U.S. FOOD & DRUG ADMINISTRATION

Successful Practices for Pharmacology/Toxicology Justification in ANDAs

SBIA 2024: Regulatory Considerations to Enhance Generic Drug Access

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April 11, 2024

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Outline

- Learning Objectives
- Role of Pharm/Tox in Generic Drugs
- Common Issues/Deficiencies
- Best Practices
- Resources

Learning Objectives

- Describe role of Pharmacology/Toxicology (Pharm/Tox) review in the Office of Generic Drugs (OGD)
- Identify Pharm/Tox safety assessment challenges
- Explain best practices for successful Pharm/Tox justifications
- Describe avenues to get advice from OGD

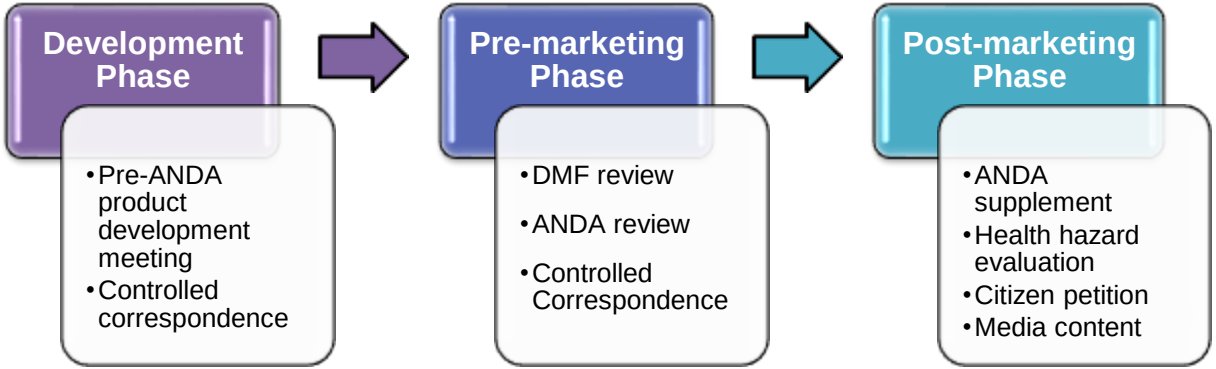
Learning Objectives

- **Describe Role of Pharmacology/Toxicology (Pharm/Tox) review in the Office of Generic Drugs (OGD)**
- Identify Pharm/Tox ent challenges
- Explain best practic l Pharm/Tox justifications
- Describe avenues t m OGD

Role of Pharm/Tox in Generics

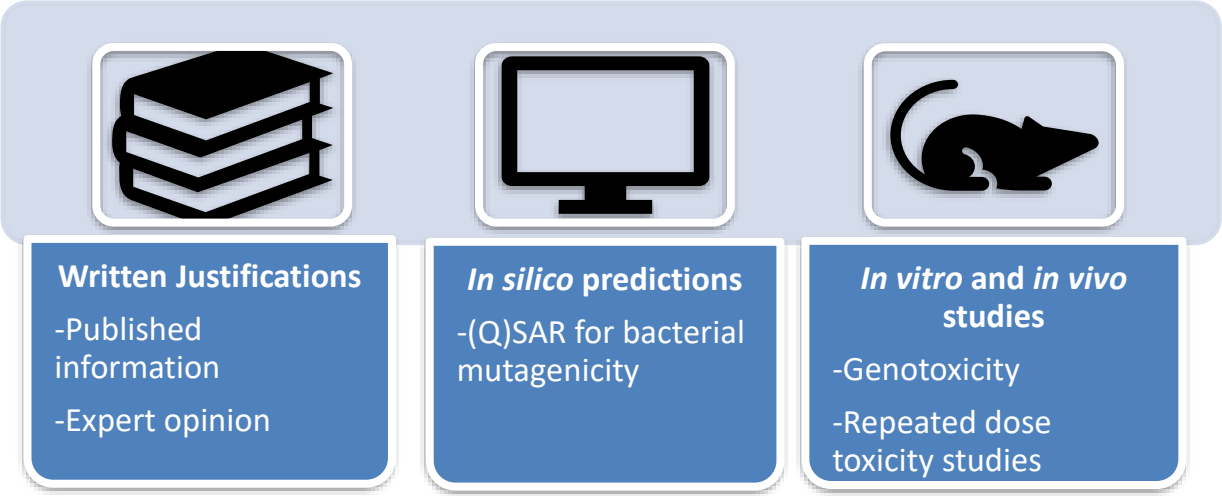
- The Division of Pharmacology/Toxicology Review (DPTR):
  - Conducts safety assessments on impurities and excipients in generic drug products on a consult-basis
  - Conducts context-specific safety review (e.g., dose, duration of exposure, patient population, and route of administration)
  - Goal: ensure the same safety profile as the reference listed drug (RLD)

