MANAGING BIOEQUIVALENCE RISKS FOR NITROSAMINE IMPACTED DRUG PRODUCTS CONTAINING BCS IV DRUG SUBSTANCES

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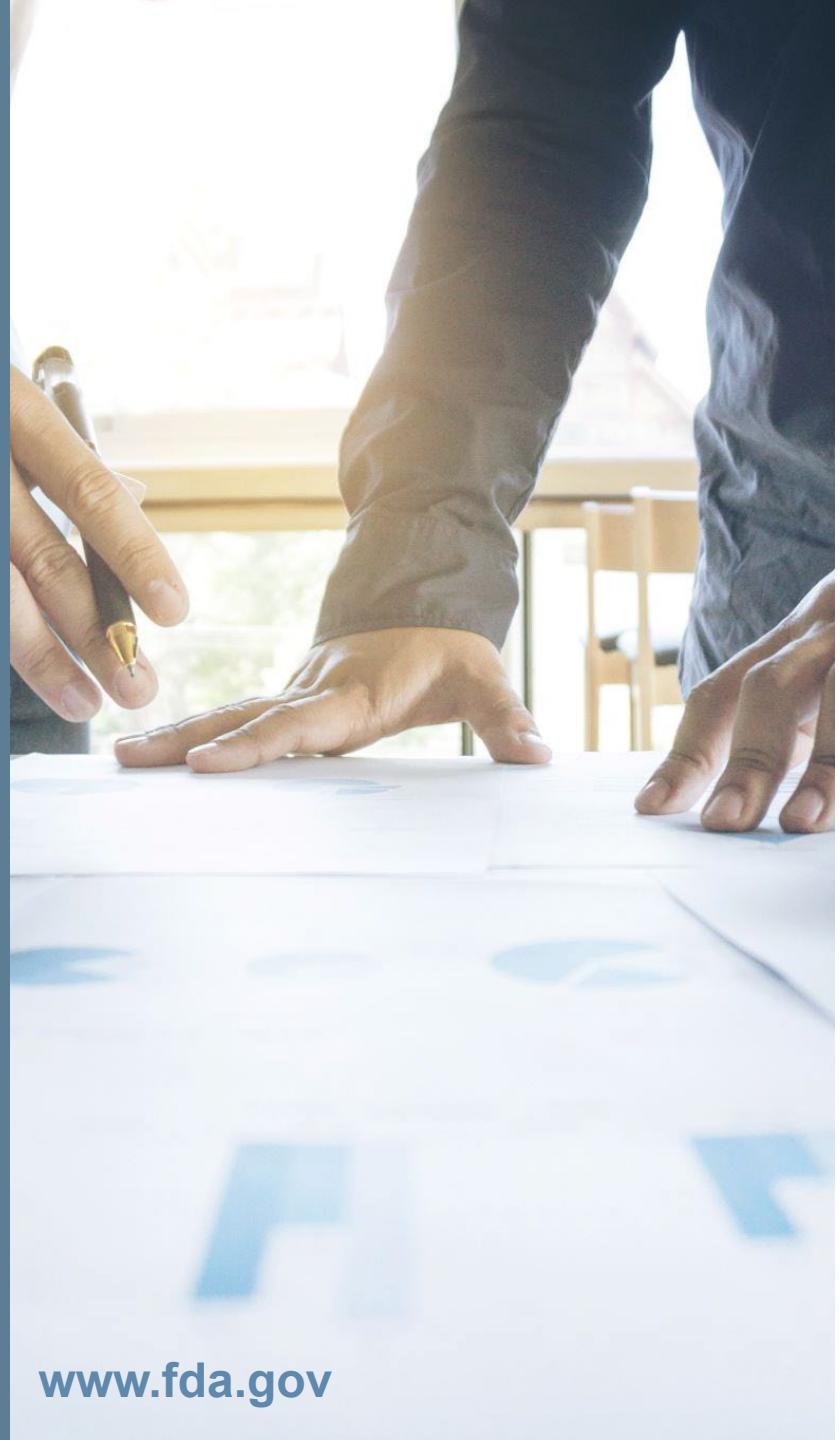


OUTLINE

- Current Approach and Risk Classification Based on BCS Classification
- Nitrosamine Impacted Drug Products Containing BCS IV Drug Substances
- Risk Factors and Management for BCS IV Drugs
- Final Thoughts and Future Direction

FDA GUIDANCE ON ALTERNATIVE BE APPROACHES FOR NITROSAMINE-IMPACTED DRUG PRODUCTS[1]

- **Focus on alternative bioequivalence (BE) approaches for products with added antioxidants and pH modifiers**

For reformulate products to include excipients such as antioxidants or pH modifiers aimed at reducing nitrosamine impurities, the FDA guidance allows for the use of alternative BE approaches to demonstrate BE without needing a traditional in vivo (fasting or fed) BE study.

