SBIA-DMF Drug Substance Workshop

March 3 & 4, 2021 (Virtual)

List of Relevant Quality Guidances & Common Deficiencies Observed During Drug Master File (DMF) Review

Sad Ahamed and Mahmut Levent
CDER/OPQ/ONDP/DLAPI

PURPOSE AND OBJECTIVE:

This presentation is intended to provide a non-exhaustive list of relevant guidances and discuss common deficiencies to improve submission quality.

This poster is organized by CTD sections. Each section includes commonly observed deficiencies and relevant guidance that are helpful to address deficiencies.

CONCLUSION:

The goal is to be able to deem the DMF submissions "adequate" in the first cycle. It is possible to limit the review cycles, and a number of ICH and FDA guidances are available. DMF holders are encouraged to consult the FDA guidances document page.

RESOURCES:

ICH Website:
https://www.ich.org/page/ich-guidelines

FDA Guidance Documents
https://www.fda.gov/regulatory-information/search-fda-guidance-documents

USP website:
https://login.usp.org/cas/login?service=https%3A%2F%2Fonline.uspnf.com%2Fcas%2Flogin

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 4th, 2021.

Follow-on webinar for both posters/presentations on April 9, 2021. Questions can be sent to the above email by 3/19/2021 for the webinar.

Please refer to the following posters for cross-referenced materials: Administrative Process (V. Selvam)

Please refer to the following presentations on March 3rd for additional information: Effective communication strategies (D. Skanchy)

ACKNOWLEDGEMENT:

Ramnarayan Randad

Erin Skoda

Wei Liu

Section 3.2.S.1: Guidances:

Drug Master Files Guidance for Industry (Draft, October 2019): https://www.fda.gov/media/131861/download
ANDAs Pharmaceutical Solid Polymorphism: Chemistry, Manufacturing and Controls Information (Final, July 2007): https://www.fda.gov/media/71375/download

Example of Deficiencies:

- The general properties section (S.1) fails to contain all relevant information. Please provide chirality, polymorphism, hygroscopicity, aqueous solubility, solubility in various organic solvents, melting range for the drug substance.
- Please provide a Letter of Authorization (LOA) for each referencing application in Module 1, section 1.4 of your DMF.

Section 3.2 S.2: Guidances:

Process Validation, General Principles and Practices (Final, January 2011)
Q11 Development and Manufacture of Drug Substances (Final, November 2012)
Q11 Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Entities) Questions and Answers (Final, February 2018)
Q7 Good manufacturing practice for active pharmaceutical ingredients (Final, September 2016)
Q8(R2) Pharmaceutical Development (Final, November 2009)
Q9 Quality Risk Management (Final, June 2006)

Example of Deficiencies:

- Please provide a statement that your manufacturing facilities are in compliance with applicable cGMP requirements. Include all contract labs' cGMP statements.
- Please revise your synthetic scheme to include chemical structures with reagents, solvents, and reaction conditions, as appropriate.
- X is expected as a potential impurity in your manufacturing process. Please discuss your control strategies for it with supporting data as necessary.
- Please provide a summary of your process validation for the manufacturing process, such as validation batch description, starting material analysis, IPCs, intermediate, and final API analysis in a tabular format.

Sections 3.2.S.3: Guidances:

M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals To Limit Potential Carcinogenic Risk (Final, March 2018)
Q3A Impurities In New Drug Substances (Final, June 2008)
ICH Q3C Maintenance Procedures for the Guidance for Industry Q3C Impurities: Residual Solvents (Final, July 2017)
Q3D(R1) Elemental Impurities (Final, July 2019)
ANDAs Impurities in Drug Substances (Final , July 2009)

Example of Deficiencies:

- In your manufacturing process, X, Y and Z are plausible impurities. Please discuss your control strategy for these impurities and their downstream derivatives. Please add tests with the justifiable limits, if needed.
- Please comment on the following possible process or degradation impurities and demonstrate that, if present, the related substances test method would detect them so that they can be controlled appropriately.

Sections 3.2.S.4: Guidances:

Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances (Final, December 2000)
Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products (Final, August 1999)
Q2B Validation of Analytical Procedures: Methodology (Final, May 1997)

Other Helpful Information:

USP43-NF38 : General chapters: <621> chromatography

Example of Deficiencies:

- Please revise the limit of any individual unspecified impurity acceptance criterion in your drug substance release and stability specifications to NMT 0.10% to be aligned with ICH Q3A.
- Per USP <621> where there is not a monograph available, the %RSD for assay determined by Table 1. RSD requirements. Please re-evaluate the %RSD requirements for the assay test and provide the updated system suitability.

