Extractable/Leachable Safety Assessment in Generic Drug Products

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Vince Crowley, PhD
Senior Pharmacologist
Division of Pharmacology/Toxicology Review (DPTR)
Office of Safety and Clinical Evaluation (OSCE)
Office of Generic Drugs (OGD)
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This presentation reflects the views of the author and should not be interpreted to represent FDA's view or policies.

Outline

Extractable/Leachable Safety Review in Generic Drugs

Key Factors for Safety Review

Common Pitfalls

E/L Safety Review in Generics

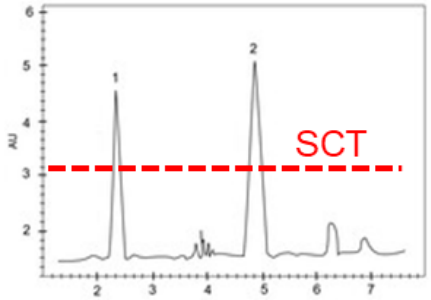
- Extractable and Leachable (E/L) studies identify compounds that may migrate from manufacturing equipment or container closure system (CCS)
  - Extractables – exaggerated laboratory conditions
  - Leachables – drug product storage conditions
- The Quality review team confirms the adequacy of study design and analytical methods, OGD Pharm/Tox evaluates E/Ls observed above safety thresholds
- Pharm/Tox assesses mutagenicity, general toxicity, and local toxicity of E/Ls based on context of use

Key Factors for Safety Review

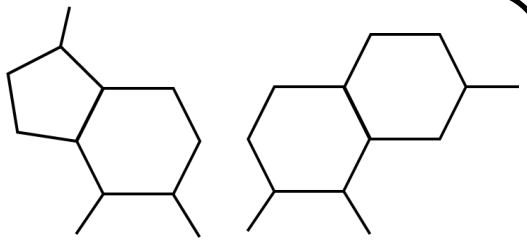
Route of Administration	Duration of Treatment >10 years	Duration of Treatment ≤10 years
Most Routes[1]	1.5 µg/day	5 µg/day
Topical Ophthalmic products[2]	Reporting Threshold: 1 ppm Identification Threshold: 10 ppm Qualification Threshold: 20 ppm	

1. Drug products administered via sensitive routes (e.g., intrathecal) may require a lower Safety Concern Threshold (SCT) (e.g., 0.15 µg/day). A Controlled Correspondence (CC) can be submitted to OGD to obtain guidance on appropriate safety thresholds for a specific drug product.
2. FDA Guidance for Industry *Quality Considerations for Topical Ophthalmic Drug Products* (December 2023); https://www.fda.gov/media/172937/download; ppm (parts per million) is used due to the risk of local toxicity to the eye.

Key Factors for Safety Review



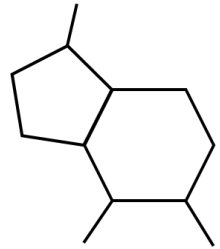
Compounds exceeding SCT



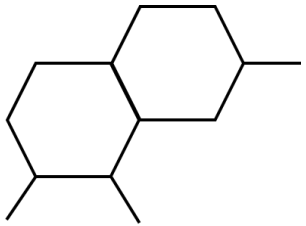
Identification by chemical structure and/or CAS number

- Identify all E/Ls exceeding SCT by CAS number and/or chemical structure
- Submit nonclinical data for E/Ls exceeding safety thresholds:
  - General/systemic toxicity = 5 µg/day
  - Mutagenicity thresholds based on duration of use
  - Local toxicity = 5 µg/day; may be lower for sensitive routes (e.g., intrathecal)
  - Q3E safety thresholds are not finalized and therefore, are not used in current review practice.

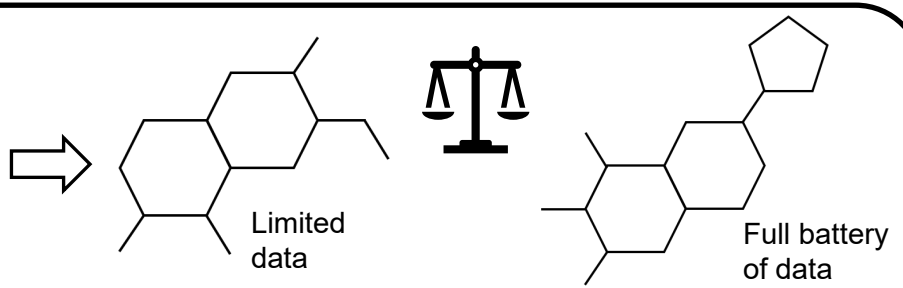
Key Factors for Safety Review



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



No safety data available



Identify surrogate based on balance of structural similarity and available safety data

Surrogate and Grouping Considerations

- Overall structural similarity
- Contain functional groups in the same chemical environment
- Undergo metabolism to yield the same, or similar, products
- Possess similar physicochemical properties
  - e.g., polarity, solubility, ionizability, molecular weight
- Provide details and justification when grouping E/L for assessment
  - Identify individual group members and consider the total exposure when assessing safety

Common Pitfalls

- Not considering the worst-case scenario MDD or maximum daily exposure (MDE) to E/Ls across studies from various timepoints/conditions
- No safety justification provided
- 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

Common Pitfalls

- Use of *in silico* methods for non-mutagenicity endpoints or Cramer classification
- Did not consider the appropriate context of use for the drug product
  - Dose, route of administration, duration of use, and patient population
- Use of ICH Q3E safety thresholds, as harmonization is ongoing and thresholds are not finalized

Summary

- OGD Pharm/Tox works closely with the Quality discipline to evaluate E/L studies and safety justifications for manufacturing equipment and CCS changes
- 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

Summary

- *In silico* assessments are only adequate for mutagenicity, other endpoint assessments are not acceptable.
- When safety data are not available for an E/L, surrogate selection should be based on a balance of:
  - Structural similarity
  - Physicochemical properties
  - Availability of reviewable toxicological data
- Controlled correspondences are a great resource for MDD and E/L study threshold (i.e., AET and SCT) inquiries.

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