Bioequivalence Recommendations for Bridging Pre- and Post-Mitigation Formulations of Nitrosamine-Impacted Drug Products: Case Studies

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Outline

- Background on Nitrosamine Impurities and Mitigation Strategies
- Bioequivalence (BE) Approaches for Drug Products Reformulated to Control Nitrosamines
- Case Studies
- Summary
- Acknowledgements

Background - Nitrosamine Impurities in Drug Products

- Unacceptable levels of nitrosamines have been detected in commonly prescribed medications
- Nitrosamines are potent genotoxic agents; classified as probable or possible human carcinogens; “cohort of concern” compounds in the ICH M7(R1)
- This issue impacts diverse drug products and dosage forms, affecting both New Drug Applications (NDAs) and Abbreviated New Drug Applications (ANDAs), with ANDAs representing the majority of cases
- Types of Nitrosamine Impurities
  - Small molecule nitrosamines: N-nitrosodimethylamine (NDMA), N-nitrosodiethylamine (NDEA), and related compounds; do not share structural similarity to the active pharmaceutical ingredient (API); found in many different drug products
  - Nitrosamine drug substance-related impurities (NDSRIs): Structurally related to the API or API fragments

Reference: FDA Guidance - *Control of Nitrosamine Impurities in Human Drugs* (September 2024)

Regulatory Strategies to Mitigate Nitrosamine Impurities

Mitigation Strategy	Examples of Changes
API Source/Process Modifications	• Modify route of synthesis or select new API suppliers • Optimize manufacturing processes to minimize nitrosamine formation • Control nitrite levels in raw materials and starting materials
Drug Product Reformulation	• Add antioxidants (ascorbic acid, α-tocopherol, propyl gallate, cysteine HCl) • Incorporate pH modifiers (e.g., sodium carbonate) • Replace problematic excipients with safer alternatives
Manufacturing Process Controls	• Modify processes or equipment to eliminate nitrosating conditions • Implement packaging changes to prevent contamination

Reference: FDA Guidance - *Control of Nitrosamine Impurities in Human Drugs* (September 2024)

BE Approaches for Drug Products Reformulated to Control Nitrosamines

For Immediate-Release (IR) Solid Oral & Oral Suspension Products*

BCS Class	Reformulation Strategy	BE Data Recommended
I, II, III	FDA-researched antioxidant(s)[†] **≤10 mg/dose or maximum daily exposure** (whichever is lower) OR pH modifier(s)	• Comparative dissolution data on the pre- and post-change products (quality control (QC) + pHs 1.2, 4.5, and 6.8)
I, II	FDA-researched antioxidant(s) **>10 mg/dose** OR Other antioxidant(s)	• Comparative dissolution data on the pre- and post-change products (QC + pHs 1.2, 4.5, and 6.8) • May request additional studies[‡]
III		• Comparative dissolution on the pre- and post-change products (QC + pHs 1.2, 4.5, and 6.8) • Permeability/transporter studies • **OR an in vivo BE study**[§]
IV	Any reformulation	• IVIVC, PBPK modeling • **OR an in vivo BE study**[§]

Modified-Release (MR) Products - All BCS Classes

➢ IVIVC, PBPK modeling, **OR an in vivo BE study**[§]

* Manufacturing process remains generally the same
[†] Ascorbic acid, α-tocopherol, propyl gallate, or cysteine HCl
[‡] In limited circumstances, may request in vitro bridging studies or in vivo BE
[§] Alternative BE approaches may be considered on a case-by-case basis

Reference: FDA Guidance - *Control of Nitrosamine Impurities in Human Drugs* (September 2024)

Hypothetical Case Studies

Hypothetical case studies related to pre-approval changes:

- Hypothetical Case 1: API source change
- Hypothetical Case 2: IR Tablet – BCS Class I - Multiple changes in formulation

Hypothetical case studies related to post-approval changes:

- Hypothetical Case 3: Delayed Release (DR) Capsule - Formulation change
- Hypothetical Case 4: IR Tablet – Formulation change and total tablet weight change

Hypothetical Case Study 1

Strengths	Multiple strengths
Original Submission	• BE studies conducted on the highest strength; waiver requested for the lower strengths • Nitrosamine impurities and cGMP compliance issues at API facility • Quality of bio-batch cannot be assured • BE studies and waiver request deemed inadequate due to quality concerns

Applicant's Mitigation Strategy and Supporting BE Data

- Changed to new API source (no other formulation changes)
- Submitted dissolution data comparing pre- and post-change drug products

Hypothetical Case Study 1 – Contd..

Agency's Evaluation and Decision

- Original API Drug Master File (DMF) closed without resolution of cGMP deficiencies. Therefore, an API source change to address nitrosamine impurities cannot be supported solely by dissolution testing comparing pre-change and post-change drug products.

