Nitrosamine-Impacted Drug Products Containing BCS IV Drug Substances

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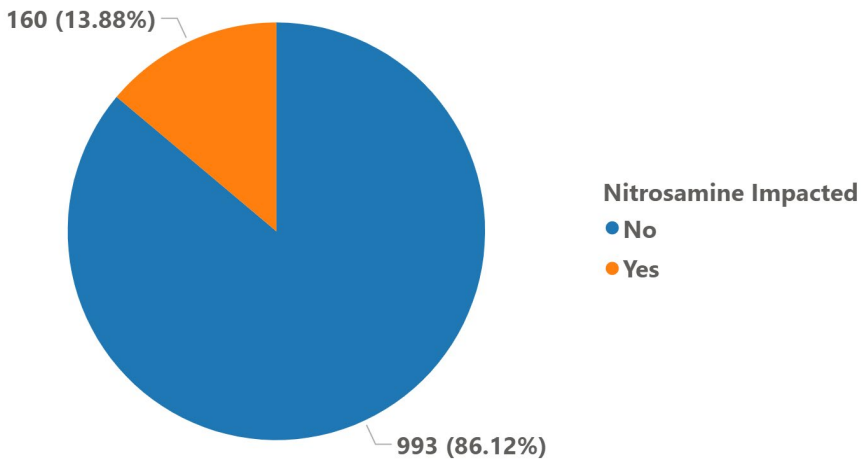
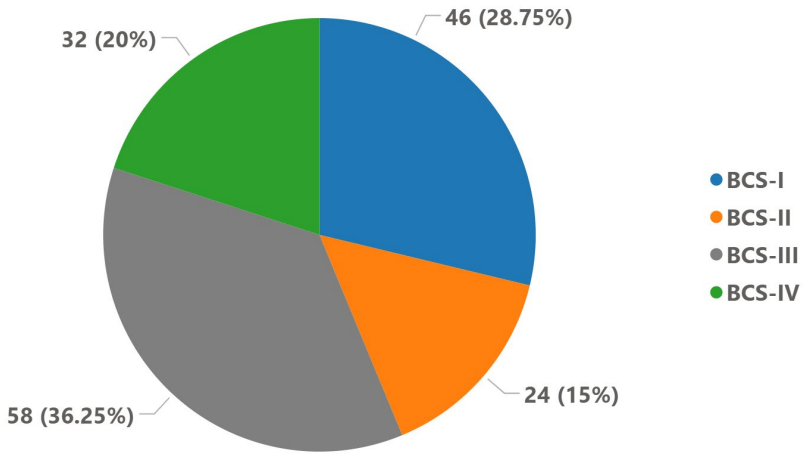
Outline

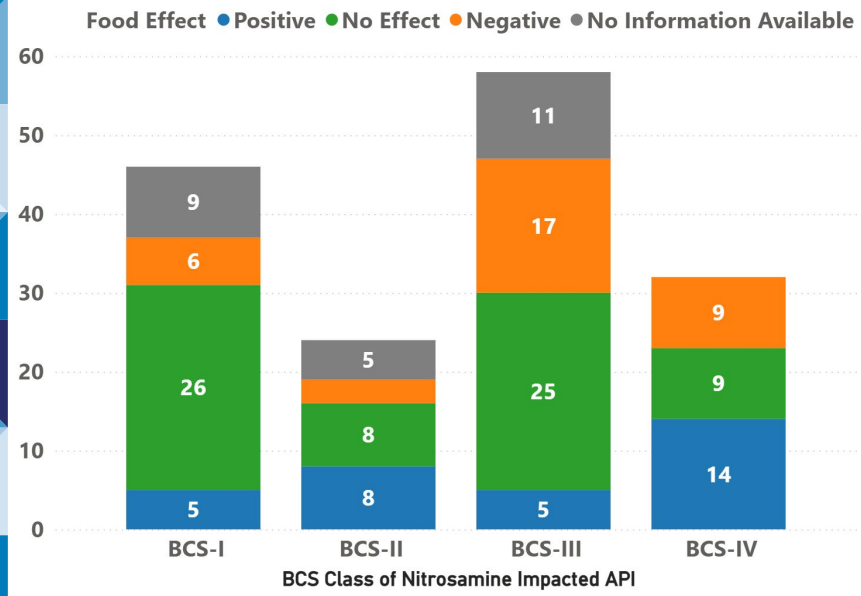
- Current nitrosamine challenges across immediate-release oral products with various BCS classifications
- FDA's alternative bioequivalence (BE) framework and BCS Class IV limitations
- Proposed risk-based subcategorization for BCS Class IV drugs
- Case study validation and regulatory implications

