U.S. FOOD & DRUG ADMINISTRATION

Excipient Safety Assessment in Generic Drug Formulations: An Overview

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By

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Outline

- Overview of generic drugs and excipients in the generic drugs
- General approach for safety assessment of excipients
- Case Studies
- Summary

How do Generic Drugs Compare to the Reference Listed Drug (RLD)?

- Generic drugs are submitted as Abbreviated New Drug Applications (ANDAs), submitted via 505(j) regulatory pathway
  - ANDAs do not contain Phase 3 clinical trial data for efficacy and safety
- Generics are pharmaceutically equivalent to the reference listed drug (RLD):
  - Active Pharmaceutical Ingredient (API), dosage strength, dosage form, and route of administration are the same as the RLD, deliver identical amounts of the active drug ingredient over identical dosing period, meet the identical compendial or other applicable standards of identity, strength, quality, and purity
- Generics must demonstrate bioequivalence to the RLD
- Generics are not always identical copies of the RLD: Differences in excipients are allowed for certain dosage forms
  - Q1/Q2 required: Products for parenteral, ophthalmic, or otic use
    - Exceptions: buffers, antioxidants, and preservatives if information is provided to support their safety
  - Not Q1/Q2 required: Products for other routes (safety must be justified)
- Despite differences in the formulation, the **safety profile** of the generic should be similar to the RLD

Excipients in Generic Drug Products

- An inactive ingredient is “any component other than an active ingredient” that is added during the manufacturing process and is present in the final (“to-be-marketed”) drug product (21 CFR 210.3)
  - Colorings, flavorings, emulsifiers, lubricants, preservatives, solvents, sustained release matrices

- Inactive ingredients in generics are evaluated by multiple offices in CDER and divisions within OGD
  - Division of Filing Review checks proposed excipient levels in a formulation against listings in the Inactive Ingredient Database (IID) to support filing of the ANDA
  - Office of Bioequivalence: Assessment of whether the proposed maximum daily exposure (MDE) for a specific route has precedent in an FDA approved product for the same route of administration
  - Quality discipline: Assesses quality parameters (e.g., impurities, identity, etc.) of the excipient

- Pharm/Tox (Division of Pharmacology/Toxicology Review) and Clinical (Division of Clinical Review) within OGD are consulted when there is a safety question on the proposed formulation during the ANDA review
  - Proposed level exceeds approved level for the same route
  - Proposed level is for a longer duration of use
  - Proposed level is new to the patient population

Safety Review of Excipient by OGD

Ultimate Question: Will the excipient at the proposed amount change the safety profile of the generic drug when compared to the RLD?

- Context of Use (dose and duration of exposure, route of administration, indicated use, patient population) drives the safety assessment
- During the ANDA review, clinical and Pharm/Tox disciplines generally jointly assess worst-case exposure: MDE calculated using the maximum daily dose (MDD)
  - Approaches detailed in the FDA guidance "Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients" (excipient guidance) are applied to assess safety of the formulation in the target population
  - Division of Clinical Review (DCR) considers evidence of safe use in humans, including previously approved levels of excipient
- The IID can inform prior evidence of safe use for the proposed level of excipient in an FDA-approved product; lists the maximum potency (highest level of excipient per unit dose in each dosage form) and MDE
  - The IID is used by the innovator and generic applicants
  - http://www.accessdata.fda.gov/scripts/cder/iig/index.Cfm

Safety Review of Excipient by OGD

- Safety of excipients is assessed based on the principles from the guidance on excipients which considers the context of use (duration of use, patient population, route of administration), of the drug product to determine whether the proposed level of excipient poses a concern.

- Excipients which have not been qualified at the proposed dose will require safety information to support the route of administration and duration of exposure in the intended patient population.

