Safety Evaluation of Impurities in Generic Drugs

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Overview

- Impurities in Drug Development: CDER Pharmacology/Toxicology (Pharm/Tox) evaluation
- Impurities in Generic Drug Development: OGD Pharm/Tox review evaluation
- Case studies highlighting key aspects and common pitfalls in safety evaluation of impurities in generic drug products

CDER: Center for Drug Evaluation and Research

Impurities

Drug Substance (DS)-Related

Any component of the drug substance that is not the chemical entity defined as the drug substance

Drug Product (DP)-Related

Any component of the drug product that is not the drug substance or an excipient in the drug product

Other Types of Impurities

Impurities that may arise during manufacturing and storage of the generic drug product

- **Residual solvents** – organic volatile chemicals used in manufacturing of drug substance/excipient/drug product
- **Elemental Impurities** – arising from residual catalysts/components of drug product/interaction with container closure system (CCS)
- **Extractables and Leachables** – organic or inorganic chemical entities that are extracted/leached from the CCS

CDER Pharm/Tox Evaluation of Impurities

- Drug substance and drug product impurities evaluated according to principles of ICH and FDA guidances
- Impurity specifications above allowable thresholds evaluated for safety (mutagenicity and general safety)
- Approaches for safety review in Office of New Drugs (OND) and Office of Generic Drugs (OGD) are similar: context-specific safety assessment

ICH: International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use

Key Principles in Safety Evaluation

- Safety profile of generic should be the same as that of the reference listed drug (RLD)
- Context of use of the drug product is key:
  - Route of administration
  - Dosing regimen
  - Duration of use
  - Clinical indication
  - Target patient population
- FDA and ICH guidances inform the regulatory framework

Key Guidances for Impurity Qualification

- **ICH Q3A(R2): Impurities in New Drug Substances**
  - https://www.fda.gov/regulatory-information/search-fda-guidance-documents/q3ar-impurities-new-drug-substances
- **ICH Q3B(R2): Impurities in New Drug Products**
  - https://www.fda.gov/regulatory-information/search-fda-guidance-documents/q3br-impurities-new-drug-products-revision-2
- **ICH M7(R1): Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk**
  - https://www.fda.gov/regulatory-information/search-fda-guidance-documents/m7r1-assessment-and-control-dna-reactive-mutagenic-impurities- pharmaceuticals-limit-potential
- **Good ANDA Submission Practices**
  - https://www.fda.gov/regulatory-information/search-fda-guidance-documents/good-anda-submission-practices-guidance-industry
- **ANDAs: Impurities in Drug Products**
  - https://www.fda.gov/regulatory-information/search-fda-guidance-documents/andas-impurities-drug-products
- **ANDAs: Impurities in Drug Substances**
  - https://www.fda.gov/regulatory-information/search-fda-guidance-documents/andas-impurities-drug-substances

Impurities in Generics

- Generics may use different manufacturing processes than the RLD, resulting in differences in impurity profiles
- OGD Pharm/Tox is consulted when there is a potential safety concern (e.g., proposed specification higher than qualification threshold (QT), potentially mutagenic impurity, etc.)
- Context-specific safety assessment is necessary to support that the proposed generic has the same safety profile as RLD
- Multiple options may be used to support proposed specification:
  - Control at QT or allowable threshold based on duration of use
  - Submit toxicology information to support safety
  - Comparative impurity analysis with RLD (often reviewed by quality discipline)

OGD Pharm/Tox Review Process

Context-of-use of drug is key:

Impacts assessment of genotoxicity and general safety

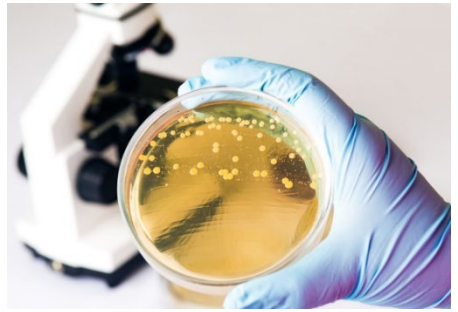
- Determination of mutagenic potential:
  - Use approaches described in ICH M7 guidance
  - Determine duration of use and identify the threshold of toxicological concern (TTC)

- Determination of general toxicity potential:
  - Use approaches described in ICH Q3A and Q3B guidances
  - Determine the maximum daily dose (MDD) and identify the QT
  - General toxicity (systemic and local) in animals if QT is exceeded

- Data gap or impurity-related adverse effects → applicant recommended to control at supported impurity limit

