SBIA-DMF Drug substance workshop

March 3 & 4, 2021 (Virtual)

Review of Secondary Type II Drug Master Files

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March 3 & 4, 2021; Virtual

PURPOSE

This poster will discuss the risk-based review approach for the acceptance of secondary DMFs for the adequacy of primary DMFs supporting Abbreviated New Drug Applications (ANDAs) or New Drug Applications (NDAs) 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. The subject of a secondary DMF could be a starting material or critical intermediate. In some cases, the secondary DMF itself is a primary DMF with an active pharmaceutical ingredient. The scope and role of a secondary DMF 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 (starting material, critical intermediate, and API) and the risk based review approach in their evaluation. Finally, some regulatory aspects of secondary DMFs will be discussed.

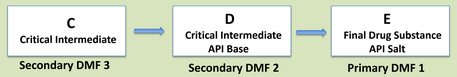
METHODS

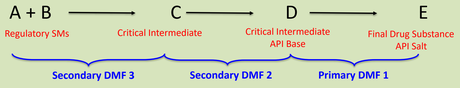
This presentation has 3 parts:

1. Definition of secondary DMFs and their implications for the review of primary DMFs
2. Several case studies to illustrate the review approach of secondary DMFs based on the role of secondary DMFs
3. Regulatory aspects of secondary DMFs

What are secondary DMFs and their implications for 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, critical 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
- 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, may require cGMP compliant per ICH Q7
- We recommend that critical intermediate facilities in secondary DMFs be listed in the referencing A/NDA 356h form





- ❖ *The manufacturing facilities of both secondary DMFs are critical intermediate facilities*
- ❖ *The regulatory starting materials for the manufacturing process of the final drug substance are A and B*

Please attend Wei Liu's presentation on March 3rd for more information on "Drug Substance Facilities – Hidden and Critical Intermediate Sites"

Case studies

Case Study 1: Secondary DMF contains information related to 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 the 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 the secondary DMF as a starting material:
  - the extent of the review of the secondary DMF is based on what is included in the primary DMF on the starting material
  - the formal review of the secondary DMF may not be required
  - the more complex the starting material, the more likely there will be a formal review

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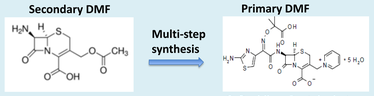
(Angew Chem Int Ed Engl. 2014 August 18; 53(34): 8840–8869)



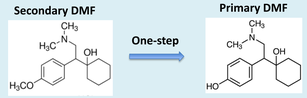
- ❖ *The secondary DMF was reviewed and accepted as a starting material for the primary DMF*

Case Study 2: Secondary DMF contains information related to critical 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 the majority of cases, the secondary DMF is also referenced by A/NDA 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 a critical intermediate and not referenced by any A/NDA applications:
  - the secondary DMF is reviewed only as a critical 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
  - in the future, if the secondary DMF is referenced by A/NDA applications, the secondary DMF holder should update the DMF for the referencing drug product applications, if applicable, and the secondary DMF will be further evaluated for the adequacy of referencing drug products

Venlafaxine is a common precursor in the synthesis of Desvenlafaxine
(Organic Process Research & Development 2011, 15, 1392-1395)



- ❖ *Quality of the secondary DMF is very critical in the evaluation*
- ❖ *Since the secondary DMF was itself a drug substance, and also referenced by A/NDA application, the DMF was reviewed as a regular drug substance*

Case Study 3: Secondary DMF contains information related to critical intermediate

➢ **If the secondary DMF is a critical intermediate:**

- The quality of information presented in the secondary DMF is very critical for the adequacy of the primary DMF
- Most of the quality sections will be critically evaluated during the review including cGMP and facilities
- ICH Q3A and ICH M7 may not apply. 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
- It is acceptable to reference the intermediate of another API DMF as a secondary DMF. However, the LoA should clearly specify the name of the intermediate sourced from the secondary API DMF

(*S*)-3-(*N*-Methylamino)-1-(2-thienyl)propan-1-ol is a precursor in the synthesis of Duloxetine Hydrochloride
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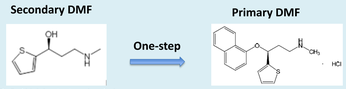
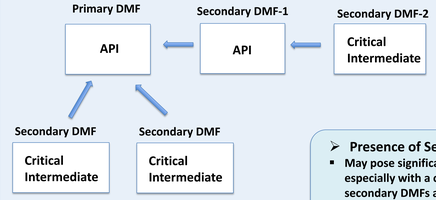


- ❖ *Quality of secondary DMF is very critical since it is a penultimate intermediate with a chiral center*

Case Study 4: Chain of secondary DMFs



➢ **Presence of Secondary DMFs:**

- May pose significant impact on review resources, especially with a chain of secondary DMFs since secondary DMFs are reviewed with the same timeline as the primary DMF guided by same target date

Regulatory aspects:

- ❖ Secondary DMF has to be adequate for the adequacy of primary DMF
- ❖ Secondary DMF 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"
- ❖ 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
- ❖ Further, as part of Timely Consults and Early Information Request (TCIR) any secondary DMFs referenced by the DMF will be checked
- ❖ 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, 3.2.S.2.2, 3.2.S.2.3, and 3.2.S.2.4) 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
- ❖ If the material sourced from the secondary DMF is a critical intermediate:
  - The facility information and cGMP statement may be listed in section 3.2.S.2.1
  - Also, we strongly recommend listing the facility in the referencing A/NDA 356h form and lack of this information may lead to Hidden Facility IR comment
  - Having the correct facility information early in the application is critical for timely evaluations of secondary DMF critical intermediate facilities.
  - Late cycle facility evaluations can delay approvals

Thank You!

