMF
Crude API	Pure API
API base/acid	API salt
API salt	API base/acid
API HCl salt	API Sulfate salt
Non-sterile API	Sterile API
Single API	Mixture of two API
API Anhydrous	API monohydrate
Racemic API	Enantiomerically pure API
API	API-Premix

What are secondary DMFs and how do they impact the review of primary DMFs

- According to the GDUFA DMF Completeness Assessment Checklist “Subject of the DMF is a single drug substance produced by one manufacturing process”

- When there are multiple secondary DMFs associated with a primary DMF we recommend primary DMF holder to make sure overall manufacturing process is similar in the secondary DMFs.



Case Study 1: Secondary DMF is a starting material

- If the secondary DMF is referred as a starting material:

- It should be justified based on ICH Q11 guidance for the process of the primary DMF drug substance
- If the agency does not accept secondary DMF as a starting material the primary DMF holder may be asked to re-designate the starting material for the process
- If the agency accepts secondary DMF as a starting material:
  - The formal review of the secondary DMF may not be required
  - The extent of review of the secondary DMF is based on what information is included in the primary DMF on the starting material
  - The review of the secondary DMF is conducted as a starting material

Case Study 2: Secondary DMF is an intermediate

- If the secondary DMF is an intermediate:

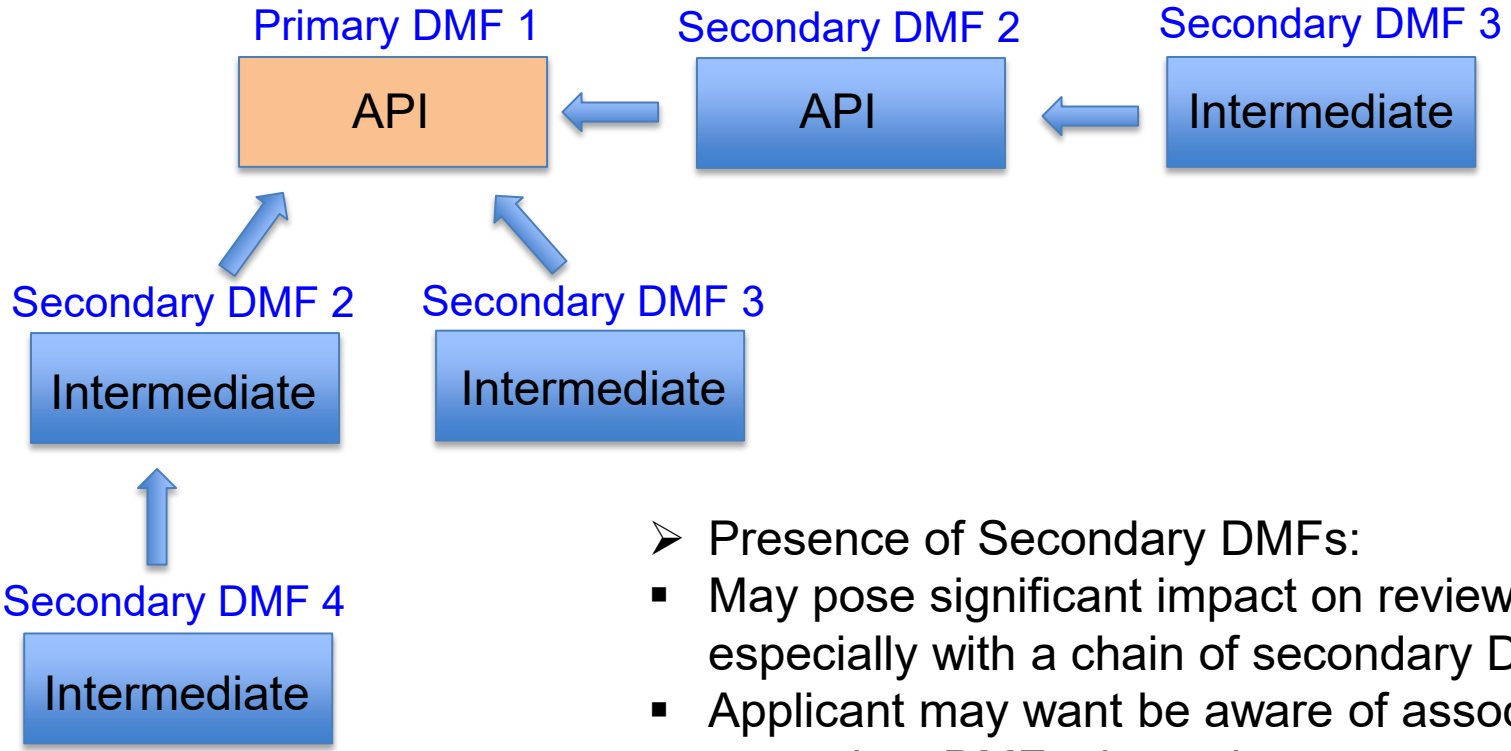
- Most of the quality sections in the DMF will be critically evaluated during the review including cGMP
- It is a primary DMF holder's responsibility to ensure proper control of all potential process impurities in the final API either in the secondary DMF or primary DMF
- If the impurities controlled in the upstream process (in secondary DMF) are higher than ICH Q3A with no downstream control (in primary DMF), supportive information (spike purge study or batch data as applicable) should be presented either in the secondary DMF or the primary DMF as an overall control strategy to demonstrate their absence in the final API. The same applies for genotoxic impurities per ICH M7

