Safety Considerations for Extractable/Leachable Evaluation in Generic Drug Products

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Outline

Role of Pharm/Tox in Generic Drug Review

Extractable/Leachable Safety Review in Generic Drugs

Key Factors for Safety Review

Common Pitfalls

Role of Pharm/Tox In Generics

- The Division of Pharmacology/Toxicology Review (DPTR):
  - Conducts safety assessments in generic drug products on a consult-basis on impurities, excipients, residual solvents, extractables/leachables (E/L)
  - Conducts context-specific safety review which considers the dose, duration of use, patient population, and route of administration

DPTR is involved throughout the lifecycle of the generic and our goal is to ensure the generic has the same safety profile as the reference listed drug (RLD)

Safety Assessment of E/Ls in Generics

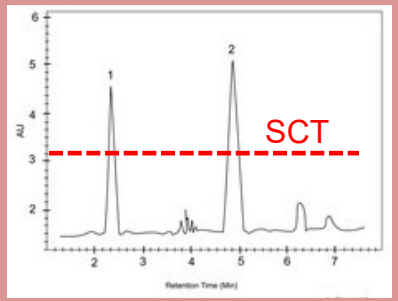
- Extractable and Leachable (E/L) studies identify compounds that may migrate from manufacturing equipment or container closure system (CCS) under:
  - Exaggerated laboratory conditions (extractables)
  - Storage conditions with the drug product (leachables)
- DPTR evaluates E/Ls above safety thresholds after OPQ* confirms the adequacy of study design and analytical methods
  - Adequate Analytical Evaluation Threshold (AET) based on an appropriate Safety Concern Threshold (SCT) and Maximum Daily Dose (MDD)
- DPTR assesses mutagenicity, general toxicity, and local toxicity of E/Ls based on context of use

*OPQ: Office of Pharmaceutical Quality

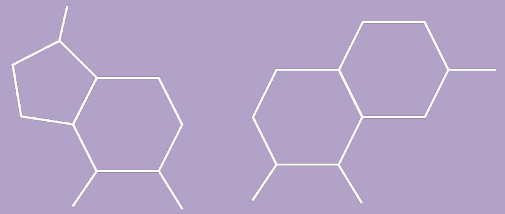
Key Factors for Safety Review

- Generally, an SCT of 1.5 mcg/day is recommended for chronically used drug products (> 10 yrs), and an SCT of 5 mcg/day is for drug products used < 10 years.
- Products administered via sensitive routes (e.g., intrathecal) may need lower SCT (e.g., 0.15 mcg/day).
- A Controlled Correspondence (CC) can be submitted to DPTR to obtain guidance on appropriate safety thresholds for a specific drug product.

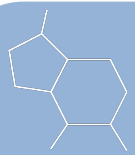
Key Factors for Safety Review



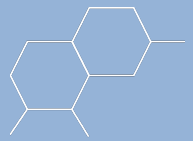
Compounds exceeding SCT



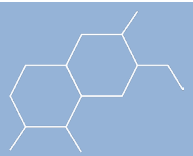
Identification by chemical structure and/or CAS number



Compound specific nonclinical data <u>available</u> for safety assessment



Compound specific nonclinical data <u>not available</u> for safety assessment



Identify structurally similar surrogate with available nonclinical data and provide rationale for selection

E/L Safety Justification

- Identify all E/Ls exceeding SCT by CAS number or chemical structure
- Submit nonclinical data for E/Ls exceeding safety thresholds:
  - General toxicity = 5 µg/day
  - Mutagenicity thresholds based on duration of use
- Provide rationale for using surrogate(s) or for grouping of E/Ls to inform safety

Common Pitfalls

Inadequate Analytical Method Sensitivity

- Inappropriate AET, SCT, MDD used during study design and execution

Inappropriate Maximum Daily Exposure (MDE) Calculation

- Not considering the worst-case scenario MDD or MDE across studies from various timepoints/conditions

Inappropriate Toxicological Safety Justification

- Inadequate structural characterization of the E/L (i.e., chemical structure and/or CAS number) or the use of surrogates when E/L is not adequately characterized
- Use of *in silico* methods or Cramer classification for evaluation of general toxicity and/or irritation/sensitization potential
- Did not consider the appropriate context of use (i.e., dose, route of administration, duration of use, and patient population) or the drug product
- No safety justification provided

Summary

- DPTR works closely with OPQ colleagues to evaluate E/L studies and safety justifications
- Compounds exceeding the SCT should be characterized by chemical structure and/or CAS number
- Safety justification should include a mutagenicity, general toxicity, and local toxicity assessment based on the exposure level and the context of use of the drug product
- *In silico* assessments for general toxicity or local toxicity endpoints are not acceptable. *In silico* assessments are only adequate for mutagenicity.
- Controlled correspondences are a great resource for MDD and E/L study threshold (i.e., AET and SCT) inquiries.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