High-Risk Drug Products and *In Vivo* Release: Defining the BE Safe Space Through IVIVC/IVIVR Development

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Outline

- Definition/Classification of High-Risk Drug Products
- Regulatory Requirement/Evidence to support development of High-Risk Drug Products
- IVIVC – principles and utility
- Case studies:
  - Establishing clinically-relevant dissolution acceptance criteria for a high-risk IR product based on a Multiple Level C IVIVC model.
  - Biowaiver for a Level 3 manufacturing site change for a high-risk ER product based on a Level A IVIVC model.

High-Risk Drug Products – Classification: What Defines High-Risk Products?

- Extended-Release (ER) Formulations:
  - Controlled-release mechanism is rate-limiting for absorption.
  - Small changes in formulation parameters (polymer levels, coating thickness, matrix composition) significantly impact PK.
  - Risk gradations exist: Matrix tablets (lower-risk) → Coated systems → Osmotic pumps/multi-layer systems (very-high risk).
    - *Example*: ER Nifedipine osmotic pump vs. matrix systems produce different PK profiles despite identical API and dose.
- Immediate-Release (IR) Products with Complex Solubilization Technologies:
  - Technologies: amorphous solid dispersions, nanoparticles, lipid-based formulations, SEDDS.
  - Designed to overcome poor aqueous solubility.
  - Create formulation-dependent bioavailability where dissolution advantage is critical for absorption.

High-Risk Drug Products – Evidence Requirements: Regulatory Strategy

- Evidence Hierarchy:
  - IVIVC:
    - BCS Class 1/Class 3 ER products: Level A IVIVC preferred (point-to-point correlation via deconvolution).
    - When Level A IVIVC not feasible (BCS Class 2 ER, complex IR with supersaturation/precipitation): Multiple Level C correlations or PBBM-based approaches.
  - PBBM:
    - Provides mechanistic understanding of release and dissolution behavior.
    - Predicts performance outside tested range using biorelevant data and supersaturation/precipitation kinetics.
- Key Principles:
  - *In vivo* studies/PBBM/IVIVC define "Bioequivalence Safe Space" — the dissolution profile range ensuring bioequivalent performance.
  - Together, they enable science-based lifecycle management and regulatory flexibility for high-risk products.

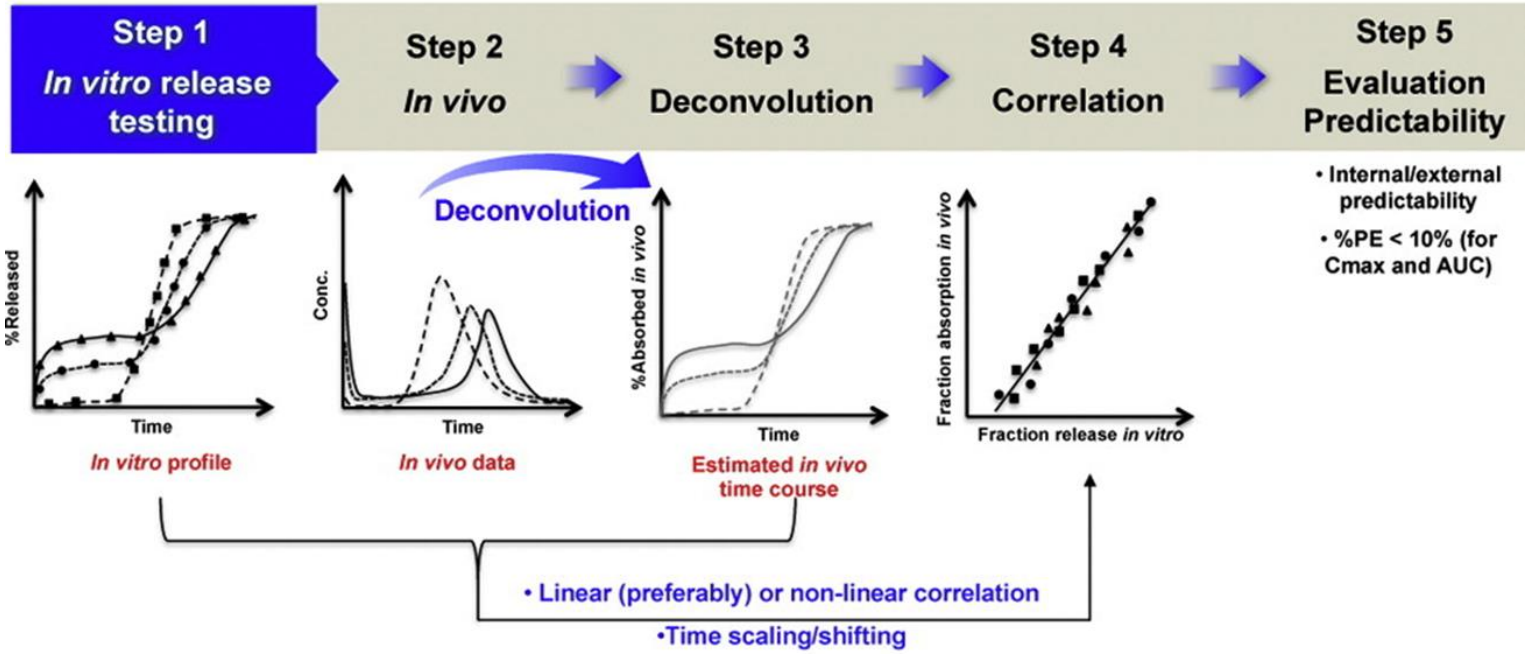
Very High-Risk Drug Products – Classification: What Defines Very High-Risk Products?