Case Study 3: Secondary DMF is an intermediate and is itself a drug substance

- If the secondary DMF is itself a drug substance:

- Evaluation of the secondary DMF is based on how the material is referenced
- In majority of cases the secondary DMF is also referenced by ANDA applicants. In this scenario the secondary DMF is reviewed as a regular drug substance
- If the secondary DMF is referenced by only the primary DMF holder as an intermediate and not referenced by any ANDA applications:
  - The secondary DMF is reviewed only as an intermediate for the adequacy of the referencing primary DMF
  - It is a primary DMF holder's responsibility to ensure proper control of all potential process impurities per ICH Q3A & ICH M7

Case Study 4: Chain of secondary DMFs



- Presence of Secondary DMFs:
  - May pose significant impact on review timelines, especially with a chain of secondary DMFs
  - Applicant may want be aware of associated secondary DMFs due to its consequences

Regulatory aspects

- Secondary DMFs have to be adequate for the adequacy of primary DMF
- Secondary DMFs inadequacy usually triggers CR letter for primary DMF

  "We acknowledge that you have referenced DMF XXXXXX for [intermediate name]. DMF XXXXXX has been reviewed and is currently inadequate. The DMF holder will be notified of any deficiencies. We will work with the DMF holder to resolve any issues if they respond in a timely manner. Please be aware that the quality review of this DMF cannot be fully completed until all DMF deficiencies including those in DMF XXXXXX are adequately resolved. Please acknowledge this in your response"

Regulatory aspects

- Secondary DMF is reviewed with the same timeline as the primary DMF guided by same target date
- Solicited and unsolicited amendments to the secondary DMF are treated the same as primary DMF and will have the same implications and consequences to the goal date and extensions
- During the DMF Completeness Assessment the following will be checked:
  - Contains Letters of Authorization for any DMFs referenced to support the DMF
  - All DMFs referenced have been filed with the Agency and are active

Regulatory aspects

- Letter of Authorizations from the secondary DMF holder should be provided in section 1.4
- The material sourced from the secondary DMF should be clearly mentioned in appropriate sections of the DMF (3.2.S.2.1) as applicable
- Late identification of secondary DMF association due to lack of information in appropriate sections of the DMF and LOA may lead to delay in review timelines and issuance of IR letter
- If the designation of material sourced from the secondary DMF as starting materials is not appropriate per ICH Q11, it may lead to Inadequate-major deficiency which has longer GDUFA goal dates

Regulatory aspects

- For the material sourced from the secondary DMF:

- The facility information and cGMP statement may be listed or refer to the secondary DMF in section 3.2.S.2.1
- Having the correct facility information early in the application is critical for timely evaluations of secondary DMF facilities as needed.
- Late cycle facility evaluations can delay approvals

Regulatory aspects

- According to the FDA Draft Guidance Drug Master Files, Revision 1, October 2019:

  - A primary DMF can incorporate information in a secondary DMF by reference. The secondary DMF holder can submit an LOA authorizing either the primary DMF holder or the drug product applicant to reference the secondary DMF. Where possible, consistent with confidentiality agreements, secondary DMF holders are encouraged to submit LOAs authorizing drug product applicants to reference the secondary DMF directly.

Acknowledgements

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Thank You!

Questions?