Bioequivalence Approaches for Nitrosamine Impacted ANDA Applications: Case Studies

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Topics for Discussion

- Background
- Bioequivalence (BE) Approaches for Drug Products Impacted by Nitrosamine Impurities
- Case Studies
- Summary

Background

- Since 2018, several commonly prescribed drug products have been found to contain unacceptable levels of nitrosamines, with some classified as probable human carcinogens.
- Nitrosamine issues impact a wide range of drug products and dosage forms, including both New Drug Applications (NDAs) and Abbreviated New Drug Applications (ANDAs) (the majority).
- The industry may need to adopt various strategies to mitigate nitrosamine impurities, including but not limited to changes to active pharmaceutical ingredient (API), drug product manufacturing process, excipient/formulation.

BE Approaches for Drug Products Impacted by Nitrosamine Impurities

- Guidance for Industry: Control of Nitrosamine Impurities in Human Drugs (Revision 2; Sept 2024) includes a recommendation for an alternative BE approach that could be utilized for reformulated products of nitrosamine impacted applications.
- The recommendation is based on FDA research results
  - Addition of certain antioxidants or pH modifiers to formulations may significantly inhibit nitrosamine formation[1]
  - Addition of small amounts of four antioxidants (ascorbic acid, α-tocopherol, propyl gallate, or cysteine) do not affect permeability of BCS Class III model drugs[2]
  - Addition of small amounts of antioxidants do not affect intestinal transporter activities[3]
- This alternative BE approach is not applicable to Narrow Therapeutic Index (NTI) drugs, sublingual, buccal, or orally disintegrating dosage forms.

[1] Shakleya et al. Journal of Pharmaceutical Sciences, 2023, 112 (12): 3075-87
[2] Lu et al. Journal of Pharmaceutical Sciences, 2024, 113 (9): 2708-14
[3] Kulkarni et al. Pharmaceutics, 2024, 16: 647

Alternative BE Approaches - Control of Nitrosamine Impurities in Human Drugs Guidance (Sept 2024)

Drug Product Dosage Form	API BCS Classification	Reformulation by Adding Antioxidant or pH Modifier	BE Data Recommended to Support the Changes*
IR solid oral or oral suspension	BCS-I, BCS-II, BCS-III	Alpha-Tocopherol; Ascorbic Acid; Cysteine HCl; Propyl Gallate NMT 10 mg/dose, or maximum daily exposure (whichever is lower) pH modifier	Comparative dissolution testing data on the pre- and post-change products (in quality control (QC) dissolution medium and multimedia of pH 1.2, 4.5, and 6.8)
	BCS-I, BCS-II	Alpha-Tocopherol; Ascorbic Acid; Cysteine HCl; Propyl Gallate, but > 10 mg/dose Other antioxidants	Comparative dissolution testing data on the pre- and post-change products in QC and multimedia In limited circumstance, may request additional in vitro bridging studies or in vivo studies
	BCS-III		Comparative dissolution testing data on the pre- and post-change products in QC and multimedia Supportive studies to demonstrate that the antioxidant does not affect passive intestinal permeability and transporter activity if the API is a transporter substrate Or in vivo BE study
	BCS-IV	Any antioxidant or pH modifier	Studies such as a validated IVIVC, PBPK modeling Or In vivo BE study
MR dosage form	BCS-I,II, III and IV		

*For other types of changes, such as modifications to the manufacturing process, API changes, or a combination of multiple changes, a case-by-case, risk-based approach is applied. In certain circumstances, other alternative BE approach may also be considered appropriate, depending on the specific case.

Case Studies

- Case 1: Immediate Release (IR) Capsule – Multiple changes in formulation
- Case 2: IR Tablet – BCS Class 3 or 4 – Addition of an antioxidant
- Case 3: Delayed Release (DR) Capsule – Addition of an antioxidant
- Case 4: Fixed-dose Combination IR/Extended-Release (ER) Tablets – Changes n manufacturing process and formulation

Case Study 1

Drug Product	• Approved ANDA • IR Capsule • Three strengths
Applicant's Proposed Approach to Control Nitrosamine Impurity	• Change in the grade and amount of a filler • Removal of glidant • Reduce the fill weight of the drug product
Applicant's Proposal for Prior Approval Supplement (PAS)	• Biowaiver request for all three strengths based on dissolution data comparing the pre-change vs post-change test products in quality control (QC) medium

Agency's Evaluation and Decision:

- No addition of antioxidant or pH modifier, thus, alternative BE approach recommended in nitrosamine guidance is not applicable
- Removal of glidant constitute a level 3 change per SUPAC-IR guidance*
- Product-Specific Guidance (PSG) recommendations: Fed BE study on the highest strength, waiver of lower strengths
- To support the proposed changes, the applicant should submit following data in PAS:
  - ✓ Fed BE study on the highest strength
  - ✓ Dissolution data comparing the pre-change vs post change test products in QC medium for all strengths

