Safety Evaluation of Drug Substance Impurities in Generics

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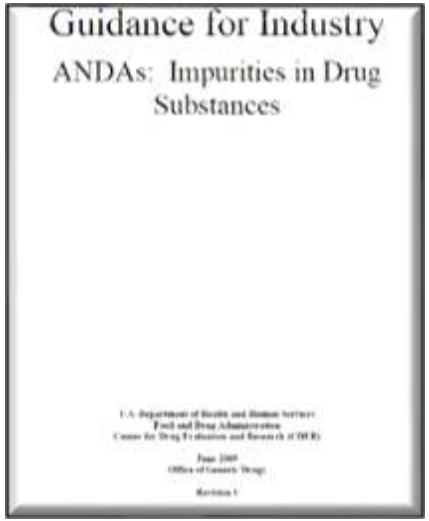
Overview

- Key aspects of the safety assessment of drug substance impurities in generic drug products
- OGD-Pharmacology/Toxicology (Pharm/Tox) review process for drug substance impurities
- Case studies highlighting key aspects and common pitfalls in safety evaluation of drug substance impurities in generic drug products

Guidances for Impurity Qualification



Key Principles in Safety Evaluation

- Safety profile of generic should be the same as that of the reference listed drug (RLD)
- Maximum Daily Dose (MDD)
- Context of use of the referencing application*
  - Route of administration
  - Duration of use
  - Dosing regimen
  - Target patient population

* Referencing application refers to the Abbreviated New Drug Application (ANDA) and/or the New Drug Application (NDA), supported by the Drug Master File (DMF)

OGD-Pharm/Tox Review Process

- **Determination of mutagenic potential**
  - Use approaches described in ICH M7(R1) guidance
  - Determine duration of use and identify the threshold of toxicological concern (TTC)
- **Determination of general toxicity**
  - Use approaches described in ICH Q3A(R2) guidance
  - Determine the MDD and identify the qualification threshold (QT)

Mutagenicity Evaluation

- If the proposed level of an impurity exceeds the TTC, approaches described in ICH M7(R1) guidance are used to address mutagenic potential
  - (Q)SAR analysis
  - Ames assay
  - Follow-up *in vitro* and *in vivo* studies

- In some cases, OGD-Pharm/Tox collaborates with in-house computational toxicology group
  - When there are questions on DMF holder's (Q)SAR justification
  - When there is lack of sufficient data for mutagenicity assessment
- OGD-Pharm/Tox collaborates with different working groups and internal experts across CDER on complex issues

(Q)SAR: Quantitative Structure-Activity Relationship
CDER: Center for Drug Evaluation and Research

General Toxicity Evaluation

- If the proposed level of an impurity exceeds the QT, approaches described in ICH Q3A(R2) guidance are used to address general toxicity
  - Systemic and local toxicity evaluation at proposed limit
  - General toxicity studies in one species, usually 14 to 90 days duration
  - Consideration of context of use to select the following:
    - Duration of nonclinical study
    - Route of administration in nonclinical study
    - Doses with sufficient margins as compared to clinical exposure

- Published scientific literature

Case Studies

Case 1: Use of *in silico* methods to characterize safety of an impurity

Case 1: Impurity A

- Impurity A is a process-related impurity in drug substance
- Proposed generic drug product is an oral tablet for chronic use
- Proposed level of Impurity A exceeds ICH M7(R1) TTC and ICH Q3A(R2) QT

TTC: Threshold of Toxicological Concern
QT: Qualification Threshold

Case 1: DMF holder's justification

- (Q)SAR analysis for evaluation of
  - Mutagenicity
  - Human adverse liver, cardiovascular, and heart effects
  - Rodent carcinogenicity
  - Mammalian reproductive and developmental toxicity

Case 1: Pharm/Tox assessment

- (Q)SAR analysis for mutagenicity is adequate (complimentary models, full study report submitted)
- Impurity A can be controlled as a non-mutagenic impurity
- (Q)SAR analysis for general toxicity is not acceptable

Conclusion: Not Acceptable

Case 1: Regulatory recommendations

- Tighten the limit of Impurity A as per recommendations of ICH Q3A(R2) guidance
- If Impurity A is controlled at a level higher than qualification threshold, address the safety of Impurity A by one of the following options:
  - Conduct a general toxicity study of 90 days duration, considering the context of use
  - Provide published literature to justify the proposed higher level

