SBIA-DMF Drug Substance Workshop

March 3 & 4, 2021 (Virtual)

Establishing Impurity Acceptance Criteria as Part of Specifications for DMFs Based on Clinical Relevance

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PURPOSE

To obtain a drug approval, an NDA/ANDA applicant must demonstrate, among other things, that its drug product is safe. The assessments of pharmaceutical quality and safety include multiple considerations; one major consideration is the acceptance criteria of impurities in the drug substance. Establishing impurity limits in drug substances represents one of the common challenges for both pharmaceutical industry and regulators especially when ICH guidelines do not apply. In this presentation, we will discuss the clinical relevance approach described in FDA's MAPPs (Manual of Policies and Procedures) for establishing of impurity limits in drug substance specifications in drug master files (DMFs).

OBJECTIVE(S)

1. Understand what types of data and information are needed when establishing impurity acceptance criteria in drug substances.
2. Illustrate how to establish drug substance impurity acceptance criterion based on clinical relevance with real case examples.

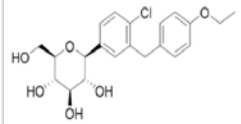
METHOD(S)

1. MAPP 5017.2 Rev. 1: Establishing Impurity Acceptance Criteria As Part of Specifications for NDAs, ANDAs, and BLAs Based on Clinical Relevance
2. MAPP 5310.7 Rev. 1: Acceptability of Standards from Alternative Compendia (BP/EP/JP)

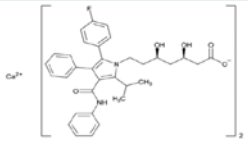
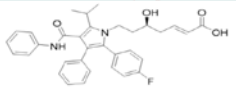
RESULT(S)

Case Studies:

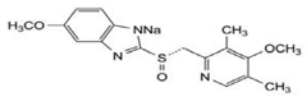
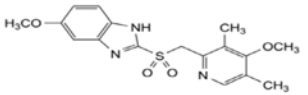
Case 1: The acceptance criterion of a specified impurity may generally be established at up to the ICH Q3A qualification threshold (QT) if there is absent other information to support the need for a lower limit.

Drug substance: Dapagliflozin	Specified Impurities: Impurity 1, Impurity 2 and Impurity 3
 Maximum Daily Dose (MDD): 10 mg Indication: Improving glycemic control in adults with type 2 diabetes mellitus.	ICH Q3A QT: 0.15% There is no USP or EP monograph Acceptance criterion for Impurity 1, Impurity 2 and Impurity 3 in DMFs: NMT 0.15% for each based on the ICH Q3A QT.

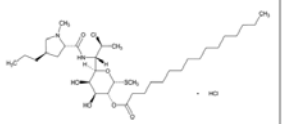
Case 2: The acceptance criterion of a specified impurity should be set at lower than the ICH Q3A QT if there is a compendial limit related to safety which is lower than the ICH Q3A QT for the impurity.

Drug substance: Atorvastatin Calcium USP	Specified impurity: Atorvastatin 3-deoxyhept-2-enoic acid
 MDD: 80 mg Indication: Prevention of cardiovascular disease.	 ICH Q3A QT: 0.15% USP limit: NMT 0.10% Acceptance criterion in DMFs: NMT 0.10%

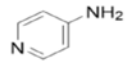
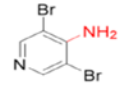
Case 3: The acceptance criterion of a specified impurity may be established at more than the ICH Q3A QT if the drug substance has a USP monograph or does not have a USP monograph but has other compendial monographs and the monograph acceptance criterion is greater than the ICH Q3A QT:

Drug substance: Esomeprazole sodium	Specified impurity: EP specified Impurity D
 MDD: 240 mg Indication: Anti-ulcerative; gastroesophageal reflux disease	 ICH Q3A Qualification threshold (QT): 0.15% There is no USP monograph. EP limit: NMT 0.2% Acceptance criterion in DMFs: NMT 0.2%