- Send questions regarding this poster to: DMFWorkshop2021@fda.hhs.gov by 2/15/2021 for inclusion in the poster Q&A session on March 4, 2021.
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- Many Type II drug master files (DMFs) refer to a secondary Type II DMF in support of their submissions
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What are secondary DMFs and their implications for the review of primary DMFs

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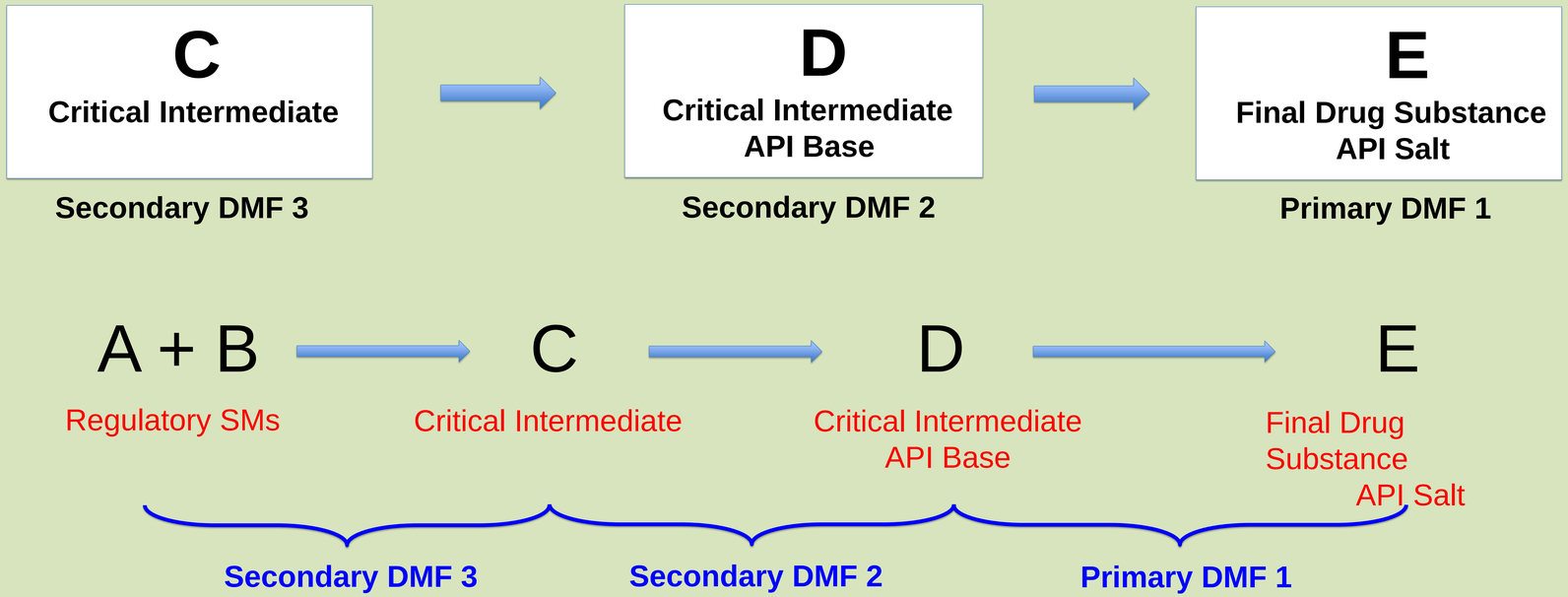
What are secondary DMFs and their implications for the review of primary DMFs



- ***The manufacturing facilities of both secondary DMFs are critical intermediate facilities***
- ***The regulatory starting materials for the manufacturing process of the final drug substance are A and B***

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Case Study 1: Secondary DMF contains information related to starting material

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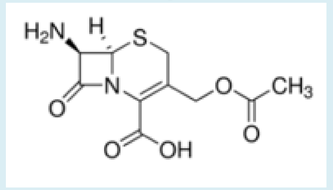
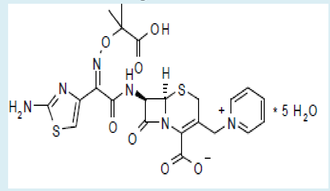
  - **the extent of review of the secondary DMF is based on what is included in the primary DMF on the starting material**
  - **the formal review of the secondary DMF may not be required**
  - **more complex the starting material the more likely there will be a formal review**