- **Importance of BCS classification in determining alternative BE approaches**

BCS I, II, III: **Comparative dissolution testing (multi-pH dissolution profiles) may be used as a surrogate**, if the reformulated IR product use pH modifiers or specific antioxidants (like ascorbic acid, alpha-tocopherol, cysteine hydrochloride, and propyl gallate) within acceptable limits (typically ≤ 10 mg per dose).

BCS IV: **Enhanced BE recommendations like physiologically based pharmacokinetic/biopharmaceutics modeling (PBPK/PBBM) to correlate in vitro to in vivo**.

- **Scientific justification and risk-based approach when selecting alternative BE approaches**

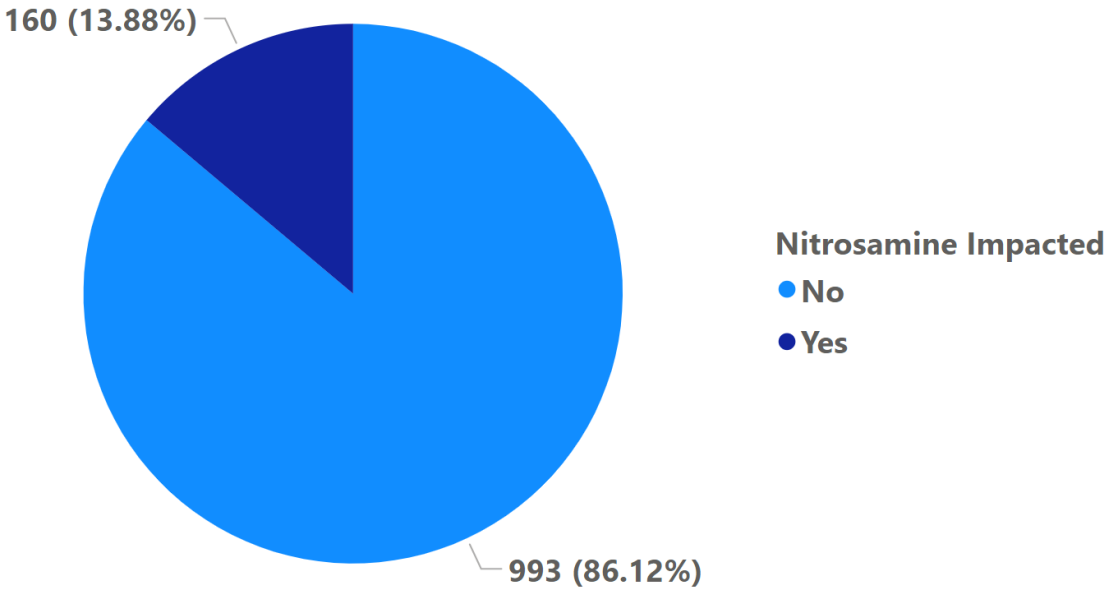
A thorough risk assessment considering factors such as drug properties, nitrosamine formation pathways, and the extend of formulation changes