- All data generated using batches manufactured with original API are unreliable, including:
  - In vivo BE studies
  - Dissolution data

- Conduct new BE studies and dissolution data using the batches manufactured with a new API source

Hypothetical Case Study 2

Drug Product	IR Tablet
Strengths	Multiple strengths
Original Submission	• BE studies conducted on the highest strength; waiver requested for the lower strengths • BE studies deemed adequate • Application deemed inadequate due to nitrosamine impurities

Applicant's Mitigation Strategy and Supporting BE Data

- Reformulation with changes in multiple excipients
- Manufacturing process change
- **Submitted BCS Class I waiver request**:
  - Conducted own solubility and dissolution studies per ICH M9 guidance*
  - Used approved reference listed drug labeling information to support high permeability

Agency's Evaluation and Decision

Submitted adequate data to support BCS Class I waiver request, waiver granted

**Guidance for Industry: ICH M9 Biopharmaceutics Classification System-Based Biowaivers, May 2021*

Hypothetical Case Study 3

Drug Product	DR Capsule
Strengths	Multiple strengths
Approval History	• BE studies on the highest strength • NDSRI risk was assessed and confirmed
Applicant's Proposed Mitigation Strategy	• Addition of an antioxidant as nitrite scavenger (<10 mg/dose)* • Antioxidant added only to drug (IR) layer - no changes to enteric coating • Addition of a pH modifier* • Modifications to maintain capsule weight • No other changes
Applicant's Proposal to Support the Changes	• Conduct permeability study to support that the antioxidant is not expected to affect the absorption of the drug • In vitro dissolution data of pre- and post-change products

**FDA Guidance - Control of Nitrosamine Impurities in Human Drugs (September 2024)*

Hypothetical Case Study 3 – Contd..

Agency's Evaluation

- Per SUPAC-MR guidance: the proposed formulation change is classified as a Level 3 change
- DR capsules belong to MR dosage forms; the Nitrosamine Guidance* does not recommend the alternative BE approach for MR products
- The added antioxidant is one of the FDA-researched antioxidants
- The amount of antioxidant is <10 mg/dose as recommended by the Nitrosamine Guidance*
- The antioxidant and pH adjuster were added only to the IR drug layer. No changes to enteric coating
- The formulation change is not expected to compromise the enteric coating integrity
- Drug substance: highly soluble, moderately permeable (BCS Class III-like)
- The DR capsule resembles an IR product. The formulation change presents risks similar to those in an IR product.

**Guidance for Industry: Control of Nitrosamine Impurities in Human Drugs, September 2024*

Hypothetical Case Study 3 – Contd..

Agency's Recommendation

- No in vivo BE study is required
- The proposed permeability study is not needed
- Submit comparative dissolution data between pre-change and post-change test products for all strengths (QC + multimedia of pHs 1.2, 4.5, and 6.8)

Hypothetical Case Study 3 – Contd..

Agency's Additional Recommendation

Justification(s) to support the safety of the antioxidant at the proposed level for all indicated patient populations including pediatric populations should be provided.

Hypothetical Case Study 4

Drug Product	IR Tablet
Strengths	Multiple strengths
Approval History	• BE studies on the highest strength • Waiver granted on the lower strengths • NDSRI issue was identified in certain strengths
Applicant's Proposed Mitigation Strategy	• Excipient amounts and total tablet weight was significantly reduced compared to original formulation • Same w/w% composition maintained for most excipients • No other changes
Applicant's Submitted Data to Support the Changes	In vitro dissolution data

Hypothetical Case Study 4 – Contd..

Agency's Evaluation

Formulation Changes

- Significant weight reduction for the proposed formulation versus approved formulation
- SUPAC-IR guidance does not address changes in total dosage form weight

Biopharmaceutics Classification & Biowaiver Assessment

- Drug substance is highly soluble (BCS Class III-like)
- Post-change drug products failed to meet BCS Class III biowaiver criteria per ICH M9

Hypothetical Case Study 4 – Contd..

Agency's Recommendation

Based on the assessment, the impact of the proposed reformulation on BE cannot be understood without the results from an in vivo BE study. Therefore, the following is recommended:

- Conduct an in vivo BE study
- Alternative approaches may be considered

Summary

- The nitrosamine impurity issue has impacted many approved and pending generic drug products.
- Applicants may adopt mitigation strategies that involve one or more changes to API, formulation and/or manufacturing process of a drug product to address nitrosamine impurities.
- FDA's Guidance for Industry: Control of Nitrosamine Impurities in Human Drugs provides an alternative BE approach for certain reformulated products, offering a potential regulatory pathway for nitrosamine-impacted applications.
- The data needed to support reformulation changes vary by application, and the acceptability of the alternative BE approach requires fact-specific analysis of each case's unique characteristics.
- The principles outlined in the Nitrosamine guidance are applicable to both pre- and post-approval changes. When pre- or post-approval changes in an ANDA present additional issues beyond nitrosamine-related concerns, application of the nitrosamine guidance alone may not constitute adequate resolution.
- ANDA applicants should engage with FDA through meeting requests or controlled correspondence to obtain feedback on proposed bridging strategies, particularly for scenarios not explicitly addressed in current guidances.

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