DPTR is involved at various stages in lifecycle of a generic drug product



Role of Pharm/Tox in Generics

- **Review safety of generic formulations**
  - Impurities, excipients, residual solvents, contaminants from container closure
  - Evaluate toxicology data submitted by Drug Master File (DMF) holders and Abbreviated New Drug Application (ANDA) applicants to support specifications



(Q)SAR = quantitative structure-activity relationship prediction

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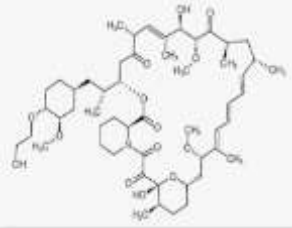
Impurity Review in Generics

- Impurities: Drug substance or drug product-related impurities, elemental impurities, residual solvents, extractables and leachables (E&L)
- Impurities exceeding safety thresholds need to be qualified
- Different approaches for impurity qualification
  - Comparative impurity analysis
  - Safety qualification
    - Genetic toxicology assays, general toxicity studies
    - Metabolite justification



DPTR Reviews	API synthesis	Drug manufacturing	Drug Formulation	Drug Product incl. Container Closure
	Drug substance process impurities and degradants	Extractables and leachables, elemental impurities	Excipients, impurities, residual solvents	Extractable/Leachables

Impurity Review: Common Deficiencies

- In silico prediction on topics other than mutagenicity
  - In silico prediction of general toxicity has not been validated for impurity qualification
  - Read across approach with surrogate compound is inadequate to justify general toxicity
- Metabolite/API as surrogate justification
  - In vitro or urinary data without evidence of systemic exposure to the metabolite
  - At relevant API exposure, metabolite levels < proposed clinical impurity exposure
  - Irrelevant justification (e.g., data for surrogate)
- Reference to proprietary data (e.g., RLD Pharm/Tox reviews)
  - Proprietary data cannot be used to justify impurity limits without permission from the owner of the data

API: Active Pharmaceutical Ingredient

Extractables & Leachables Review in Generics

- Extractable and Leachable (E&L) studies identify compounds that are extracted or may leach from the container closure system (CCS)
  - Pharm/Tox reviews the safety of E&Ls above safety thresholds
- Different approaches for E&L qualification
  - Demonstrate extractables are not present in leachable study
  - Demonstrate E&Ls are below the Safety Concern Threhold (SCT)
  - Genetic toxicity assay, general toxicity studies for compounds exceeding safety thresholds
  - Using surrogate molecules to predict toxicity of E&Ls

E&L Review: Common Deficiencies

- Inappropriate analytical evaluation threshold (AET)
- All compounds above AET/SCT are not properly identified (chemical structure)
- Cramer classification (1978) as basis for safety review threshold
  - Classifying E/Ls by the Cramer classification method in lieu of submitting a safety assessment is not acceptable
- Surrogate approach without proper identification of E/L compounds
  - A surrogate approach may be used for safety assessment of E&Ls when compound-specific toxicological information is not available
  - To determine if proposed surrogate is appropriate, the specific E/L compound must be adequately identified

Excipient Review in Generics

- Excipients are ingredients that are intentionally added but do not exert therapeutic effect at proposed dosage
- Goal: To ensure the proposed generic drug has the same safety profile as RLD when used according to labeling
- Initial excipient assessment includes:
  - Comparison with approved levels in similar context of use using the IID
  - If these comparisons cannot justify the proposed use of excipient, additional assessment is conducted on a consult basis to Pharm/Tox
- Different approaches for excipient qualification
  - Levels in products with similar context of use
  - Available Pharm/Tox data to inform safety for the route, dose and duration
  - Considerations for specific patient populations (e.g., pediatrics)

IID: Inactive Ingredient Database

Excipient Review: Common Deficiencies

- Reference to the IID for excipient used under a different context of use
- Reference to an unspecified grade of excipient in the IID for a specified grade of excipient in the formulation (e.g., hydroxypropyl cellulose)
- Missing justification to support safety via alternate routes
  - Certain routes of administration may warrant additional safety assessment (e.g., ophthalmic, rectal, vaginal, buccal, sublingual, dermal)
  - In addition to systemic exposure, local tissue tolerance is also evaluated
- Missing safety information in sensitive populations
  - Pediatric patients, particularly in newborns and young infants that may be critically ill or have immature metabolism
  - Elderly patients or patients with conditions needing dosage adjustments (e.g., renal or hepatic impairment)