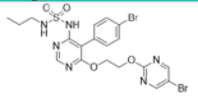
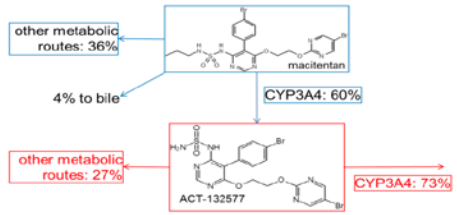
Case 4: The acceptance criterion for a specified impurity in a DMF referenced by an ANDA or a 505(b)(2) NDA product may be supported by a side-by-side comparative impurity analysis for the proposed product and the RLD using the same validated analytical method that is shown to be suitable for its intended purpose. The comparison should be conducted on multiple batches (n≥3) of the proposed product and the RLD using the same validated method.

Drug substance: Clindamycin Palmitate Hydrochloride	Specified Impurity: Impurity 1
 Maximum Daily Dose (MDD): 1.8 g Indication: Treatment of serious infections caused by susceptible anaerobic bacteria/strains of *streptococci, pneumococci, staphylococci.*	There is a USP monograph, but there is no control of specified impurities in USP. ICH Q3A Qualification threshold (QT) does not apply due to the semi-synthetic antibiotic nature of the Drug substance. Acceptance criterion for Impurity 1 in DMFs: NMT 0.5% based on side-by-side comparative impurity analysis of 3 batches of the proposed drug substance and the RLD using the same validated analytical method

Case 5: The acceptance criterion of a specified impurity may not be set at the ICH Q3A QT if there are known safety data for the impurity based on its structural class (e.g. the presence of a structural alert for mutagenicity).

Drug substance: Dalfampridine USP	Specified impurity: 3,5-dibromo-4-aminopyridine
 MDD: 20 mg Indication: Treatment of multiple sclerosis.	 ICH Q3A QT: 0.15% USP limit: NMT 75 ppm Acceptance criterion in DMFs: 75 ppm

Case 6: The proposed acceptance criterion may be supported by data or literature demonstrating that the impurity is a significant metabolite of the drug substance.
The clinical significance of a metabolite may be subject to pharm/tox and/or clinical pharmacology consults.

Drug substance: Macitentan	Specified Impurity: ACT-132577
 MDD: 10 mg Indication: treatment of Pulmonary arterial hypertension (PAH)	ICH Q3A Qualification threshold (QT): 0.15% There is no USP or EP monograph Acceptance criterion for Impurity ACT-132577: NMT 0.15% based on a literature demonstrating that the impurity is a significant metabolite of the drug substance Macitentan.
Macitentan metabolism pathway (Reference: Clinical Pharmacokinetics Vol.55, 369–380, 2016) 	

CONCLUSION(S)

The FDA MAPP 5017.2 and MAPP 5310.7 provide guiding principles and approaches for establishing drug substance impurity acceptance criteria for non-mutagenic impurities as part of specifications for DMFs based on the consideration of clinical relevance. These polices can serve as useful tools for both drug applicants and FDA assessors, helping accelerate the approval processes of drugs to the American public.

Establishing Impurity Acceptance Criteria As Part of Specifications for DMFs Based on Clinical Relevance

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FDA CDER Manual of Policies & Procedures: MAPP

What's MAPP?

FDA CDER's Manual of Policies and Procedures (MAPPs) are federal directives and documentation of internal policies and procedures. MAPPs are required by law, and made available to the public to make FDA a more transparent organization.