- High-Risk elevated by formulation/process complexity and/or clinical factors:
  - Formulation/Process Complexity:
    - Sensitive ER release mechanisms (coated multi-particulates, osmotic pumps, multi-layer systems).
    - Poorly understood or difficult-to-control interacting release mechanisms.
    - Novel technologies without an established precedent.
  - Clinical Risk Factors (independent of biopharmaceutical complexity):
    - Narrow Therapeutic Index (NTI) drugs.
    - Black box warnings or serious safety concerns.

Evidence Requirements: Regulatory Strategy

- *In vivo* studies are the default for development and significant post-approval changes.
- PBBM-IVIVC may be acceptable – only a case-by-case basis

IVIVC – Introduction and Principles



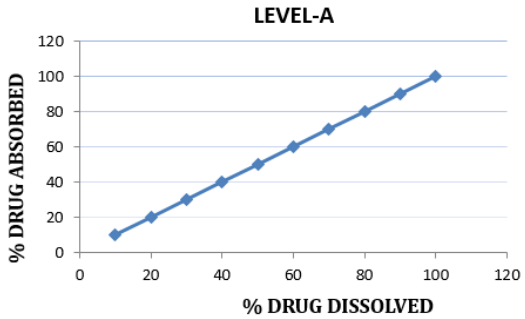
J. Shen, D.J. Burgess / Journal of Controlled Release 219 (2015) 644–651

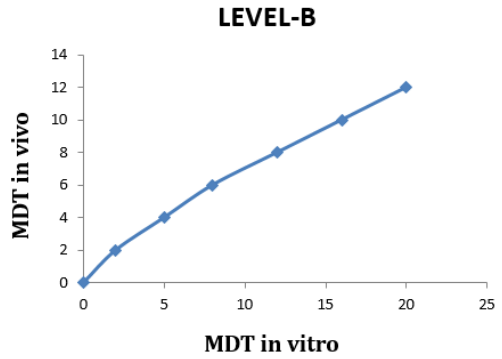
What is an IVIVC?

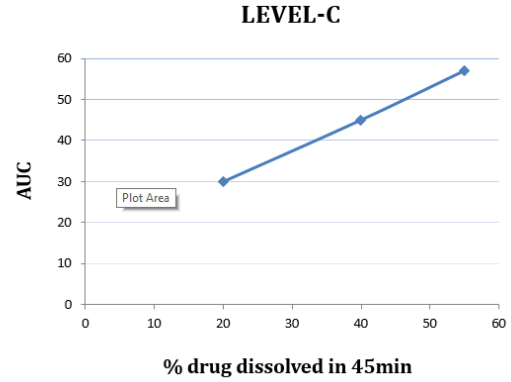
A mathematical relationship between an *in vitro* property of a dosage form (e.g., dissolution) and its *in vivo* performance (e.g., concentration-time profiles), with the goal to accurately predict the *in vivo* plasma concentration-time profile of a drug formulation.