Mutagenicity Evaluation

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



- In some cases, OGD Pharm/Tox collaborates with in-house computational toxicology group
  - When there are questions on Applicant'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

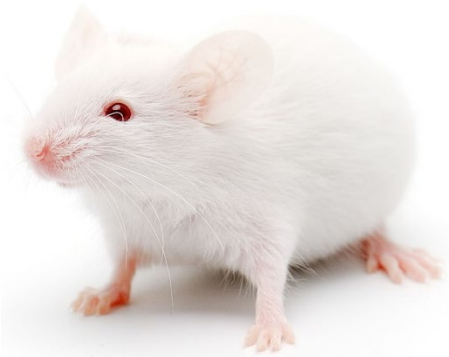
(Q)SAR: Quantitative Structure-Activity Relationship

Additional Considerations for Genetic Toxicology Evaluation

- (Q)SAR models
  - Expert rule-based and statistical-based models
  - Validated and fit-for-purpose per ICH M7
  - Full study reports for *in silico* predictions
- Ames assay
  - ICH S2(R1) and OECD 471 guidelines
  - Neat impurity
- For highly cytotoxic impurities, Ames assay may not appropriately characterize genotoxic potential and alternate *in vitro*/*in vivo* mutagenicity assays may be necessary
- Maximum daily intake (MDI) of impurity >1 mg/day and proposed drug is for chronic use, additional genetic toxicology and general toxicology studies are needed, as described in ICH Q3A/Q3B

General Toxicity Evaluation

- If the proposed level of an impurity exceeds the QT, approaches described in ICH Q3A and ICH Q3B guidances are used to address general toxicity
- Similar approaches apply for DS and DP impurities
  - Safety 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
    - Specific parameters (e.g., local toxicity) that need to be included in risk assessment to support safety of proposed specification



Other Approaches of Impurity Qualification

- Scientific literature
  - Full articles of the supporting publications
- Metabolite argument for impurity qualification
- Comparative analytical studies (chemistry)
  - Comparison of impurity profile of generic with RLD
  - Validated, stability-indicating analytical procedures

OGD Pharm/Tox collaborates with OND Pharm/Tox colleagues to align on issues that impact safety assessment of impurities (e.g., MDD, duration of use, changes in indications, specific considerations in general toxicology studies, etc.)

Additional Considerations for General Toxicology Evaluation

- Metabolite argument for impurity qualification
  - Both qualitative and quantitative information is needed
  - Adequate margin of exposure between the metabolite levels in plasma of animals/humans and proposed clinical exposure to impurity
- *In silico* prediction of general toxicity has not been validated for the qualification of an impurity in a drug product
- Cramer classification and read across approach using surrogate compounds are not adequate to justify general toxicity

Impurities in Advanced Cancer Drugs

- ICH S9 applies to drugs for advanced cancer-serious and life-threatening malignancy that is resistant and refractory to available therapy
- For products falling under ICH S9, TTC limits do not apply
- While genotoxicity concern for impurities is low, additional nonclinical studies may be warranted to address general safety

Case Studies

Case 1:

Use of *in silico* Methods to Characterize Safety of an Impurity

Case Study 1

- Impurity A proposed at not more than (NMT) 0.5% in drug substance
- RLD is indicated for chronic use via oral route of administration
- Proposed specification exceeds the QT per ICH Q3A
- **Consult question:** Is the proposed specification for Impurity A acceptable?

DMF Holder's Justification:

- *In silico* prediction [(Q)SAR analysis] to address:
  - Mutagenicity
  - Carcinogenicity
  - Reproductive and developmental toxicity
  - Liver and cardiovascular effects

OGD Pharm/Tox Safety Assessment

- At MDD 1000 mg and proposed specification of NMT 0.5%, the total daily intake (TDI) of Impurity A is 5 mg/day
  - Mutagenic impurities in the chronically used drug should be limited to TTC of 1.5 µg/day
  - QT per ICH Q3A is 0.15% or 1.0 mg per day intake, whichever is lower
  - Proposed specification exceeds the ICH Q3A QT and TTC per ICH M7

OGD Pharm/Tox Safety Assessment: Continued

- Full study report submitted, one expert-based and one statistical-based method used for (Q)SAR analysis
- Submitted (Q)SAR analysis for mutagenicity is adequate
  - Impurity A can be controlled as a non-mutagenic impurity
- (Q)SAR analysis for general toxicity is not acceptable→ general safety inadequately addressed