FDA MAPPs can be found at:
https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/cder-manual-policies-procedures-mapp)

FDA CDER Impurity MAPPs

- MAPP 5017.2 Rev. 1: Establishing Impurity Acceptance Criteria As Part of Specifications for NDAs, ANDAs, and BLAs Based on Clinical Relevance (Effective Date: 5/1/2020)

- MAPP 5310.7 Rev. 1: Acceptability of Standards from Alternative Compendia (BP/EP/JP) (Effective Date: 10/13/2017)

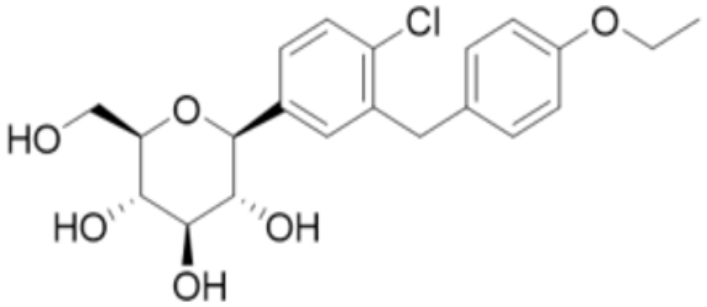
Purposes of FDA Impurity MAPPs

- Provide guiding principles and approaches for establishing drug substance and drug product impurity acceptance criteria for non-mutagenic impurities in NDAs, ANDAs, and BLAs based on the consideration of clinical relevance.

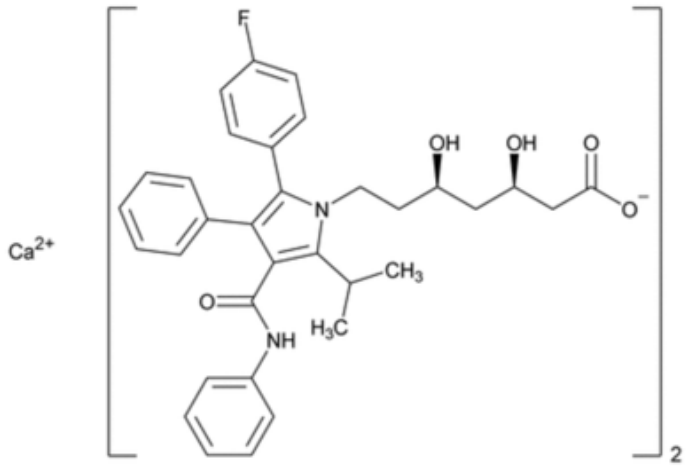
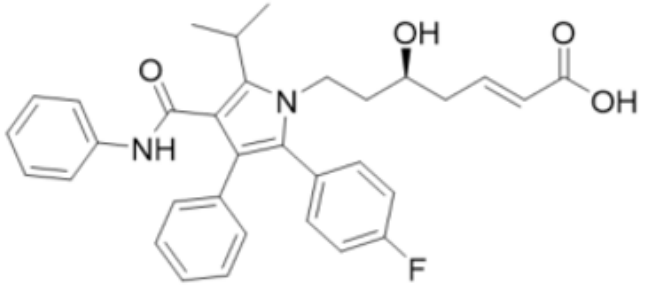
- Clarify what types of data and information are needed when establishing impurity acceptance criteria in drug substances and drug products.

Illustrate how to use the clinical relevance approach in FDA MAPPs to establish impurity limits in drug substance specifications in drug master files (DMFs) with real case examples

Case 1: The acceptance criterion of a specified impurity may generally be established at up to the ICH Q3A qualification threshold (QT) if there is absent other information to support the need for a lower limit.

Drug substance: **Dapagliflozin**	**Specified Impurities:** **Impurity 1, Impurity 2 and Impurity 3**
 **Maximum Daily Dose (MDD):** 10 mg **Indication:** Improving glycemic control in adults with type 2 diabetes mellitus.	**ICH Q3A QT: 0.15%** **There is no USP or EP monograph** **Acceptance criterion for Impurity 1, Impurity 2 and Impurity 3 in DMFs:** **NMT 0.15% for each based on the ICH Q3A QT.**

Case 2: The acceptance criterion of a specified impurity should be set at lower than the ICH Q3A QT if there is a compendial limit related to safety which is lower than the ICH Q3A QT for the impurity.

