Common CMC Issues in Type II DMFs and How to Avoid Them

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Objective

- Explain DMF assessment expectations from CMC perspective
- Discuss common issues in Type II DMFs
- Provide points to consider when responding to the deficiency letter

Abbreviations

- SM – Regulatory Starting Material
- DS – Drug Substance
- EBR – Executed Batch Record
- RT/IT/QT – Reporting /Identification / Qualification Threshold
- PMI – Potential Mutagenic Impurity
- TTC – Threshold of Toxicological Concern
- PDE – Permitted Daily Exposure

Facilities in DMFs

- List ALL facilities involved in the manufacturing and routine testing of drug substance in S.2.1 in DMF.
- Clearly indicate the responsibility for each facility.
  - If an intermediate site, indicate which intermediate
  - If a testing site, indicate which test(s)
- This section needs to be updated if re-designation of the regulatory SM is requested.
  - If a secondary DMF is referenced, list the DMF number and manufacturing site information as appropriate.
- The addition of a new facility may be considered as a major amendment to the referencing applications according to FDA guidance.
- See presentation of Drug Substance Facilities – Hidden and Critical Intermediate Sites by Cassandra Abellard and Wei Liu.

Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers, Guidance for Industry, October 2019, Revision 1

Blending Batches of Intermediates or Drug Substances

- Blending is defined as the process of combining materials within the same specification to produce a homogeneous intermediate or drug substance, according to ICH Q7.
- The information below should be provided in the DMF, if applicable, when a manufacturing process involves blending operation:
  - Confirm each batch is tested and meets specifications.
  - The retest/expiry date of the blended batch should be based on the manufacturing date of the oldest batch in the blend.
  - Where physical attributes of the drug substance are critical, blending operations should be validated to show homogeneity of the combined batch.
  - In EBR, the batch record of the blending process should allow traceability back to the individual batches that make up the blend.

Regulatory Starting Material (SM)

- An accepted regulatory SM is the starting point of cGMP.
- ICH Q11 and its Q&A represent the Agency's current thinking on selection of regulatory SM.
  - See presentation of ICH Q11 Q &A, a Supporting Document for the Selection and Justification of Starting Materials by Anita Tiwari.
- Inadequate selection or justification of regulatory SM may be considered as a major deficiency according to FDA Guidance.

ANDA Submissions - Amendments to ANDA under GDUFA, Guidance for Industry, July 2018

Regulatory Starting Material (SM)

Common Deficiency:

The starting material [XYZ] that you have identified does not allow for adequate evaluation of the control of the process and/or the critical quality attributes of the drug substance, and is thus not appropriate as regulatory SM.

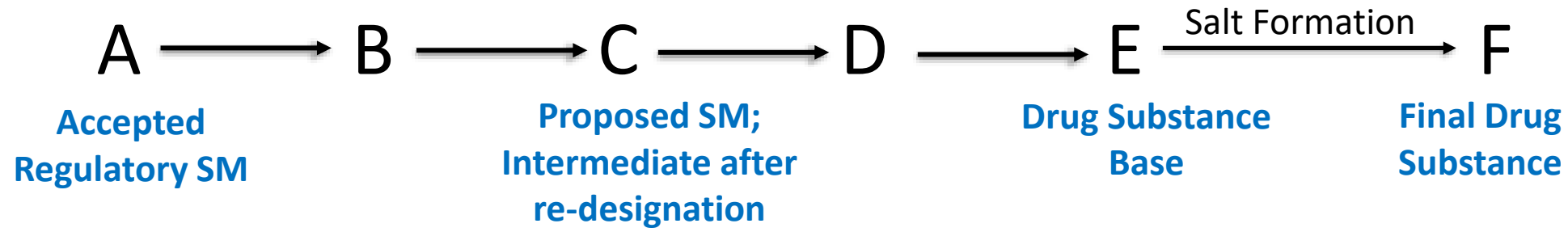
Points to Consider:

- Update GMP statement and/or provide the LOA if a secondary DMF is referenced.
- All affected sections of DMF should be updated, such as but not limited to process description, process validation and EBR.

Regulatory Starting Material (SM)

Points to Consider (cont.):

- The proposed SM becomes an intermediate after the re-designation:
  - Its facility may be subjected to evaluation
  - Hold time study for this intermediate might be necessary when site transfer is involved



Polymorphism of Drug Substances

- The drug substance in a generic product does not need to have the same polymorphic form as the RLD. The drug product does, however, have to exhibit sufficient stability and is bioequivalent to the RLD.
- From DMF perspective, the information below should be provided, if applicable, when a drug substance shows polymorphism:
  - The same polymorphic form produced consistently by the manufacturing process
  - The effect of milling/micronization (if any) on the polymorphism
  - The stability of polymorphic form at the end of retest period
  - Appropriate test in the drug substance release and stability specification to ensure the same polymorphic form if a potential polymorphic change is a risk.