Conclusion: Proposed specification of Impurity A is not acceptable

Regulatory Recommendation and Pitfalls

- Regulatory recommendation
  - Control Impurity A at QT as per recommendations of ICH Q3A guidance
  - If Impurity A is controlled at a level higher than QT, address the safety of Impurity A using one of the following options:
    - Conduct a 90-day oral toxicity study with doses that provide adequate margins of exposure to support proposed specification
    - Provide published literature to justify the safety of proposed higher level
- Pitfalls
  - (Q)SAR submitted for general toxicity evaluation - not validated for the endpoints of general toxicity studies
  - Single model submitted
  - Full study report not submitted

Case 2:

Metabolite Justification to Control an Impurity Above ICH Limits

Case Study 2

- Impurity B proposed at NMT 0.5% in drug product
- RLD is indicated for oral route of administration
- Proposed specification exceeds the QT per ICH Q3B
- **Consult question:** Is the proposed specification for Impurity B acceptable?

Applicant's Justification:

- (Q)SAR to address mutagenicity
  - Full study report submitted, one expert-based and one statistical-based method used for (Q)SAR analysis
- Metabolite justification to address general toxicity
  - Claims Impurity B is metabolite of the active pharmaceutical ingredient (API) using information from published literature
    - Based on *in vitro* data conducted using human liver microsomes

OGD Pharm/Tox Safety Assessment

- At MDD 60 mg and proposed specification of NMT 0.5%, the TDI of Impurity B is 300 µg/day
  - RLD labeling suggests the lifetime duration of use is 1-10 years. Mutagenic impurities should each be limited to 10 µg/day
  - QT per ICH Q3B is 0.2% or 3 mg TDI, whichever is lower
  - Proposed specification exceeds the ICH Q3B QT and TTC per ICH M7
- Submitted (Q)SAR analysis is ICH M7–compliant and Impurity B is non mutagenic

OGD Pharm/Tox Safety Assessment: Continued

- *In vitro* data to support the metabolite justification is not acceptable and there is no quantitative information regarding metabolite levels in plasma of in either animals or humans

- Applicant's justification was inadequate and did not support qualification of the impurity as a metabolite

Conclusion: Proposed specification of Impurity B is not acceptable

Regulatory Recommendation and Pitfalls

- Regulatory recommendation:
  - Tighten the limit of Impurity B at QT, per ICH Q3B guidance.
  - If Impurity B is controlled at a level higher than QT, address the safety of Impurity B by one of the following options:
    - Provide quantitative data that indicates Impurity B is a metabolite in plasma upon oral administration of the drug in humans or in animals and that the level formed in plasma equals or exceeds the proposed clinical exposure
    - Conduct a general toxicity study, considering the context of use
    - Conduct comparative impurity analysis with RLD
- Pitfall:
  - Lack of quantitative information regarding metabolite levels in plasma of animals or humans

Case 3:

Read-Across (Surrogate) Approach Used to Justify General Toxicity of an Impurity

Case Study 3

- Impurity C is proposed at not more than (NMT) 0.4% in drug product
- RLD is indicated for chronic use via intravenous route of administration
- Proposed specification exceeds the QT per ICH Q3B
- **Consult question:** Is the proposed specification for Impurity C acceptable?

Applicant's Justification:

- (Q)SAR analysis using expert rule-based methodology to address mutagenicity
- Identified surrogates and used read-across approach to address general toxicity

OGD Pharm/Tox Safety Assessment

- At MDD 300 mg and proposed specification of NMT 0.4%, the TDI of Impurity C is 1200 µg/day
- Mutagenic impurities in the chronically used drug should be limited to TTC of 1.5 µg/day
- QT per ICH Q3B is 0.5% or 200 µg TDI, whichever is lower
- Proposed specification exceeds the ICH Q3B QT and TTC per ICH M7
- Applicant's (Q)SAR assessment was incomplete as only one model was used
  - Statistical-based (Q)SAR methodology not used
- Collaboration with FDA's computational toxicology team was necessary for in-house (Q)SAR analysis

OGD Pharm/Tox Safety Assessment: Continued

- Impurity C was predicted to be negative for bacterial mutagenicity, but positive in mouse lymphoma assay and *in vivo* mouse micronucleus assay due to the presence of same structural alert as API
- OGD Pharm/Tox determined that Impurity C would not significantly add to cancer risk of API, as API is itself genotoxic at therapeutic concentrations
- Therefore, additional genotoxicity studies would not be needed, and Impurity C can be controlled as a non-mutagenic impurity
- Read-across approach was not adequate to support the general safety of Impurity C