*SUPAC-IR: Immediate-Release Solid Oral Dosage Forms: Scale-Up and Post-Approval Changes: Chemistry, Manufacturing and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation (November 1995)

Case Study 2

Drug Product	• Approved ANDA • IR Tablet • Two strengths
Applicant's Proposed Approach to Control Nitrosamine Impurity	• Addition of an antioxidant • Adjust the level of microcrystalline cellulose to maintain the constant tablet weight
Applicant's Proposal for Prior Approval Supplement (PAS)	• Biowaiver request for both strengths based on dissolution data comparing the pre-change vs post-change test products in QC medium

Agency's Evaluation:

- Drug substance BCS Class – III or IV due to conflicting information regarding solubility.
- Proposed antioxidant is one of the antioxidants studied in FDA research.
- Proposed amount of antioxidant is less than 10 mg/day. The maximum daily intake level is within the FDA-approved levels for adults but exceeds the level in pediatrics for the same route of administration and similar context of use.

Case Study 2 (cont.)

Agency's Decision/Recommendation to the Applicant:

- Confirmation that there are no other changes e.g., manufacturing site, process etc.
- Dissolution data in QC and multimedia for each strength comparing pre- and post-change test products.
- Solubility data of API used in the test product as per recommendations in M9 BCS Guidance* to demonstrate high solubility. If high solubility is not demonstrated, provide evidence that antioxidant at the proposed level in the post-change test product does not impact the absorption of drug substance as compared to the pre-change test product based on studies such as a validated in vitro-in vivo correlation, PBPK modeling, or other studies as appropriate.
- Justification/data to support the safety of antioxidant at the proposed level in pediatric population.

*M9 Biopharmaceutics Classification System-Based Biowaivers (May 2021)

Case Study 3

Drug Product	• Approved ANDA • DR Capsule • Multiple strengths
Applicant's Proposed Approach to Control Nitrosamine Impurity	• Addition of an antioxidant and a pH adjuster • Reduce the weight of sugar spheres to keep the approved capsule weight
Applicant's Proposal for PAS	• Conduct Caco-2 study to prove that antioxidant is not expected have an impact on API absorption • Dissolution data in QC medium comparing the pre-change vs post-change test products

Case Study 3 (cont.)

Agency's Evaluation:

- Drug substance belongs to BCS Class III.
- The proposed antioxidant is one of the antioxidants studied in FDA research.
- Proposed amount of antioxidant is less than 10 mg/day.
- Formulation design: DR formulation consists of IR drug layer and enteric coating layer. The proposed antioxidant is added to only IR layer. Change in amount of sugar spheres falls under Level 1 changes per SUPC-MR guidance*
- No other changes to the composition or manufacturing process.
- Based on the totality of evidence, it was that considered that the risk of change in drug absorption by adding antioxidant in IR drug layer is low.

*SUPAC-MR: Modified Release Solid Oral Dosage Forms Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation (October 1997)

Case Study 3 (cont.)

Agency's Recommendation to the Applicant:

- Submission of Caco-2 permeability study is not needed.
- Provide comparative dissolution data between pre-change and post-change test products for all strengths in QC dissolution medium and multimedia of pH 1.2, 4.5, and 6.8.

Case Study 4

Drug Product	• Approved ANDA for Fixed-dose IR (API A)/ER (API B) Tablets • Multiple strengths
Applicant's Proposed Approach to Control Nitrosamine Impurity	• Addition of an (i) additional purification step for API A, and (ii) antioxidant • Change in (i) processing solvent used during granulation, and (ii) amount of non-release controlling excipient used in ER part
Applicant's Question Agency	• Are BE studies or just dissolution data in multimedia comparing the pre-change vs post-change test products are required?

Agency's Evaluation and Decision:

- Both APIs belongs to BCS Class III.
- The proposed type of antioxidant and its amount are acceptable.
- A change in the type of processing solvent, as well as change in amount of non-release controlling excipient, was considered a Level 3 change
- The applicant was requested to:
  - ✓ Conduct a single-dose in vivo fasting BE study comparing the highest strength of the reformulated test product vs reference standard.
  - ✓ Provide comparative dissolution data between pre-change and post-change test products for all strengths in QC and multimedia.

Summary

- To apply an alternative BE approach in bridging the drug product changes, it is essential to carefully evaluate the physical and chemical properties of the drug substance, level of the changes, and formulation release mechanism.
- Requests for Agency to consider other alternative approaches (not specified in the Nitrosamine Guidance) to demonstrate BE for BCS Class IV and modified-release drug products will be evaluated on a case-by-case basis.
- For scenarios not covered by Agency guidance, the applicants are encouraged to discuss their alternative BE approach with Agency through appropriate pathways, such as meetings, controlled correspondences, general correspondences, etc.

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