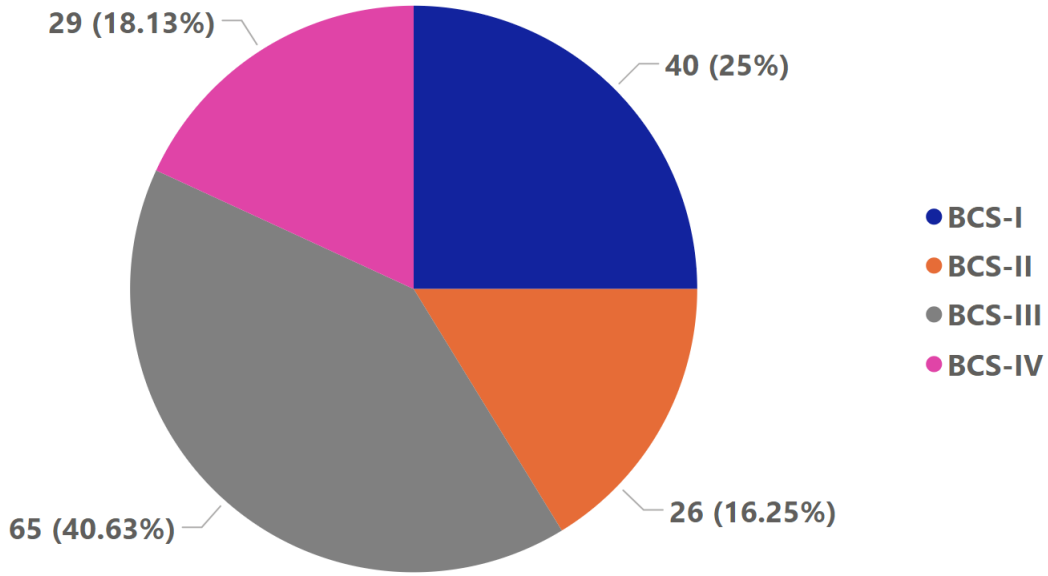
[1]Guidance For Industry: Control of Nitrosamine Impurities in Human Drugs (September 2024)

BCS IV CHALLENGES

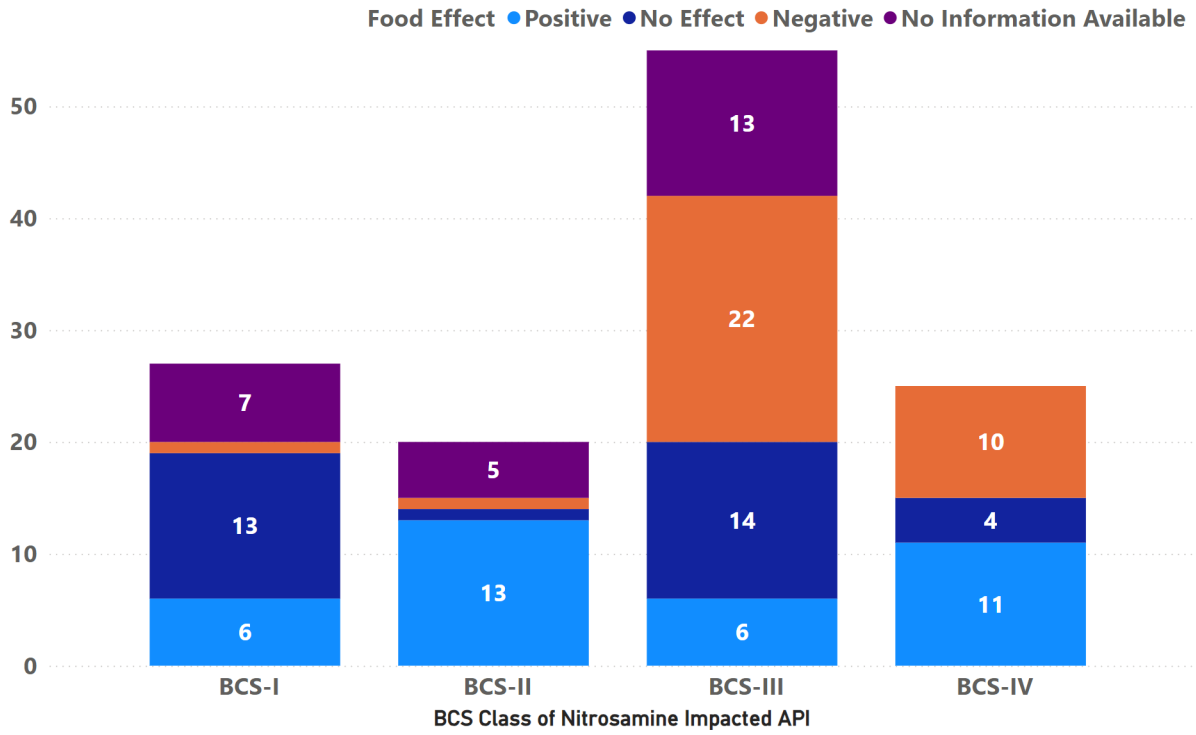
- Complexity in absorption: BCS IV are characterized by both low solubility and permeability which makes their BA/BE unpredictable and challenging.
- Comparable dissolution tests may not reliably predict the complex absorption behavior, as would be possible with more soluble and permeable drugs
- Due to the intrinsic challenges of BCS IV drug, even minor formulation adjustments necessitate rigorous BE evaluation methods to ensure that therapeutic performance is not compromised.
- **However, with a robust risk-based approach-including rigorous dissolution and, when necessary, PBPK/PBBM – there is a pathway to potentially waive in vivo BE studies for BCS IV drugs, especially if the changes involve antioxidants or pH modifiers with limited impact on the overall absorption.**