IVIVC – Types and Utility

Category	Description	Graphical representation	Applicability/Utility
Level A	A point-point relationship between in vitro dissolution and in vivo drug absorbed	% dissolved in vitro vs. % absorbed in vivo	Most informative and useful; applicable for setting dissolution specifications and supporting biowaivers
Level B	A usage of the principles of statistical moment analysis	Mean in vitro dissolution time vs. mean residence time in vivo	Least useful; not applicable for setting dissolution specifications and supporting biowaivers
Level C	A single point relationship between a dissolution parameter and a PK parameter	% dissolved at specific time-point vs. AUC and/or C_{max}	Very limited usage for justifying dissolution specifications
Multiple Level C	Correlation relates to one or several PK parameters of interest to the amount of drug dissolved at several time-points of the dissolution profile	% dissolved (at 10, 30, 60 min) vs. AUC and/or C_{max}	Can be as useful as a Level A correlation







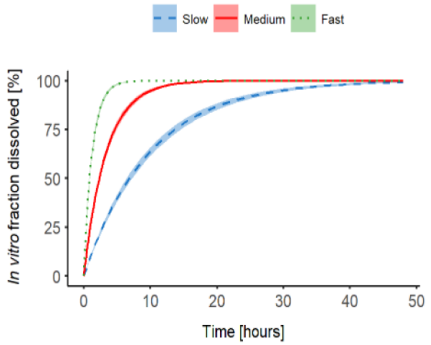
www.fda.gov: Guidance for Industry: Extended-Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations, September 1997

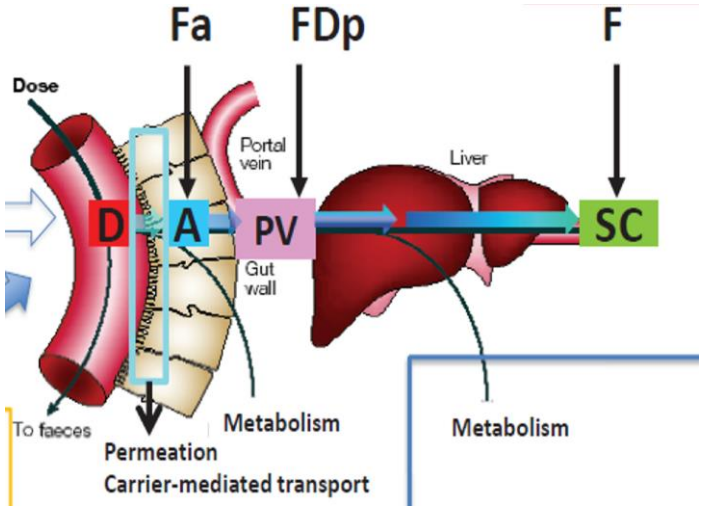
Mechanism Absorption-based IVIVC/R

Drug Substance/formulation properties (e.g., solubility, pKa, LogP, particle size, permeability, etc.)

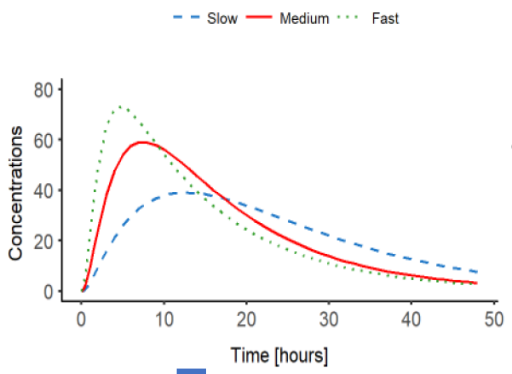
In vivo performance absorption, bioavailability, blood concentration profiles

In vitro Dissolution

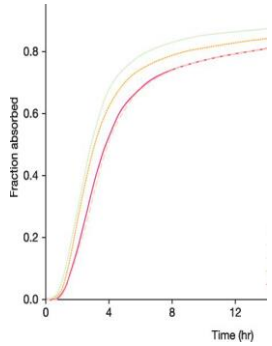




In vivo PK profiles



In vivo Dissolution



Mechanistic Deconvolution

www.fda.gov

- Mechanism absorption-based IVIVC/R (e.g., PBBM-IVIVC) combines the physicochemical characteristics of the API and/or formulation of the drug product (PBBM component) to develop the IVIVC model.
- PBBM-IVIVC can be used to simulate and predict drug behavior across a wider range of scenarios, including different formulations, doses, food effects, and special populations (e.g., pediatrics, elderly, patients with GI disorders).

