Local Toxicity Considerations For Qualifying Excipients in Generic Drugs

SBIA 2020: Advancing Innovative Science in Generic Drug Development Workshop

Session 2: Excipient and Formulation Considerations

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Disclaimer

This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

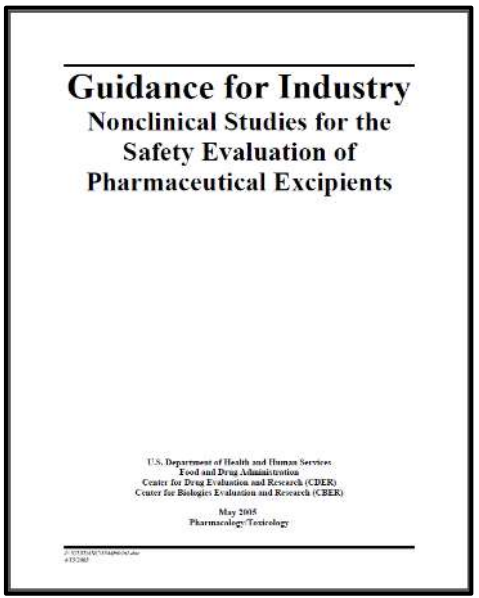
Learning Objectives

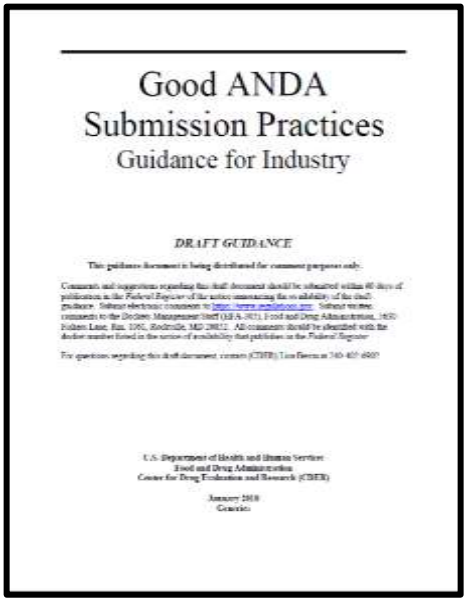
- Introduce the concept of local safety assessment of excipients in generic drugs
- Illustrate key aspects of excipient local safety review
- Provide cases to demonstrate how safety information, data gaps, and context of use impact recommendations

Excipient Safety Qualification

FDA guidances are key resources

- Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients
- Good ANDA Submission Practices


Guidance for Industry
Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
May 2005
Pharmacology/Toxicology


Good ANDA Submission Practices
Guidance for Industry
DRAFT GUIDANCE
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
January 2018
Generics

Excipient Safety Qualification in Generics

Generic formulations

- Same active ingredient(s), strength, dosage form, route of administration, conditions of use as the reference listed drug (RLD)
- Permissible differences in generics: excipients, impurities, etc.
- Demonstration of bioequivalence to the RLD
- No clinical safety studies: submitted information should support that the generic has a similar safety profile as RLD

Key aspects in safety assessment of excipients

- Joint clinical and Pharm/Tox review of excipients conducted on a consult basis when there is a safety concern
- Context of use: dose, route of administration, duration of use, and patient population
- Systemic and local toxicity: some products require local toxicity assessment due to continuous exposure at site of administration

Why Does Local Toxicity Matter?

- Excipients can cause local toxicity at the site of administration
  - Irritation, sensitization
- Some tissues are more sensitive to local toxicity
- Route of administration matters
  - buccal, parenteral (intramuscular and subcutaneous), ophthalmic, topical, rectal, and vaginal
- Dosage form matters
  - gum, lozenge, orally disintegrating tablet (ODT), and sublingual film

➢ Safety assessment of local toxicity is done to ensure proposed product is similar to RLD, in terms of risk

Case 1: Safety Evaluation of Excipient A in a Topical Lotion

Case 1: Safety Evaluation of Excipient A in a Topical Lotion

Background

- ANDA product: topical lotion for short-term, repeated and/or intermittent use.
- Patient population: pediatrics (age: > 6 months) and adults.
- RLD does not contain Excipient A.

Applicant's Justification

- Use of Excipient A in products on market (prescribed drugs, over the counter drugs, cosmetics).
- Nonclinical toxicity data to support proposed level of Excipient A: acute toxicity, dermal toxicity (no genotoxicity, no repeated-dose toxicity).
- RLD labeling regarding local adverse effects (skin irritation).