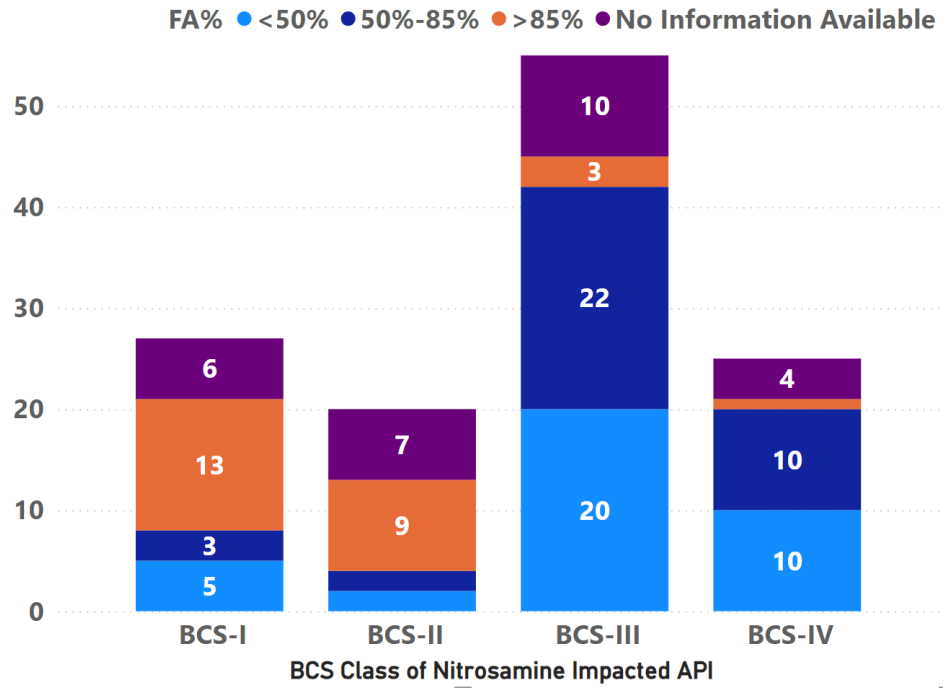
NITROSAMINE-IMPACTED IMMEDIATE RELEASE DRUG PRODUCTS





NITROSAMINE-IMPACTED ACROSS BCS: FOOD EFFECT AND FA%[2]





[2] Fraction absorbed%: estimated based on absolute bioavailability and the results of mass balance studies from labeling information.

BCS IV SUBCATEGORIES AND RISK FACTORS

- This table presents a classification of BCS IV subcategories along with their associated risk factors and critical excipients. It breaks down BCS IV drugs into different subcategories based on their dominant limitations – whether solubility or permeability – and identifies the corresponding challenges relevant to each category.

Category	Solubility limited (BCS II like)			Dual limited	Permeability limited (BCS III like)		
Risk factors	pH-dependent solubility (weak acid and base)	Precipitation (weak base)	Low solubility and poor dissolution	Low solubility and low passive permeability	Low passive permeability	Efflux transporter	Short absorption window
Food effects	Positive effects with higher Fa%			Unpredictable	No effects or negative effects with lower Fa%		
Critical excipients	pH modifiers	Polymers, nanoparticles, solid dispersions	Solubilizers, lipid based	Solubilizers, permeability enhancers	Surfactants, lipid based	Permeability enhancers	Lipid excipients