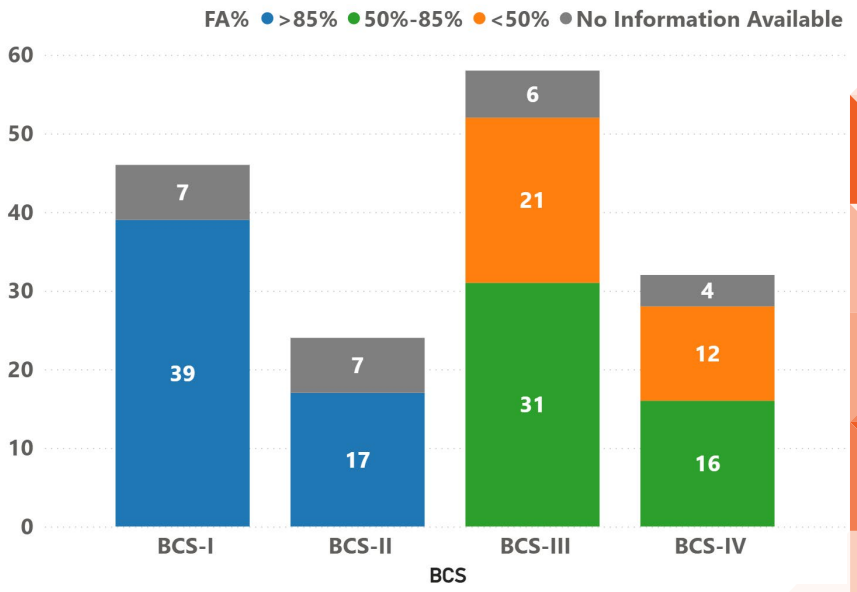
Nitrosamine-impacted Immediate-Release (IR) Oral Drug Products





Nitrosamine-impacted IR products across BCS: Food Effect and Fa%[1]





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

FDA Guidance on alternative BE approaches for nitrosamine-impacted drug products[2]

- **Focus on alternative BE approaches for products with added antioxidants and pH modifiers**
  - For reformulated 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 the need for 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 an alternative BE approach**, if the reformulated IR product uses 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**: **Supported by studies such as a validated in vitro-in vivo correlation, physiologically based pharmacokinetic modeling (PBPK) or in vivo BE studies.**
- **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 extent of formulation changes

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

BCS IV challenges

Absorption Complexity

- BCS IV drug substances are characterized by both low solubility and permeability, making bioavailability/bioequivalence unpredictable and challenging.
- Comparative dissolution tests may not reliably predict complex absorption behavior, particularly compared to their effectiveness with more soluble and permeable drugs.

Formulation Sensitivity

- Due to intrinsic challenges to BCS IV drugs, even small formulation changes may necessitate rigorous BE evaluation methods to ensure that the therapeutic performance is maintained.

Pathway Forward

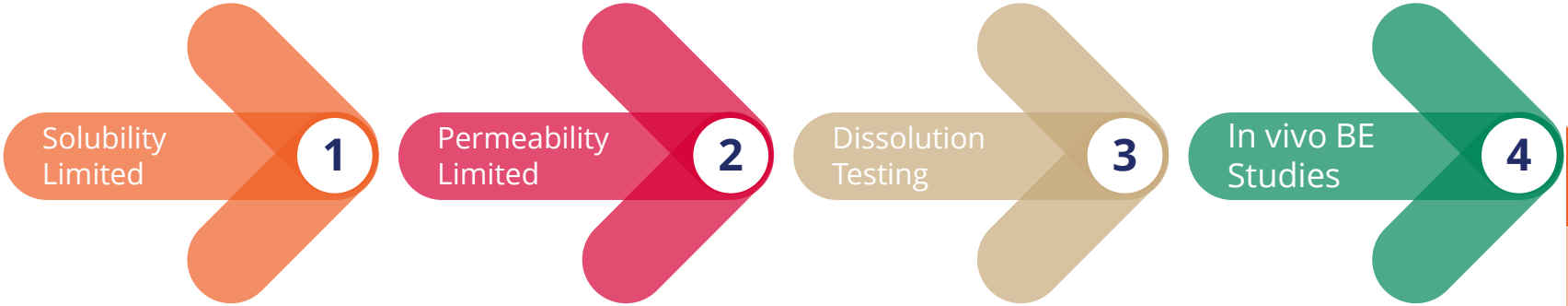
- **A robust risk-based approach — including rigorous dissolution testing and PBPK modeling methods when necessary — can provide a pathway to waive in vivo BE studies.**
- This approach is particularly applicable for BCS IV drugs when changes involve antioxidants or pH modifiers with limited impact on overall absorption.

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	Permeability limited (BCS III like)			Dual limited			
	Solubility limited (BCS II 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

4 Tier risk evaluation for BCS IV reformulated drug products[3]



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.