Case 1: Common pitfalls in (Q)SAR justifications

- (Q)SAR submitted for general toxicity evaluation - not validated for the endpoints of general toxicity studies
- (Q)SAR for mutagenicity evaluation
  - Single model submitted
  - Models not fit-for-purpose per ICH M7(R1)
  - Full study report not submitted

Case 2: Consideration of duration of use of the drug to set impurity limits

Case 2: Impurity B

- Impurity B is a potential mutagenic impurity in drug substance
- Proposed generic drug product is an emulsion foam for chronic use
- Proposed level of Impurity B is 120 µg/day

Case 2: DMF holder's justification

- DMF holder made the following claims:
  - Duration of use of referencing drug product is limited to 2 weeks, based on RLD labeling
  - Proposed limit of 120 µg/day for Impurity B is justified per ICH M7(R1), as treatment duration is ≤1 month

Case 2: Pharm/Tox assessment

- DMF holder did not consider the total number of dosing days in a lifetime of a patient
- Proposed drug product can be used intermittently, multiple times throughout the patient's lifetime
- Based on clinical indication, duration of use of proposed drug product is chronic i.e., >10 years to lifetime → TTC is 1.5 µg/day
- OGD-Pharm/Tox uses similar thresholds as FDA/CDER's review division for the RLD

Conclusion: Proposed limit not acceptable

Case 2: Regulatory recommendations

- Duration of use of referencing drug product is chronic, based on total number of dosing days in a patient's lifetime → TTC is 1.5 µg/day
- Tighten the limit of Impurity B to the TTC
- If Impurity B is controlled at a level higher than TTC
  - Perform QSAR analysis on Impurity B, using approaches described in ICH M7(R1)
  - If Impurity B is predicted to be positive for bacterial mutagenicity, control Impurity B at TTC. Alternatively, to support a level higher than TTC, perform mutagenicity assessment described in ICH M7(R1)

Case 2: Common pitfalls in setting impurity limits

- Context of use is not taken into consideration while setting limits for mutagenic impurities
  - Clinical indication
  - Duration of use (total number of dosing days in a patient's lifetime)

Case 3: DMF shared between multiple ANDAs

Case 3: Impurity C and Impurity D

- Impurity C and D are degradation impurities of drug substance
- DMF is referenced by two proposed drug products

	Dosage form	Daily doses
ANDA #1	Oral	1.5 g/day
ANDA #2	Intravenous	Loading dose 7 g/day Maintenance dose 1.5 g/day

- DMF holder controlled both impurities C and D at NMT 0.15%. No safety justification was submitted

Case 3A: Mutagenicity assessment

- OGD-Pharm/Tox collaborated with FDA's computational toxicology team for in-house (Q)SAR analysis
- Impurity C predicted to be positive for bacterial mutagenicity, whereas Impurity D was predicted to be negative for bacterial mutagenicity
- Duration of use of both ANDA #1 and ANDA #2 is chronic, i.e., >10 years to lifetime

ICH M7(R1) Mutagenic Impurities

Duration of treatment	≤ 1 month	>1 - 12 months	>1 - 10 years	>10 years to lifetime
Daily intake [µg/day]	120	20	10	1.5

Case 3A: Mutagenicity assessment

The DMF is referenced by two ANDAs with different dosage forms and MDDs.

Question: Which MDD should be used to determine the control limit for impurity C (potential mutagenic impurity)?

Answer: For mutagenic impurities, chronic MDD amongst various referencing products should be considered to account for exposure to cumulative levels of impurity throughout the duration of use

	Dosage form	Daily doses
ANDA #1	Oral	1.5 g/day
ANDA #2	Intravenous	Loading dose 7 g/day Maintenance dose 1.5 g/day

Chronic MDD

Case 3A: Regulatory recommendations

- For Impurity C (potential mutagenic impurity)
  - Control at ICH M7(R1) recommended TTC of 1.5 µg/day,
  - Use chronic MDD of 1.5 g/day to calculate concentration limit in ppm (1.5 µg/day ÷ 1.5 g/day)
  - If Impurity C is controlled at a level higher than TTC, conduct an Ames assay to address the mutagenicity concern

Case 3B: General toxicity assessment

The DMF is referenced by two ANDAs with different dosage forms and MDDs.