Pharmaceutical Solid Polymorphism, Guidance for Industry, 2007

Impurity Controls and Qualifications

- A hazard assessment on actual and potential impurities per ICH M7 is expected to support the proposed impurity classifications.
  - See presentation of ICH M7 –Chemistry and Manufacturing Control Perspective on Hazard Assessment by Barbara Scott.
- Include **ALL** potential impurities in the submission:
  - SMs
  - Intermediates, including in-situ intermediates as appropriate
  - By products
  - Impurities in SMs and intermediates as well as their continued reactions in the process
- If identified impurities are controlled as any unspecified impurity, information should be provided to demonstrate the impurity test method is able to detect them if present.
- Degradation impurities should be controlled in the stability specification.
- Inadequate control/qualification of impurities may be considered as a major deficiency.

Impurity Controls and Qualifications

Impurity controls in the drug substance specifications

- Impurity qualification methods for mutagenic and non-mutagenic impurities are covered in earlier sessions.
  - Application of (Q)SAR and Expert Knowledge for ICH M7 Impurity classification by Naomi Kruhlak
  - Consideration for Impurity Qualification – ICH Q3A/Q3C/Q3D, RLD & MDD by Hongbiao Liao
  - Safety Evaluation of Impurities in Drug Substances by Chanchal Gupta
- For most drug substances, the acceptance criteria of any unspecified impurities:
  - Should not exceed the identification threshold (IT) in ICH Q3A, even in the case when higher limit is listed in the USP monograph.
  - If the limit for any unspecified impurities in USP is lower than the IT, the limit should be set to USP level.

ANDAs: Impurities in Drug Substances, Guidance for Industry, June 2009

Impurity Controls and Qualifications

Impurity	Qualification Method	Assessment Timelines
Non-Mutagenic Impurity	Same limit in USP monograph	Immediate
	ICH Q3A Qualification Threshold	Immediate
	Side-by-side comparative analytical studies against RLD	Immediate
	Scientific literature and significant metabolites	Pharm/Tox consult, ~ 3 months
	Toxicity studies	Pharm/Tox consult, ~ 3 months
Mutagenic Impurity	General control options per ICH M7	Immediate
	ICH M7 Note 4 and Note 5	Pharm/Tox consult, ~ 3 months
	Ames report	Pharm/Tox consult, ~ 3 months
	Scientific literature	Pharm/Tox consult, ~ 3 months
Solvent	ICH Q3C limit	Immediate
	PDE derived under ICH Q3C Appendix 3,	Pharm/Tox consult, ~ 3 months
	Scientific literature and Toxicity studies	Pharm/Tox consult, ~ 3 months

Impurity Controls and Qualifications

Common Deficiency:

All unspecified impurities exceeding the ICH Q3A identification threshold should be appropriately identified. Please tighten the limit for "any unspecified impurity" in the drug substance based on ICH Q3A.

Points to Consider:

- IT in ICH Q3A is 0.10% or 1.0 mg/day whichever is lower
- Below 1.0%, the results should be reported to two decimal places based on ICH Q3A
- Update the drug substance stability specifications accordingly in S.7

Impurity Controls and Qualifications

Common Deficiency:

You state impurity A, if present, is controlled as any unspecified impurity in the drug substance specification. Please demonstrate your related substances method of the drug substance is able to detect and quantify this impurity.

Points to Consider:

- Include impurity A in the method validation study in S.4.3 and provide the representative chromatograms.
- Add a footnote in drug substance specification and COA that this impurity is controlled as any unspecified impurity if it is a USP specified impurity.

Impurity Controls and Qualifications

Impurity controls in the upstream, but not in drug substance specification:

- If controlled at a limit higher than acceptable limit:
  - Information to demonstrate the subsequent process is able to purge out this impurity, such as spike/purge study, needs to be provided.
  - The relevant downstream impurities due to continued reaction in subsequent process should be considered.

Impurity Controls and Qualifications

Common Deficiency:

Please justify the assay limit of 85% in the specification for intermediate Y with demonstration that the origin and fate of the impurities are understood and the later process is capable of purging out the impurities at this level.

Points to Consider:

- Include all potential impurities in this intermediate with appropriate limits.
- The relevant downstream impurities due to continued reaction in subsequent process should be considered.
- The controls of mutagenic impurities are covered by presentation of ICH M7 – Chemistry and Manufacturing Control Perspective on Hazard Assessment by Barbara Scott.
- Include the information about the analytical method, method specificity, LOD/LOQ in the response as appropriate.