Evaluation: Focus on product design and critical excipients; conduct comparative dissolution testing in QC medium and multi-pH media
Key indicators: Dissolution not similar

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

[3]Qi Zhang, Managing Bioequivalence Risks for Nitrosamine Impacted Drug Products Containing BCS IV Drug Substances, CRCG, Nov 2024

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[4]	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

Research[5] on the BCS III model drugs show that antioxidants do not alter the 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 the permeability.

For BCS IV drugs where permeability is not the primary limiting factor, antioxidants is not expected to affect drug permeability and absorption.

In more complex BCS IV formulations, it's essential to confirm that the antioxidant amount threshold (e.g., above 10 mg) do not interfere with other excipients (solubilizers, surfactants, etc.) or introduce permeability alterations.

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

[5]Lu, D., et al. (2024). Antioxidants had No Effects on the In-Vitro Permeability of BCS III Model Drug Substances. *Journal of Pharmaceutical Sciences*, *113*(9), 2708-2714.

Case Study

- IR tablet with multiple strengths
- Antibiotic
- Nitrosamine impurities
  - Detected in all tested batches of marketed product
  - Exceeded acceptable intake limit of 1500 ng/day
- Root cause
  - Nitrite impurities in excipients
  - Manufacturing process conditions
  - Storage conditions during shelf life

Case Study – Cont'd

- Nitrosamine risk mitigation strategy:
  - Reformulation by adding antioxidant (less than 10 mg) as nitrite scavenger through prior approval supplement

Ingredients	Approved Composition	Revised Composition
API	✓	✓
Diluent	✓	Adjusted
Disintegrant	✓	✓
Nitrate scavenger	X	✓
Binder	✓	✓
Extragranular	✓	✓

- Risk assessment:
  - Low risk per ICH M13A guidance

Case Study – Cont'd

- Maximum single dose is 780 mg
- BCS Class IV
- pH-dependent solubility:
  - pH 1.2: 18 mg/mL
  - pH 4.5: 68 mg/mL
  - pH 6: 4 mg/mL
  - pH 6.8: precipitated
- Moderate to high permeability:
  - 68%-72% absolute bioavailability
  - Food effect (Fed/Fast): AUC: 0.75 -0.80, Cmax: 0.70 -0.75

Case Study – Cont'd

- Comparative dissolution profile (QC media) – Before reformulation

Collection Time	10 min	20 min	30 min
Cumulative average % Dissolved	98	101	104

- Comparative dissolution profile (QC media) – After reformulation

Collection Time	10 min	15 min	20 min	30 min
Cumulative average % Dissolved	93	94	98	100

- Very rapid dissolution: >85% dissolved within 15 minutes (all strengths)

Case Study – Cont'd

- PK profile – Before reformulation

Parameter	T/R Ratio (Fasting)	T/R Ratio (Fed)
AUC_{0-t} Ratio	95.74%	104.93%
$AUC_{0-\infty}$ Ratio	95.23%	104.73%
C_{max} Ratio	90.48%	101.88%

- PK profile – After reformulation

Parameter	T/R Ratio (Fasting)	T/R Ratio (Fed)
AUC_{0-t} Ratio	99.76%	100.27%
$AUC_{0-\infty}$ Ratio	98.82%	101.15%
C_{max} Ratio	99.34%	100.58%

- Antioxidant addition did not impact BE, confirming predictable antioxidant effects similar to established BCS I/II/III approaches

Framework Application Potential

- Case study demonstrates key principles:
  - Antioxidant addition (less than 10 mg) maintained BE
  - Supports theoretical basis for predictable antioxidant impact
- Framework relevance:
  - Case shows high solubility up to pH 6 and moderate to high permeability (68-72% Fa) with no significant food effects, supports the 4-tier risk-based framework leveraging the established BCS I/II/III approaches.
  - Suggests feasibility for BCS IV drugs with similar absorption characteristics and reformulation strategies
- Future research needs:
  - Additional BCS IV cases to refine and validate the proposed framework
  - Evidence generation for alternative BE approaches

Final thoughts and future direction

- Key Considerations
  - Formulation changes for nitrosamine mitigation must not compromise solubility, permeability, or bioavailability/bioequivalence.
  - BCS Class IV drugs present unique BE challenges due to dual solubility and permeability limitations.
- Strategic Approach
  - Food effects guide BCS IV subclassification:
    - Positive food effects → solubility-limited
    - Negative/minimal food effects → permeability-limited
  - Leverage existing knowledge: Antioxidants minimally impact permeability; established BCS I/II/III approaches can guide BCS IV assessments.
- Future Research Focus
  - For complex BCS IV formulations with antioxidants and other excipients:
    - Assess existing PK data
    - Evaluate dissolution across pH ranges
    - PBPK modeling and cross-validate in vitro findings with in vivo data

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