Question: Which MDD should be used to determine the qualification threshold for impurity D (non-mutagenic)?

Answer: Non-mutagenic impurities can have unique toxicity profiles across organs and their effects may manifest either after acute exposure or after repeated exposure. Therefore, maximum possible daily dose is considered to determine qualification threshold

ICH Q3A Drug Substance Impurities

Maximum Daily Dose[1]	Reporting Threshold[2,3]	Identification Threshold[3]	Qualification Threshold[3]
≤ 2g/day	0.05%	0.10% or 1.0 mg per day intake (whichever is lower)	0.15% or 1.0 mg per day intake (whichever is lower)
> 2g/day	0.03%	0.05%	0.05%

Maximum possible daily dose in this case is 7 g/day

Case 3B: Regulatory recommendations

- For Impurity D (non-mutagenic)
  - Control Impurity D at ICH Q3A(R2) recommended QT, based on maximum possible daily dose of 7 g/day for referencing intravenous product
  - If Impurity D is controlled at a level higher than QT, conduct a repeated-dose toxicity study, considering the context of use of the referencing product

Case 3: Common pitfall when DMF is shared between multiple ANDAs

- DMF holders do not consider the MDD and context of use of all referencing drug products, when their DMFs are shared between multiple ANDAs
- Duration of use, patient population, and route of administration are not considered in setting impurity limits and respective safety justifications

Case 4: Inappropriate test concentrations in Ames assay

Case 4: Impurities E and F

- Impurities E and F are potential mutagenic impurities in drug substance
- Proposed generic drug product is an oral tablet for chronic use
- Proposed levels of impurities E and F exceed ICH M7(R1) TTC

Case 4: DMF holder's justification

- DMF holder submitted two independent Ames assays to evaluate the mutagenicity of impurities E and F
- Based on negative results in the submitted Ames assay, DMF holder concluded that impurities E and F are non-mutagenic

Case 4: Pharm/Tox assessment

- Impurity E caused extreme cytotoxicity, i.e., greater than 50% decrease in the background lawn
- Impurity F was not a neat impurity and was spiked in the drug substance
- Top concentrations of impurities E and F tested in the submitted Ames assays were ~500-fold lower than the OECD 471 guideline recommended maximum test concentration, i.e., 5000 µg/plate

Conclusion: Mutagenicity potential not adequately characterized

Case 4: Regulatory recommendations

- Tighten the limits of impurities E and F to TTC as per recommendations of ICH M7(R1) guidance
- If the two potential mutagenic impurities are controlled at levels higher than the TTC
  - Impurity E: Conduct an in vitro mammalian cell assay using neat impurity
  - Impurity F: Conduct an Ames assay, using neat impurity and maximum test concentration as described in OECD 471 guideline

Case 4: Common pitfalls in Ames assays

- Excessive cytotoxicity – inadequate characterization of mutagenic potential
- Neat impurity is not used
- Ames assay not conducted per OECD 471 guideline
- Selection of top dose is not adequate

Summary

- OGD-Pharm/Tox safety evaluation of drug substance impurities in generic drugs typically relies on the following:
  - FDA and ICH guidances
  - Maximum daily dose to determine evaluation thresholds
  - Context of use of drug product

- Highlights common, recurring deficiencies related to impurities in DMFs
- Provides recommendations on ways these common deficiencies can be avoided

Resources

- Q3A(R) Impurities in New Drug Substances
- ANDAs: Impurities in Drug Substances
- M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals To Limit Potential Carcinogenic Risk
- Good ANDA Submission Practices Guidance for Industry
- OECD Test No. 471: Bacterial Reverse Mutation Test
- S2(R1) Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use
- Drug Master Files

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Thank You!

- For any questions regarding this presentation, please type them into the “Q&A Box” so that they can be addressed during the Q&A panel after this session.

- To submit questions on this presentation for inclusion in the follow-on webinar on April 9, 2021, please send them to DMFWorkshop2021@fda.hhs.gov by March 19, 2021.


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