Drug substance: **Atorvastatin Calcium USP**	**Specified impurity:** **Atorvastatin 3-deoxyhept-2-enoic acid**
 **MDD:** 80 mg **Indication:** Prevention of cardiovascular disease.	 **ICH Q3A QT: 0.15%** **USP limit: NMT 0.10%** **Acceptance criterion in DMFs: NMT 0.10%**

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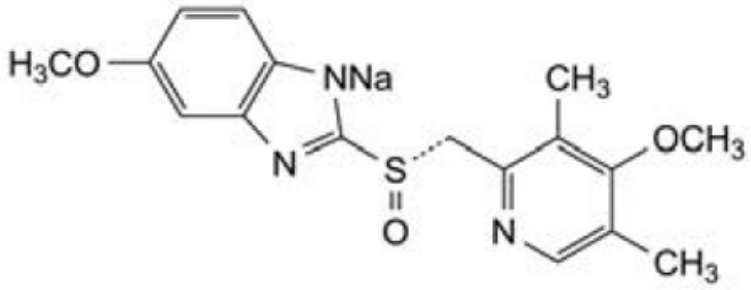
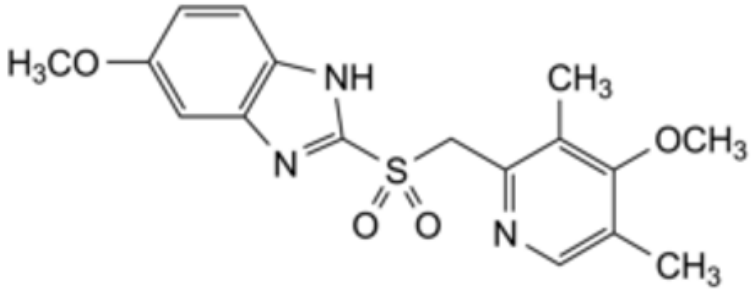
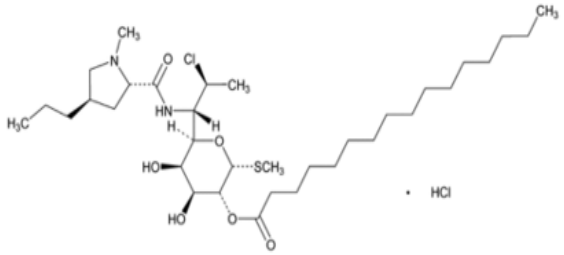
Case 3: The acceptance criterion of a specified impurity may be established at more than the ICH QT if available compendial monograph acceptance criterion is greater than the ICH OT:

Drug substance: **Esomeprazole sodium**	**Specified impurity:** **EP specified Impurity D**
 **MDD:** 240 mg **Indication:** Anti-ulcerative; gastroesophageal reflux disease	 **ICH Q3A Qualification threshold (QT): 0.15%** **There is no USP monograph.** **EP limit: NMT 0.2%** **Acceptance criterion in DMFs: NMT 0.2%**

Case 4: The acceptance criterion for a specified impurity in a DMF referenced by an ANDA or a 505(b)(2)NDA product may be supported by a side-by-side comparative impurity analysis for the proposed product and the RLD.

Drug substance: **Clindamycin Palmitate Hydrochloride**	**Specified Impurity:** **Impurity 1**
 **Maximum Daily Dose (MDD):** 1.8 g **Indication:** Treatment of serious infections caused by susceptible anaerobic bacteria/strains of *streptococci*, *pneumococci*, *staphylococci*.	**There is a USP monograph, but there is no control of specified impurities in USP.** **ICH Q3A Qualification threshold (QT) does not apply due to the semi-synthetic antibiotic nature of the Drug substance.** **Acceptance criterion for Impurity 1 in DMFs: NMT 0.5% based on side-by-side comparative impurity analysis of 3 batches of the proposed drug substance and the RLD using the same validated analytical method**

- The comparison should be conducted on multiple batches (n≥3).
- The same analytical method should be used for the analysis.
- The analytical method should be validated to demonstrate that it is suitable for its intended purpose.