ANTIOXIDANTS: RATIONALE TO EXTEND BCS III FINDINGS TO BCS IV

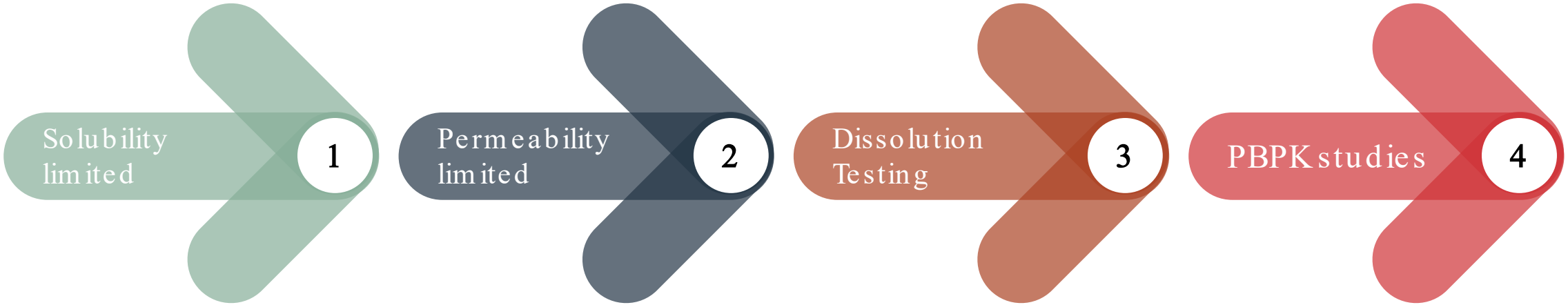
BCS III Model Drugs	Estimated BCS Class	Dosage form	Estimated Fa%	Estimated food effect AUC	Estimated food effect Cmax
CIMETIDINE	BCS-III	TABLET	56-68%	0.9	1.1
ACYCLOVIR	BCS-III/IV[3]	CAPSULE (200 mg)	10-15%	1	1
ACYCLOVIR	BCS-III/IV	SUSPENSION (800 mg)		1.3	1
ACYCLOVIR	BCS-III/IV	TABLET (800 mg)		~1.5	~1.5
ATENOLOL	BCS-III	TABLET	50%	~0.9	~0.9
RANITIDINE	BCS-III	TABLET	50-60%	1	1
RANITIDINE	BCS-III	CAPSULE		1	1
RANITIDINE	BCS-III	TABLET, EFFERVESCENT		1	1

3

- Research on the BCS III model drugs show that antioxidants do not alter permeability
- For BCS IV drugs with comparable or better permeability/absorption than BCS III model drugs (Fa >10%), antioxidants are expected to have minimal or no effect on permeability
- For BCS IV drugs where permeability is not the primary limiting factor (BCS II like), antioxidants is not expected to affect drug permeability and absorption
- In more complex BCS IV formulations it's essential to confirm that concentration threshold (e.g., above 10 mg) do not interfere with other excipients (solubilizers, surfactants, etc.) and introduce permeability alternations

[1]Solubility is estimated for acyclovir with the highest single dose of 800 mg

4 TIER RISK EVALUATION FOR BCS IV REFORMULATED DRUG PRODUCTS



Evaluation: Conduct solubility-pH testing
Key indicators: Positive food effects. pH dependent solubility

Evaluation: Estimate Fa by comparing the reformulated drug to known model drugs
Key indicators: No or negative food effects. Fa% is less than 50%

Evaluation: Focus on product design and critical excipients; conduct dissolution-pH testing with adequate QC dissolution conditions
Key indicators: Dissolution not similar

Evaluation: Perform in vivo BE study if dissolution results or absorption predictions suggest high risk
Key indicators: Non-BE

FINAL THOUGHTS AND FUTURE DIRECTION

- For nitrosamine-impacted drug products, it is critical to ensure that formulation changes made to control nitrosamine do not affect solubility, permeability, and in vivo BA/BE.
- BCS IV classification reflects both solubility and permeability limitations, complicating both dissolution and absorption making them particularly challenging for BE evaluations.
- Food effects are critical in subcategory classification. Positive food effects with higher Fa% often indicate solubility limitations (BCS II like), while low Fa% without or with negative food effects suggest permeability limitations (BCS III like).
- Predictability of antioxidant effects allows for tailored BE waiver assessments for BCS IV drugs.
  - Research on BCS III drugs shows that antioxidants have minimal or no impact on permeability, a finding that can extend to BCS IV with comparable or better permeability.
  - Established alternative BE approaches for BCS II and III can guide BCS IV BE assessments.
  - For dual limited BCS IV, future research should focus on complex formulation in the presence of antioxidants, including pH modifiers, solubilizers, and permeability enhancers, or other special formulation design: 1) assess existing PK data, 2) determine how these excipients affect dissolution across pH ranges using adequate QC dissolution method, and 3) investigate how these excipients affect solubility in complex formulations, cross-validating finding with in vivo data to address formulation related risks.

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FDA Nitrosamine-Impacted Drug Products BCS Working Group

FDA ICH M13 Implementation Working Group