Overall Challenges

- Broad/Submission quality
  - Data integrity
    - Suspicious data patterns: data repetition, biologically implausible data
    - GLP compliance issues
    - Different species/study, same data!
    - False negative results
  - Missing information in data reports
    - Missing data, incomplete methods or results, unsigned study reports/quality assurance documents
  - Incomplete literature references
  - Missing quantitative data for metabolite levels in plasma of animals or humans
  - Reference to proprietary data under another application without right of reference
  - Major versus Minor Amendment
    - Safety justifications are generally defined as Major
    - Data submitted within cycle that requires consult to Pharm/Tox may extend your goal date

Learning Objectives

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Best Practices

- Evaluate safety of proposed level in context of use for your drug product
- For Impurities:
  - Conduct comparative impurity analysis with RLD and control impurities at limits supported by this analysis
  - A mutagenicity assessment is necessary to support impurity specifications that exceed the threshold of toxicological concern (TTC)
    - Perform (Q)SAR analysis using appropriate models; if predicted negative for bacterial mutagenicity, control at up to the qualification threshold (QT)
  - General toxicity data are necessary to support impurity specifications that exceed QT
    - Provide full literature reference and full study reports to justify the safety of proposed higher level
    - When conducting a general toxicity study, consider the context of use

Best Practices

- For Metabolites:
  - Quantitative information regarding metabolite levels in plasma of either animals or humans is needed to support qualification of the impurity as a metabolite
- For E&Ls:
  - Structurally similar E&Ls can be grouped together for safety assessment with appropriate justification but identification of individual E&Ls in a group with a CAS # and/or structure is necessary
- For Excipients:
  - Comparison with RLD formulation
  - Comparison with approved levels for proposed route using the IID
  - Literature data to justify safety of a proposed level for the intended context of use

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- **Describe avenues to get advice from OGD**

Avenues to Get Advice

- Controlled correspondences (CC) are a great resource!
- Inquiries that are within scope of CCs
  - Requests related to inactive ingredients
  - Requests for Q1/Q2 formulation assessment
  - Maximum daily dose determination
  - Thresholds for E&L studies (e.g., AET, SCT)
  - Questions pertaining to ICH M7 (e.g., treatment duration, acceptable intakes, exclusions, etc.)
  - Acceptable intakes for nitrosamines
  - Input on a proposed nonclinical study design
- Limitations:
  - No safety call or full study review

Resources

- Good ANDA Submission Practices Guidance for Industry
- ANDAs: Impurities in Drug Products
- Q3A(R) Impurities in New Drug Substances
- Q3B(R3) Impurities in New Drug Products
- Guidance for Industry Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients (2005)
- Recommended Acceptable Intake Limits for Nitrosamine Drug Substance-Related Impurities
- M7(R2) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk
- GDUFA Reauthorization Performance Goals and Program Enhancement Fiscal Years 2023-2027

- **Prior SBIA Presentations:**
  - Impurity Case Studies: Pharmacology/Toxicology (22of28) Generic Drugs Forum (April 2019)
  - Local Toxicity Considerations for Qualifying Excipients in Generic Drugs (September 2020)
  - Safety Evaluation of Drug Substance Impurities in Generics (March 2021)
  - Safety Review of Flavors in Generic Drug Products (September 2021)
  - Impact of Data Integrity Issues on Pharmacology/Toxicology Studies in ANDAs (April 2021)
  - Data Integrity in Pharmacology/Toxicology Studies (April 2022)

Challenge Question 1

Which one of the following is **NOT** an acceptable approach to assess general toxicity of an impurity that exceeds the qualification threshold (QT) per ICH Q3B?

A. Perform comparative analysis of impurity levels in the generic drug and RLD
B. Use a read across approach with a surrogate compound to justify general toxicity of an impurity
C. Cite published scientific studies demonstrating the impurity is a metabolite of the drug in vivo at levels that exceed the proposed maximum exposure
D. Perform a repeated dose study in rats, taking into consideration context of use

Challenge Question 2

OGD Pharmacology/Toxicology does **NOT** address which of the following inquiries in a Controlled Correspondence?

A. Questions pertaining to ICH M7 (e.g., treatment duration, acceptable intakes, exclusions, etc.)
B. Questions regarding a protocol of a proposed nonclinical study
C. Determination of analytical evaluation threshold (AET) and/or safety concern threshold (SCT) for extractables and leachables studies
D. Review of genetic toxicology study report to characterize genotoxicity prior to ANDA submission

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