Case 1: Safety Evaluation of Excipient A in a Topical Lotion

DCR Pharmacology/Toxicology and Clinical Evaluation

- At the maximum daily intake (MDI), Excipient A is a skin irritant and allergen; and at 1/10 of the proposed MDI, Excipient A is an eye irritant.
- Excipient A can increase the dermal penetration of other chemicals.
- Systemic over-exposure to API may cause adverse effects, particularly in young children.
- Excipient A could worsen the adverse effects (both local and systemic) caused by API: skin irritation, metabolic dysregulation, neurotoxicity.

➢ *Recommendation: (1) Remove Excipient A and reformulate the product; or (2) Provide additional data to show that proposed level of Excipient A does not affect safety of the product.*

Case 2: Safety Evaluation of Excipient B in a Vaginal Cream

Case 2: Safety Evaluation of Excipient B in a Vaginal Cream

Background

- ANDA product: vaginal cream for repeated, intermittent use in non-pregnant women
- Excipient B is not present in the RLD

Applicant's Justification

- Use of Excipient B in FDA-approved products (IID)
- Nonclinical data on both local and systemic toxicities associated with Excipient B: dermal irritation and sensitization, genotoxicity, acute toxicity, repeated-dose toxicity (dermal and oral), reproductive and developmental toxicity
- Clinical data in literature: dermal irritation and sensitization
- A single-dose bioequivalence (BE) study of the ANDA product with comparative clinical endpoints

Case 2: Safety Evaluation of Excipient B in a Vaginal Cream

DCR Pharmacology/Toxicology and Clinical Evaluation

- No safety concern for systemic toxicity based on nonclinical data (genotoxicity, repeat-dose toxicity) at the proposed MDI.
- Used in higher amounts in other FDA-approved products (oral and dermal).
- Literature data show that Excipient B did not cause irritation or sensitization in humans after repeated skin patch testing.
- The BE study is a single dose study. The local safety (vaginal irritation, inflammation) of Excipient B upon repeated and intermittent use is not well-characterized in the BE study.

➢ *Conclusion: Data gap identified; Justification insufficient to support safety via the vaginal route; Not acceptable.*

Case 2: Safety Evaluation of Excipient B in a Vaginal Cream

DCR Pharmacology/Toxicology and Clinical Evaluation

- *Recommendation:*

  Conduct a nonclinical study to characterize the local safety of Excipient B by the vaginal route. Study outcomes should include evaluation of clinical signs, gross necropsy, vaginal histopathology, and severity of irritation.

  The need for additional clinical safety data should be revisited based on results of the rabbit vaginal irritation study. However, such additional clinical data cannot be submitted under a generic drug application per FDA Guidance: Determining Whether to Submit an ANDA or a 505-B2 Application.

Case 3: Safety Evaluation of Excipient C in Buccal Films

Case 3: Safety Evaluation of Excipient C in Buccal Films

Background

- ANDA product: Buccal films for chronic use in adults.
- ANDA product has different dose strengths.
- Excipient C is not present in the RLD.

Applicant Justification

- Nonclinical data: genotoxicity and systemic toxicity associated with Excipient C.
- Permissible daily exposure (PDE) was calculated based on No-Observed-Adverse-Effect-Level (NOAEL) of Excipient C. However, a full toxicological study report, in which the NOAEL was determined, was not provided.

Case 3: Safety Evaluation of Excipient C in Buccal Films

DCR Pharmacology/Toxicology and Clinical Evaluation

- MDI of Excipient C needs to be recalculated based on practically feasible number of buccal films.
- Excipient C is unlikely to be absorbed through the buccal mucosa due to its considerably large molecular weight.
- Excipient C did not cause irritation/sensitization in nonclinical studies.
- Excipient C has a wide safety margin based on nonclinical data.
- Similar grades (molecular weight and chemical composition) of Excipient C are present in FDA-approved oral drug products at higher levels.

➢ *Conclusion: Acceptable*

Summary

Three case studies to illustrate key aspects of excipient safety review

- Safety justification for excipients in a generic formulation considers context of use of proposed product: route of administration, patient population, duration of treatment, and duration of exposure at the site of administration.
- Dosage form determines need for local toxicity assessment.
- Local toxicity assessment is needed when there is continuous exposure at site of administration.
- Safety justification can include clinical and nonclinical data (study reports, publications, etc.).
- Full toxicological study reports are needed.

Summary

DCR evaluates the safety of generics

- Safety profile of excipients are reviewed from clinical and nonclinical perspectives.
- Both systemic and local safety of excipients are considered for certain dosage forms (e.g., buccal, sublingual, topical, vaginal).
- Two FDA guidances are key resources.
  - Good ANDA Submission Practices
  - Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients

The goal of generic drug safety review of excipients

- To ensure that the proposed formulation does not change the risk profile, when compared with the RLD.

Challenge Question

Which one of the oral dosage forms does NOT require local safety assessment of excipients?

A. Gum
B. Film-coated tablet intended for swallowing
C. Orally disintegrating tablet (ODT)
D. Sublingual film

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