Case study 1: Establishing clinically-relevant dissolution acceptance criteria based on a 'Multiple-Level C IVIVC'-design-space model for an IR product

Drug Product: Characteristics

- Drug Product: Immediate Release tablet
- Route: Oral
- T_{max}: 1–2 hours

Drug Substance: Characteristics

- BCS: Class 2/Class 4
- Solubility: Low solubility of the crystalline form across the pH range of 2 to 8.

  The crystalline form is converted to a more soluble and more bioavailable amorphous form using the Hot Melt Extrusion technology.

  This amorphous form is blended with excipients, compressed into a core tablet, and film-coated to form the final tablet.

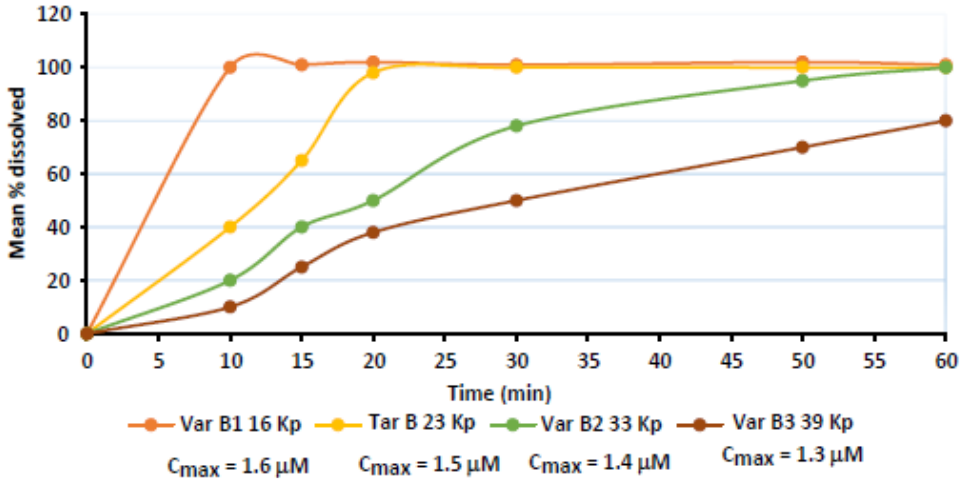
  - **Satisfies the definition/classification of a High-risk product**

Case study 1 (cont'd):

In vitro dissolution method/acceptance criterion

Originally proposed in vitro dissolution method			*Originally proposed in vitro* dissolution acceptance criterion
Apparatus	Medium/ Volume	Agitation speed/ Temperature	
USP apparatus 2	Medium: 0.2% Surfactant Volume: 900 mL	Speed: 100 rpm Temp: 37 °C	Q = 75% in 30 minutes

Tablet hardness – *In vitro* dissolution



List of potential CQAs

- **CMA**
  - Crystalline content of the API.
  - Tablet tensile strength/tablet hardness.
  - A relationship among the four IR batches varying in tablet hardness for C_{max} was seen.
  - There were no significant changes in AUC_{inf}.