7-Aminocephalosporanic acid (7-ACA) is the core chemical structure for the synthesis of cephalosporin antibiotics *(Angew Chem Int Ed Engl. 2014 August 18; 53(34): 8840–8869)*

Secondary DMF → **Multi-step synthesis** → **Primary DMF**



7-aminocephalosporanic acid



Ceftazidime Pentahydrate

❖ ***The secondary DMF was reviewed and accepted as starting material for the Primary DMF***

Case Study 2: Secondary DMF contains information related to critical intermediate and is itself a drug substance

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Venlafaxine is a common precursor in the synthesis of Desvenlafaxine
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Secondary DMF → **One-step** → **Primary DMF**

Venlafaxine Desvenlafaxine

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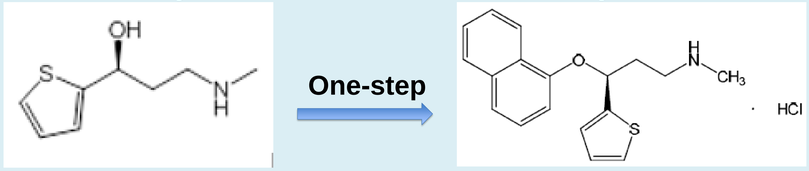

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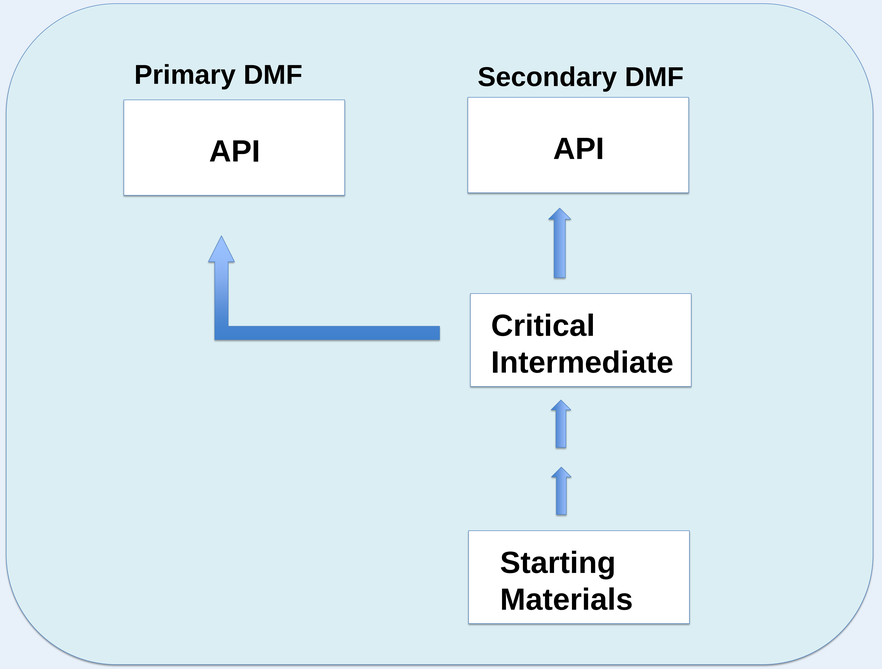

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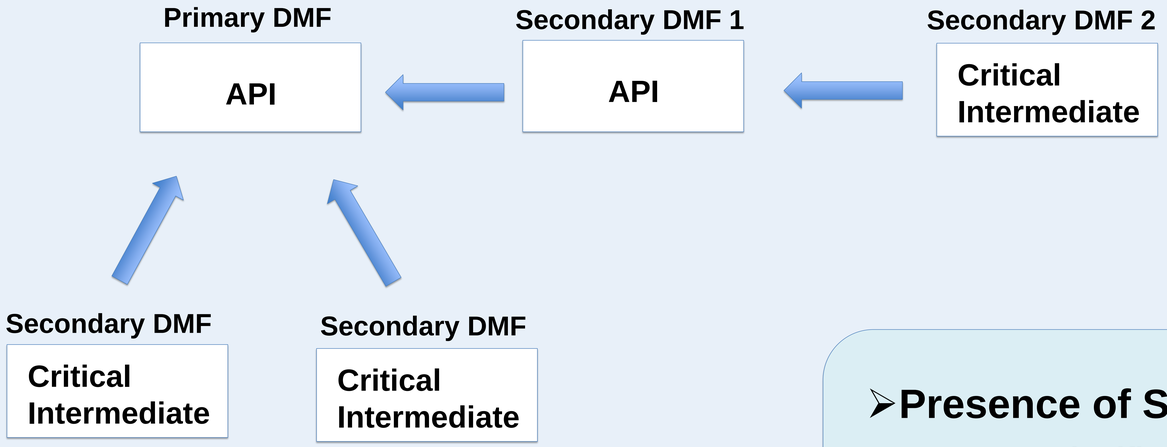

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Regulatory aspects

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