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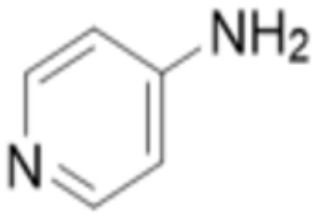 **MDD:** 20 mg **Indication:** Treatment of multiple sclerosis.	 **ICH Q3A QT: 0.15%** **USP limit: NMT 75 ppm** **Acceptance criterion in DMFs: 75 ppm**

Case 6: The proposed acceptance criterion may be supported by data or literature demonstrating that the impurity is a significant metabolite of the drug substance.

The clinical significance of a metabolite may be subject to pharm/tox and/or clinical pharmacology consults.

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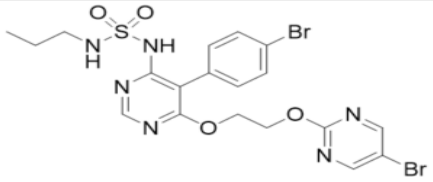
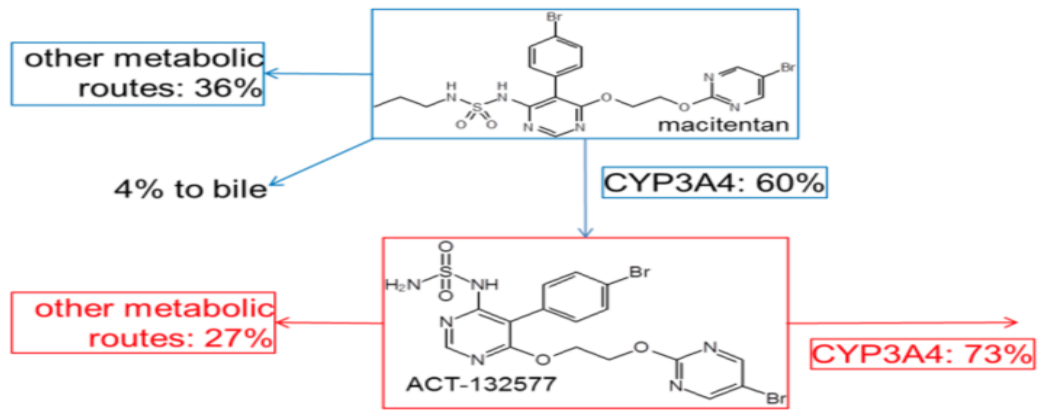
 **MDD:** 10 mg Indication: treatment of Pulmonary arterial hypertension (PAH)	**ICH Q3A Qualification threshold (QT): 0.15%** **There is no USP or EP monograph** **Acceptance criterion for Impurity ACT-132577: NMT 0.15% based on a literature demonstrating that the impurity is a significant metabolite of the drug substance Macitentan.**
Macitentan metabolism pathway (Reference: Clinical Pharmacokinetics Vol.55, 369–380, 2016) 	

Summary

The FDA MAPPs provide guiding principles and approaches for establishing drug substance impurity acceptance criteria for non-mutagenic impurities as part of specifications for DMFs based on the consideration of clinical relevance. These polices can serve as useful tools for both drug applicants and FDA assessors, helping accelerate the approval processes of drugs to the American public.

Thank You!

- Send questions regarding this poster to: DMFWorkshop2021@fda.hhs.gov by 02/15/2021 for inclusion in the poster Q&A session on *March 4th.*

- 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 presentation on March 4th for additional information: Considerations for Impurity Qualification - ICH Q3A/Q3C/Q3D, RLD & MDD