Tablet hardness – *In vitro* dissolution and PK comparison

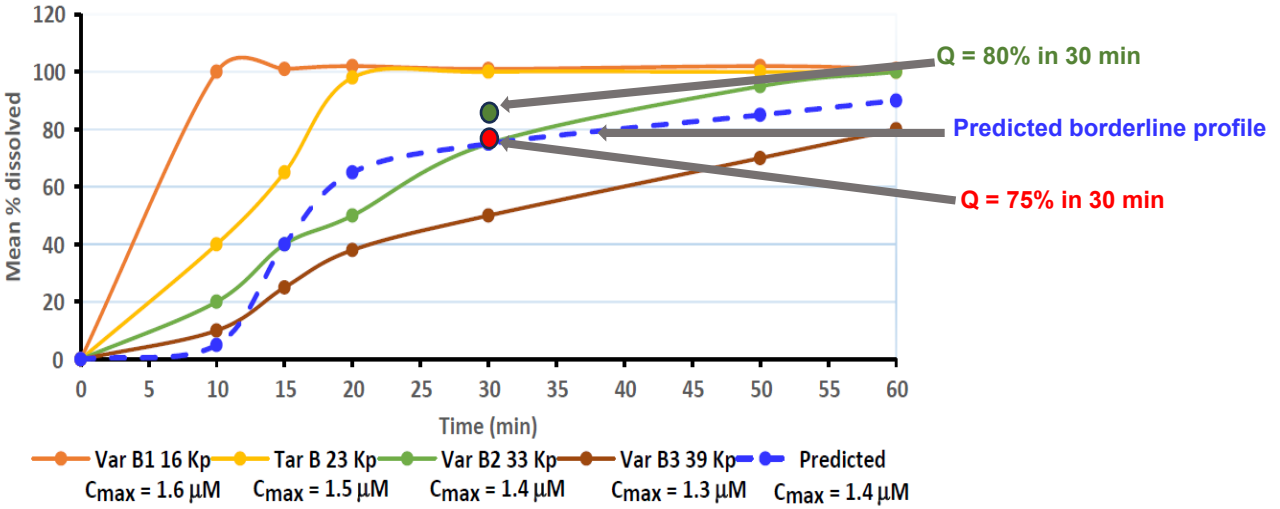
Parameter		Tar B vs Var B1	Tar B vs Var B2	Tar B vs Var B3
In vitro dissolution	*f2*	<50	<50	<50
In vivo PK	C_{max}	Not BE	Not BE	Not BE
	AUC_{inf}	BE	BE	BE

Case study 1 (cont'd):

Establishing *in vitro* dissolution specifications based on a Multiple Level C IVIVC model

- A Multiple Level C IVIVC model was constructed using the dissolution profiles of the batches and PK data (C_{max}) of the batches.
- Based on the IVIVC model, a dissolution profile (**Blue dashed line**) was generated representing the border-line for bioequivalence to the target formulation (within 10% of mean C_{max} relative to target).
- Originally-proposed dissolution specification of 'Q = 75% (i.e., 80% dissolution) in 30 min' would result in a product that would be bio-inequivalent to the target.
- A dissolution specification of 'Q = 80% (i.e., 85% dissolution) in 30 min' would yield a product that would be bioequivalent to the target.

Predicted *in vitro* dissolution profile based on a Multiple Level C IVIVC model against C_{max}



In vitro dissolution method/acceptance criterion

Final in vitro dissolution method			*Final in vitro* dissolution acceptance criterion
Apparatus	Medium/ Volume	Agitation speed/ Temperature	
USP apparatus 2	Medium: 0.2% Surfactant Volume: 900 mL	Speed: 100 rpm Temp: 37 °C	Q = 80% in 30 minutes

Case study 2: Application of a 'Level A IVIVC model-based biowaiver' for a Level 3 manufacturing site change for an ER product

Drug Product: Characteristics

- Drug Product: Extended Release tablet
- Route: Oral
- T_{max}: 2–4 hours

Drug Substance: Characteristics

- BCS: Class 1 (no formal claim)
- Solubility: High solubility across the pH range of 1.2 to 7.

  The API is combined with the excipients including the Release Controlling Polymer (RCP) and film-coated to form the final tablet.

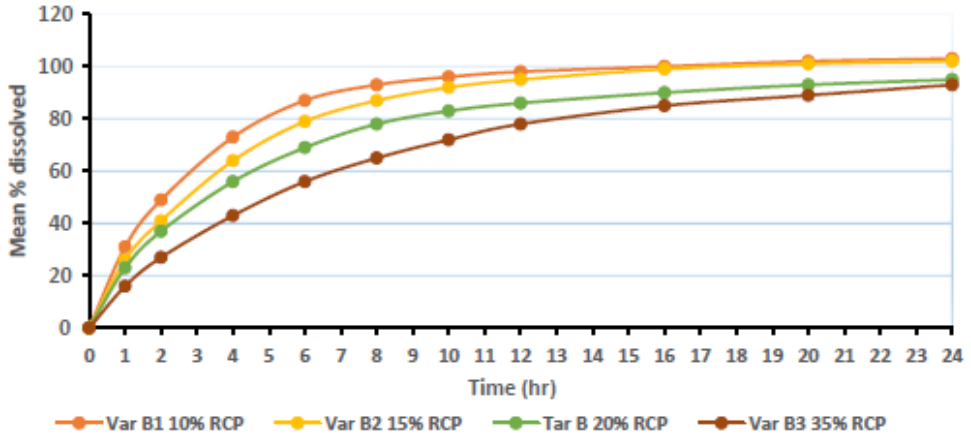
  - **Satisfies the definition/classification of a High-risk product**