- DPTR considers relevant toxicology information (e.g., general toxicity, reproductive toxicity, genotoxicity, carcinogenicity, etc.), that are not easily assessed in human clinical trials.
  - "Dose makes the poison": margins of exposure are considered

Duration of Use	• Acute (≤ 14 days per treatment episode): • Intermediate (2 weeks to 3 months per treatment episode) • Long-Term Use (> 3 months per treatment episode)
Toxicology Studies	• General toxicology (route-specific) with histopathology: Acute: 14 days to 1 month, 2 species Intermediate: 3 months, 2 species Long-Term: 6 months (rodent), 9 months (nonrodent) • ADME (ICH S3) • Genotoxicity (ICH M7, ICH S2) • Reproductive toxicology (ICH S5) • Carcinogenicity (ICH S1) • Additional toxicology studies, as needed
Pharmacology Studies and Other Considerations	• Safety Pharmacology • Study requirements for Pulmonary, Injectable and Topical Products • Photosafety testing

Safety Review of Excipients by OGD

- A Controlled Correspondence (CC) may be submitted to OGD or a pre-ANDA meeting may be requested (if applicable) to obtain feedback on proposed levels of excipients in a specific formulation
  - Guidance for Industry: Controlled Correspondence Related to Generic Drug Development
  - Guidance for Industry: Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA

- About 90% of the prescription drugs in the U.S. pharmaceutical market are generic. Although Pharm/Tox and clinical disciplines don't review all the submitted ANDAs, we are consulted when there is a safety concern

- If the safety of the generic drug product is not justified due to unacceptable levels of excipients, ANDA will not receive approval

- After review, if a gap in safety data remains:
  - Non-clinical information may be requested if it addresses the data gap
  - In cases where clinical data are required or a novel excipient is proposed which needs an extensive battery of safety studies, the applicant will be advised to reformulate or pursue a 505(b)(2) pathway

CASE STUDIES

Case 1: Safety Evaluation of Excipient A in an Oral Capsule

- ANDA product: Central Nervous System Stimulant, Delayed Release Oral Capsules
- Indicated for use in patients ≥ 6 years of age and above; chronic use
- Proposed level of excipient A (a high molecular weight polymer) exceeds the level in FDA-approved products with similar context of use

Applicant's Justification

Applicant referred to the public Inactive Ingredient Database (IID) and indicated that the highest IID levels by oral route exceed the proposed level of excipient A

Pharm/Tox Safety Review

Applicant's justification included MDE from a drug product with different context of use, i.e., it was an acute use drug indicated only in adult patients

Relevant data in the published literature were identified during the review:

- Non-genotoxic and non-carcinogenic
- Generally, not expected to be absorbed due to high molecular weight; lower molecular weight forms have toxicity concerns

Pharm/Tox Safety Review

- No overt toxicities noted in 90-day repeat dose oral toxicity study in rats
- High margins of safety for the proposed MDE of excipient from chronic toxicology study
- Based on published toxicity data, estimated acceptable daily intake (ADI) is much higher than the proposed MDE

No Safety Concern

Clinical Safety Review

- Based on medical literature and by its presence in an FDA-approved drug product with similar context of use, safety of the excipient A in pediatric patient is justified
- Daily average exposure in adults and young children as food additive is much higher than the proposed MDE

No Safety Concern

Regulatory Recommendation

- Proposed MDE of excipient A is acceptable in the current drug product

Case 2: Safety Evaluation of Excipient B in an Oral Suspension

- ANDA product: Cough Syrup, short term/ repeated / intermittent use
- Patient population: pediatrics age: ≥ 2 years and older (can be given to as young as 6 months based on physician's advice)
- Excipient B level exceeds the levels in FDA-approved products with similar context of use

Applicant's Justification

- Comparative study with RLD and indicated similar level of excipient in the RLD as proposed level
- Published literature indicating excipient as Generally Recognized As Safe (GRAS) and published toxicology data

Pharm/Tox Safety Review

- Excipient B is rapidly absorbed from the GI tract after oral ingestion
- Based on pharmacokinetics, the half-life of excipient B in infants is about 10 times longer than in adults raises the risk of over-exposure in pediatric patients
- Insufficient non-clinical toxicology data to assess the safety in pediatric patient