Section S.5: Guidance:

Analytical Procedures and Methods Validation for Drugs and Biologics (Final, July 2015)

Other Helpful Information:

USP 43–NF 38: General Chapter <11>, "Reference Standards,"

Example of Deficiencies:

- Please provide qualification of your in-house Reference Standard against USP Reference Standard (if available).
- Please provide the [source, lot#, COA] for the [primary reference standard / working reference standard] for each of the following identified impurities.

Sections 3.2.S.6: Guidances:

Code of Federal Regulations-Title 21-Food and Drug (Current as of April 1, 2020)
Q1A (R2) Stability Testing of New Drug Substances and Products (Final, November 2003)

Other Helpful Information:

USP monographs

Example of Deficiencies:

- Please revise the storage temperature on the drug substance label to USP controlled room temperature, or 20 °C to 25 °C with excursions permitted between 15 °C -30 °C or provide long term stability data that supports a 30 °C storage temperature.
- Please align your caution statement with 21 CFR 201.122(a) to contain "Caution: for manufacturing, processing, or repacking. Rx Only."

Sections 3.2.S.7: Guidances:

Q1A(R2) Stability Testing of New Drug Substances and Products (Final, November 2003)
Q1B Photostability Testing of New Drug Substances and Products (Draft, March 1996)
Q1C Stability Testing for New Drugs and Products (Final, May 1997)
Q1D Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products (Final , January 2003)
Q1E Evaluation for Stability Data (Final, June 2004)
ANDAs Stability Testing of Drug Substances and Products (Final, June 2013)
ANDAs Stability Testing of Drug Substances and Products, Questions and Answers (Final, May 2014)

Example of Deficiency:

- We acknowledge you have provided 6M of accelerated and 12M of long-term stability data from the three validation batches. Please clearly indicate the retest date for your drug substance.

List of Relevant Quality Guidances & Common Deficiencies Observed During Drug Master File (DMF) Review

Sad Ahamed - Chemist
Mahmut Levent - Chemist

On behalf of
Division of Lifecycle API
Office of New Drug Products
Office of Pharmaceutical Quality, FDA/CDER

Purpose & Objective

- This presentation is intended to provide a non-exhaustive list of relevant guidances and discuss common deficiencies to improve submission quality.

- Poster is organized by CTD sections. Each section includes commonly observed deficiencies and relevant guidance that are helpful to address deficiencies.

Section 3.2.S.1:General Information

Guidances:

- Drug Master Files Guidance for Industry (Draft, October 2019)

https://www.fda.gov/media/131861/download

- ANDAs Pharmaceutical Solid Polymorphism: Chemistry, Manufacturing and Controls Information (Final, July 2007)

https://www.fda.gov/media/71375/download

Example of Deficiencies:

- The general properties section (S.1) fails to contain all relevant information. Please provide chirality, polymorphism, hygroscopicity, melting range for the drug substance.
- Please provide a Letter of Authorization (LOA) for each referencing application in Module 1, section 1.4 of your DMF.

Section S.2: Manufacture

Guidances:

- Process Validation: General Principles and Practices (Final, January 2011)
- Q11 Development and Manufacture of Drug Substances (Final, November 2012)
- Q11 Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Entities) Questions and Answers (Final, February 2018)
- Q7 Good manufacturing practice for active pharmaceutical ingredients (Final, September 2016)
- Q8(R2) Pharmaceutical Development (Final, November 2009)
- Q9 Quality Risk Management (Final, June 2006)

3.2.S.2:Manufacture (Continue)

Example of Deficiencies:

- Please provide a statement that your manufacturing facilities are in compliance with applicable cGMP requirements. Include all contract labs cGMP statement.
- Please revise your synthetic scheme to include chemical structures with reagents, solvents, and reaction conditions, as appropriate.
- Potential impurity X is expected in your manufacturing process. Please discuss your control strategies for it with supporting data, as necessary.
- Please provide a summary of your process validation for the manufacturing process, such as validation batch description, starting material analysis, IPCs, intermediate and final API analysis in a tabular format.