Case study 2 (cont'd):

In vitro dissolution method

Final in vitro dissolution method (Lower and Higher strengths)		
Apparatus	**Medium/ Volume**	**Agitation speed/ Temperature**
USP apparatus 1	Medium: 50 mM Phosphate buffer, pH 6.8 Volume: 900 mL	Speed: 100 rpm Temp: 37 °C

Concentration of RCP – *In vitro* dissolution



List of potential CQAs

- **CFV**
  - Concentration of the RCP was considered a CQA.
  - A rank-order relationship among the four ER formulations varying in the concentration of the RCP for C_{max} was seen.
  - There were no significant changes in AUC_{inf}.

Concentration of RCP – *In vitro* dissolution and PK comparison

Parameter		Tar B vs Var B1	Tar B vs Var B2	Tar B vs Var B3
In vitro dissolution	*f2*	<50	>50	<50
In vivo PK	C_{max}	Not BE	Not BE	Not BE
	AUC_{inf}	BE	BE	BE

Case study 2 (cont'd):

Constructing a Level A IVIVC model

- Using the higher strength, a 2-stage procedure was used to construct the Level A IVIVC model
  - Deconvolution of plasma conc vs. time profiles.
  - Comparison of F_{abs} vs. F_{diss}.
- There existed a rank-order correlation between the *in vitro* dissolution profiles and the *in vivo* absorption profiles.
- The IVIVC model met the acceptability criteria for validation and predictability.

In vitro dissolution profile comparison (*f*2) pre- vs. post-change batches

Lower strength Pre-change batch	Lower strength Post-change batches (Level 3 change in manufacturing site)		
	B1	B2	B3
B1	82.53	89.35	90.05

Predicted PK comparison pre- vs. post-change batches

Lower strength Post-change batches	PK Parameter	Reviewer's Evaluation		
		Lower strength Post-change batches Predicted	Lower strength Pre-change batch (B1) Predicted	% Difference in Predicted PK parameters
B1	AUC_{inf}	253.5	249.4	1.6
	C_{max}	25.9	25.2	2.7
B2	AUC_{inf}	254.2	249.4	1.9
	C_{max}	25.3	25.2	0.4
B3	AUC_{inf}	251.9	249.4	1.0
	C_{max}	24.9	25.2	1.2

Biowaiver for the Lower strength post-change product

- % Difference in predicted PK values between the pre- vs. post-change batches complied with the acceptability criteria of ≤20%.
- Dissolution profile comparison (*f*2) between the pre- vs. post-change batches >50.
- Post-change batches complied with the dissolution acceptance criteria.
- Pre- and post-change products are similar. BE study to support the Level 3 change in manufacturing site is not required.

Regulatory Applications of IVIVC

- Support dissolution specifications.
- Support biowaivers – during drug product development and life-cycle management (e.g., site changes, changes in non-release controlling excipients, process changes as defined in the *Guidance*, addition of lower strengths).
- Alternate BE approach.
- Aid clinically-relevant manufacturing design space and product specification (e.g., establishing API-PSD).

High-Risk Drug Products, BE Safe Space, and IVIVC/R Development – Take Home Message

- High-Risk Drug Products:
  - ER products – the release mechanism is rate-limiting for absorption, and small changes in the formulation significantly impact the dissolution and the PK of the drug product.
  - IR products – complex solubilization technologies such as ASD, nanoparticles, lipid-based formulations impact the dissolution and the PK of the drug product.
- IVIVC/R – principles and utility:
  - IVIVC/R aid in establishing a BE safe-space, setting dissolution specifications, and supporting biowaivers.
  - IVIVC/R enable science-based lifecycle management and regulatory flexibility for high-risk products.
- Case studies:
  - High-risk IR product where the low-solubility API is formulated as an ASD in the drug product. Clinically-relevant dissolution acceptance criteria were established based on a Multiple Level C IVIVC model.
  - High-risk ER product where the *in vivo* absorption is controlled by the RCP. A biowaiver for a Level 3 manufacturing site change was granted based on a Level A IVIVC model.

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