Case Study: Impurity Controls in Intermediate Y

S ⟶ X ⟶ Y ⟶ Z (crude DS) ⟶ Final DS

Impurity	Origin and Fate	Proposed Limit	Test Data in Intermediate Y
Impurity 1	Process impurity; Convert to Impurity A	3.0%	2.0%
Impurity 2	Process impurity; No continued reaction	2.0%	1.6%
Impurity 3	Process impurity; No continued reaction	2.0%	0.15%
Impurity 4	Process impurity; No continued reaction	0.13%	0.09%
Impurity 5	Degradant	0.13%	0.08%
Impurity 6	Process impurity; Class 3 based on positive (Q)SAR predictions; No continued reaction	0.50%	0.05%
Any unspecified	--	2.5%	2.1%
Total impurities	--	10.0%	6.2%
Assay	--	85.0%	93.7%

Case Study: Impurity Controls in Intermediate Y

Impurity	Limit/Test data	Subsequent Control in DMF	Assessment
Impurity 1	3.0% / 2.0%	Relevant Impurity A controlled in final DS	Its downstream impurity A controlled in final API at acceptable limit.
Impurity 2	2.0% / 1.6%	Not detected in final DS	LOD = 0.03% is below RT; acceptable.
Impurity 3	2.0% / 0.15%	Not detected in final DS	Actual level is much lower than the limit. Need to tighten the limit or provide spike/purge.
Impurity 4	0.13% / 0.09%	No further controls	Controlled at ICH QT; acceptable.
Impurity 5	0.13% / 0.08%	No further controls	Further control is required due to the degradation.
Impurity 6	0.50% / 0.05%	No further controls	Further control is required due to the impurity being a PMI. Impurity should be controlled per ICH M7.
Any unspecified	2.5% / 2.1%	--	Limit needs to be tightened. Consider controlling routinely observed impurities at higher levels as specified impurities.
Total impurities	10.0% / 6.2%	--	Need to revise or justify.
Assay	85.0% / 93.7%	--	

MDD = 800 mg; RT = 0.05%; IT = 0.10%; QT = 0.13%; TTC = 1.875ppm

Analytical Method and Method Validation

- ICH Q2 and USP <621> represent the Agency's current thinking on analytical method and method validation.
  - See presentation of Commonly Observed Deficiencies Related to Chromatography Based Analytical Methods in Drug Substances by Xinghua Wu.
- USP <621> has relative standard deviation (RSD) requirement for assay test unless it is specified in the individual monograph.
- If a USP compendial method is chosen, the adjustment of operation conditions should be within the allowable ranges outlined in USP <621>; otherwise it is considered as an in-house method.
- Method equivalency study should be provided when USP compendial method is available while in-house method is used.

Analytical Method and Method Validation

Common Deficiency:

As you have chosen not to use the USP method for related substances test of final drug substance, please provide a method equivalency study to demonstrate the proposed method is equivalent or better than the compendial method.

Points to Consider:

- Demonstrate the proposed in-house method is able to detect and quantify all USP specified impurities, unless justified appropriately.
- Provide batch data from multiple batches by both in-house method and USP method to show the test results are comparable.

Stability and Retest Date

- Principles in ICH Q1E is used to establish the retest period
  - Drug substances intended for room temperature storage
  - Drug substances intended for storage below room temperature
- Stability specification should be updated as necessary when you are requested to revise the drug substance release specification
  - The degradation impurities should be controlled in the stability specification
  - The stability data needs to be tested per updated stability specification for on-going stability batches

ANDAs: Stability Testing of Drug Substances and Products, Guidance for Industry, 2013
ANDAs: Stability Testing of Drug Substances and Products, Q&A, Guidance for Industry, 2014

Summary

- Some common deficiencies in DMFs and approaches to mitigate them are discussed.

- In 80% of cases, impurity controls and qualifications is the main reason for major deficiencies in DMFs. In-depth understanding the formation, fate, and purge will facilitate selection of appropriate control strategy and may reduce the number of potential deficiencies.

Acknowledgement

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Thank You!

- Send questions regarding this presentation to: DMFWorkshop2021@fda.hhs.gov by 3/19/2021 for inclusion in the follow-on webinar April 9, 2021.

- Please refer to the following presentations for additional information:
  - Drug Substance Facilities – Hidden and Critical Intermediate Sites by Cassadra Abellard and Wei Liu.
  - ICH Q7 Process Validations by David Amspacher.
  - ICH Q11 Q &A, a Supporting Document for the Selection and Justification of Starting Materials by Anita Tiwari.
  - ICH M7 –Chemistry and Manufacturing Control Perspective on Hazard Assessment by Barbara Scott.
  - Application of (Q)SAR and Expert Knowledge for ICH M7 Impurity classification by Naomi Kruhlak.
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