Conclusion: Proposed specification of Impurity C is not acceptable

Regulatory Recommendation and Pitfalls

- Regulatory recommendation:
  - Tighten the impurity limit to QT per recommendations in ICH Q3B guidance

  (Or)

  - Conduct a 90-day oral toxicity study with doses that provide adequate margins of exposure to support proposed specification of Impurity C
- Pitfalls:
  - Incomplete safety justification, lack of general toxicity assessment
  - Mutagenicity and general toxicity data are necessary to support impurity specifications that exceed QT or TTC
  - Read-across approach using surrogates to support safety impurity specification

Case 4:
Consideration of Duration of Use of the Drug to Set Impurity Limits

Case Study 4

- Impurity D is proposed at not more than 0.1% in drug substance.
- RLD is indicated for chronic use via dermal route of administration.
- **Consult question:** Is the proposed specification for Impurity D acceptable?

DMF Holder's Justification:

- Duration of use of referencing drug product is limited to 2 weeks, based on RLD labeling.
- Proposed exposure to Impurity D is justified per ICH M7, as treatment duration is ≤1 month.

OGD Pharm/Tox Safety Assessment

- At MDD 100 mg and proposed specification of NMT 0.1%, the TDI of Impurity D is 100 µg/day
- Based on the clinical indication, the duration of use of proposed drug product is chronic "i.e., >10 years to lifetime" and the allowable exposure to a potentially mutagenic impurity is 1.5 µg/day
- QT per ICH Q3B is 0.5% or 200 µg TDI, whichever is lower
- Proposed specification is lower than the QT, thus general toxicity assessment is not needed to qualify Impurity D

OGD Pharm/Tox Safety Assessment: Continued

- The proposed exposure to Impurity D exceeds the TTC of 1.5 µg/day per ICH M7
- DMF holder did not consider the total number of dosing days in a lifetime of a patient

Conclusion: Proposed specification for Impurity D is not acceptable as it results in exposure to higher than allowable limit for mutagenic impurity

OGD-Pharm/Tox uses similar thresholds as the OND review division for the RLD

Regulatory Recommendation and Pitfalls

- Regulatory recommendation:
  - Duration of use of referencing drug product is chronic, based on total number of dosing days in a patient's lifetime
  - Tighten the limit such that exposure to Impurity D is 1.5 µg/day
  - To support higher exposure than TTC
    - Perform (Q)SAR analysis on Impurity D, using approaches described in ICH M7; if predicted negative for bacterial mutagenicity, control Impurity D at up to QT per ICH Q3A
    - If Impurity D is predicted to be positive for bacterial mutagenicity, perform mutagenicity assessment (Ames study) as described in ICH M7
- Pitfall:
  - 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)

Summary

OGD Pharm/Tox conducts safety assessment of impurities in proposed generic drugs to ensure that the safety profile of the generic drug is comparable to that of its RLD

- Is based on FDA and ICH guidances
- Uses the same principles as the RLD division in OND
- Considers the MDD and duration of use to determine safety thresholds (QT and TTC)
- Considers the context of use (route of administration, dosing regimen, duration of use, clinical indication, target patient population) when qualifying impurities

Summary

- When qualifying impurities, consider:
  - *In silico* data generated using complementary models are accepted for mutagenicity assessments only
  - Full study reports are needed
  - Quantitative information regarding metabolite levels in plasma of either animals or humans is needed to support qualification of the impurity as a metabolites
  - Read-across approach is not adequate to support the general safety
  - Clinical indication and total number of dosing days in a patient's lifetime should be considered for setting limits for mutagenic impurities
- The Good ANDA Submission Practices Guidance is a key resource:

  https://www.fda.gov/regulatory-information/search-fda-guidance-documents/good-anda-submission-practices-guidance-industry
  - Highlights common, recurring deficiencies related to impurities assessments in ANDAs
  - Provides recommendations to avoid common deficiencies

Additional References

- ICH S2(R1): Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use
  - https://www.fda.gov/regulatory-information/search-fda-guidance-documents/s2r1-genotoxicity-testing-and-data-interpretation-pharmaceuticals-intended-human-use
- OECD Test No. 471: Bacterial Reverse Mutation Test
  - https://www.fda.gov/regulatory-information/search-fda-guidance-documents/s2r1-genotoxicity-testing-and-data-interpretation-pharmaceuticals-intended-human-use
- ICH S9: Nonclinical Evaluation for Anticancer Pharmaceuticals
  - https://www.fda.gov/regulatory-information/search-fda-guidance-documents/s9-nonclinical-evaluation-anticancer-pharmaceuticals

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