Safety Concern

Clinical Safety Review

- Based on medical literature, significant concerns with excipient B in patients with renal or hepatic insufficiency and in children less than 4 years of age
- Due to immature hepatic and renal function in young children, the potential for excipient B accumulation increases which may cause aggravated toxicity in this population
- No FDA-approved drug product with similar context of use was found to support the safety of the proposed MDE of excipient B in patient as young as 6 months

Safety Concern

Regulatory Recommendation

Deficiency Identified

- Reformulate to remove excipient B or reduce level to what is in FDA-approved products with similar context of use (Use CC process to obtain feedback on formulation)

Update: Applicant complied and reduced the level of excipient B to an acceptable amount, ANDA approved

Case 3: Safety Evaluation of Excipient C in a Topical Lotion

- 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 C (based on the product labeling)

Applicant's Justification

- Use of excipient C in prescribed drugs, over the counter drugs, cosmetics
- Nonclinical toxicity data to support proposed level of excipient C: acute toxicity, dermal toxicity (no genotoxicity, no repeated-dose toxicity)

Pharm/Tox Safety Review

- Excipient C is listed as active ingredient under 21 CFR 310.545 and is used as active ingredient for topical drug products
- Non-genotoxic but no juvenile toxicity study to inform safety in pediatric patients from 6 months and older
- RLD labeling indicates API may cause local adverse effects (skin irritation)
- Excipient C can increase the dermal penetration of other chemicals; may increase the exposure to API and thus the local adverse effects from API

Safety Concern

Clinical Safety Review

- Based on medical literature, at the MDE excipient C is a skin irritant and allergen; and at 1/10 of the proposed MDE, excipient C is an eye irritant in adult and children
- Systemic over-exposure to API may cause adverse effects, particularly in young children
- Excipient C could worsen the adverse effects (both local and systemic) caused by API: skin irritation, metabolic dysregulation, neurotoxicity
- Applicant's justification not acceptable as cited prescription drugs are for a different context of use, i.e., indicated in adults only or indicated to be used in hospital setting
- Use in cosmetics generally not considered appropriate for supporting safe use in drugs
- No FDA-approved drug product with similar context of use was found to support the safety of the proposed MDE of excipient C in pediatric patient

Safety Concern

Regulatory Recommendation

Deficiency Identified

- Provide additional data to show that proposed MDE of Excipient C does not change the safety and efficacy of the drug product *OR*
- Reformulate (Use CC process to obtain feedback on formulation)

Summary

- ANDAs must be pharmaceutically equivalent to the RLD
- In general, generic drugs may differ in composition from the RLD due to excipients in the formulation, with some exceptions
- Safety review of excipients is generally handled by clinical and pharm/tox disciplines on a consult basis
  - Principles from the FDA's Guidance for Industry: Nonclinical Studies for the Safety Evaluation of Pharmaceutical are applied
  - Context of use (duration of use, patient population, route of administration) of the drug product drives the safety assessment to determine whether the proposed level of excipient poses a concern
- The IID is one tool used to identify prior evidence of safe use. Information in the published literature, relevant human safety data, and toxicology studies are also used to inform risk

Summary (continued)

- If a safety data gap is identified, a deficiency may be issued, which means the ANDA does not receive approval
  - Applicant may be recommended to reformulate or submit a revised justification to address the safety concern for the proposed context of use
  - In cases where clinical data are required or a novel excipient is proposed which needs an extensive battery of safety studies, the applicant will be advised to reformulate or pursue a 505(b)(2) pathway

- Ultimately, the goal of safety review of excipients in generics is to ensure that the safety profile of the generic is similar to the RLD
  - Support OGD's mission to bring high quality, safe generics to the American public

Links to Excipient Related Resources

- Inactive Ingredient Database

https://www.accessdata.fda.gov/scripts/cder/iig/index.cfm

- Guidance For Industry: Using the Inactive Ingredient Database

https://www.fda.gov/media/128687/download

- Guidance For Industry: Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients

https://www.fda.gov/media/72260/download

- Guidance For Industry: Good ANDA Submission Practices

https://www.fda.gov/media/110689/download

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