Sections 3.2.S.3:Characterization

Guidances:

- M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals To Limit Potential Carcinogenic Risk (Final, March 2018)
- Q3A Impurities In New Drug Substances (Final, June 2008)
- ICH Q3C Maintenance Procedures for the Guidance for Industry Q3C Impurities: Residual Solvents (Final, July 2017)
- Q3D(R1) Elemental Impurities (Final, July 2018)
- ANDAs Impurities in Drug Substances (Final, July 2009)

Example of Deficiencies:

- In your manufacturing process, X, Y and Z are plausible impurities. Please discuss your control strategy for these impurities and their downstream derivatives. Please include them to the specification with the justifiable limits, if needed.
- Please comment on the following possible process or degradation impurities and demonstrate that, if present, the related substances test method would detect them so that they can be controlled appropriately.

Sections 3.2.S.4: Control of Drug Substance

Guidances:

- Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances (Final, December 2000)
- Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products (Final, August 1999)
- Q2B Validation of Analytical Procedures: Methodology (Final, May 1997)

Other Helpful Information:

- USP 43-NF 38 : General chapters: <621> chromatography

Example of Deficiencies:

- Please revise the limit of any individual unspecified impurity acceptance criterion in your drug substance release and stability specifications to NMT 0.10% to be aligned with ICH Q3A.

- Per USP <621> where there is not a monograph available, the %RSD for assay determined by Table 1 RSD requirements. Please re-evaluate the %RSD requirements for the assay test and provide the updated system suitability.

Section S.5: Reference Standards or Materials

Guidance:

- Analytical Procedures and Methods Validation for Drugs and Biologics (Final, July 2015)

Other Helpful Information:

- USP 43–NF 38: General Chapter <11>, "Reference Standards,"

Example of Deficiencies:

- Please provide qualification of your in-house Reference Standard against USP Reference Standard (if available).
- Please provide the [source, lot#, COA] for the [primary reference standard / working reference standard] for each of the following identified impurities.

Section S.6: Container Closure System

Guidances:

- CFR-Code of Federal Regulations-Title 21 (Current as of April 1, 2020)
- Q1A (R2) Stability Testing of New Drug Substances and Products (Final, November 2003).

Other Helpful Information:

- USP monographs

Example of Deficiencies:

- Please revise the storage temperature on the drug substance label to USP controlled room temperature, or 20 °C to 25 °C with excursions permitted between 15 °C -30 °C or provide long term stability data that supports a 30 °C storage temperature.
- Please align your caution statement with 21 CFR 201.122(a) to contain “Caution: for manufacturing, processing, or repacking. Rx Only.”

Sections 3.2.S.7: Stability

Guidances:

- Q1A(R2) Stability Testing of New Drug Substances and Products (Final, November 2003)
- Q1B Photostability Testing of New Drug Substances and Products (Draft, March 1996)
- Q1C Stability Testing for New Drugs and Products (Final, May 1997)
- Q1D Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products (Final , January 2003)
- Q1E Evaluation for Stability Data (Final, June 2004)
- ANDAs Stability Testing of Drug Substances and Products (Final, June 2013)
- ANDAs Stability Testing of Drug Substances and Products: Questions and Answers (Final, May 2014)

Example of Deficiency:

- We acknowledge you have provided 6M of accelerated and 12M of long-term stability data from the three validation batches. Please clearly indicate the retest date for your drug substance.

Resources

- ICH Website:

https://www.ich.org/page/ich-guidelines

- FDA Guidance Documents

https://www.fda.gov/regulatory-information/search-fda-guidance-documents

- USP website:

https://login.usp.org/cas/login?service=https%3A%2F%2Fonline.uspnf.com%2Fcas%2Flogin

Conclusion

- The goal is to be able to deem the DMF submissions “adequate” in the first cycle.
- It is possible to limit the review cycles, and a number of ICH and FDA guidances are available.
- DMF holders are encouraged to consult the FDA guidances document page.

Acknowledgement

Ramnarayan Randad, PhD

Erin Skoda, PhD

Wei Liu, PhD

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 4th, 2021.

Follow-on webinar for both posters/presentations on April 9, 2021. Questions can be sent to the above email by 3/19/2021 for the webinar.

Please refer to the following posters for cross-referenced materials: Administrative Process (V. Selvam)

Please refer to the following presentations on March 3rd for additional information: Effective communication strategies (D. Skanchy)