Biorelevant Dissolution Testing for In Vitro In vivo Correlation/Relationship (IVIVC/R) Development: Regulatory Perspective

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IVIVC/R Concept

- IVIVC: "a predictive mathematical model describing the relationship between an in vitro property of a dosage form (e.g., the rate or extent of drug dissolution or release) and a relevant in vivo response (e.g., plasma drug concentration or amount of drug absorbed)"

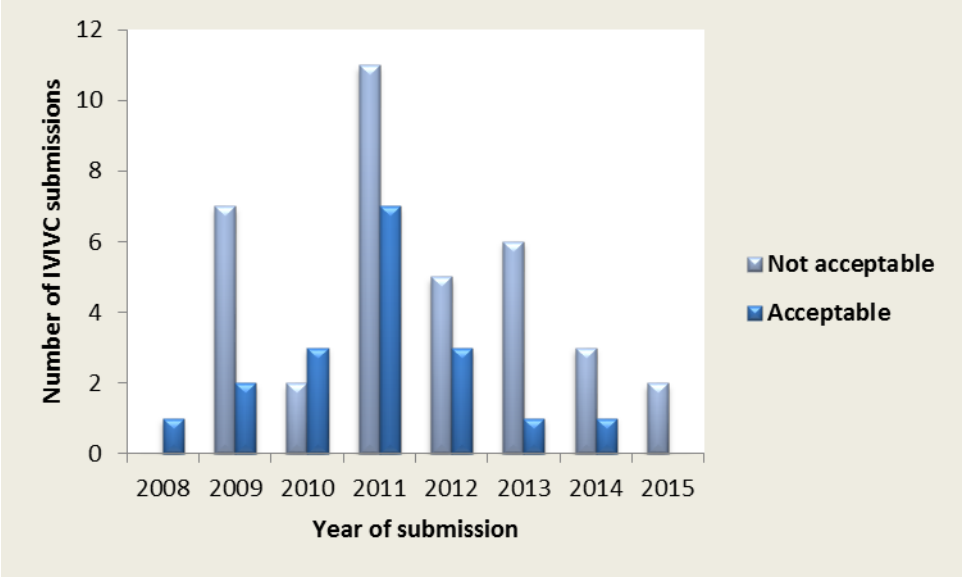
- IVIVR: a semi-quantitative or rank-order relationship between an in vitro property of a dosage form (e.g., the rate or extent of drug dissolution or release) and a relevant in vivo response (e.g., plasma drug concentration or amount of drug absorbed)

- IVIVC/R applications:
  - Biowaiver (IVIVC)
  - Clinically relevant dissolution specification
  - Risk assessment and clinically relevant design space/specifications in QbD

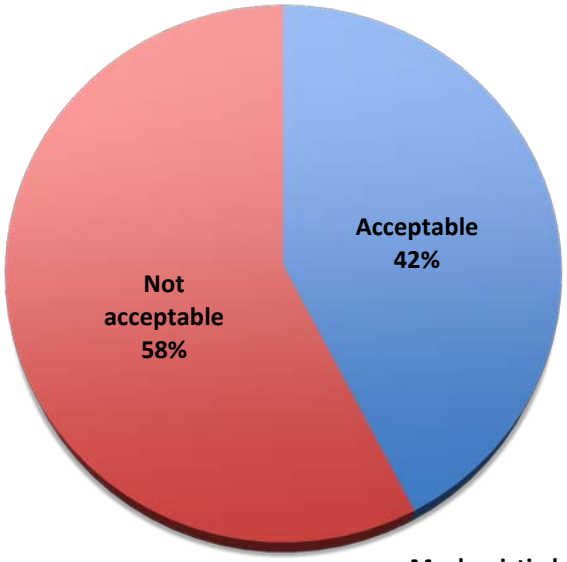
Guidance for Industry Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations (Sept 1997)

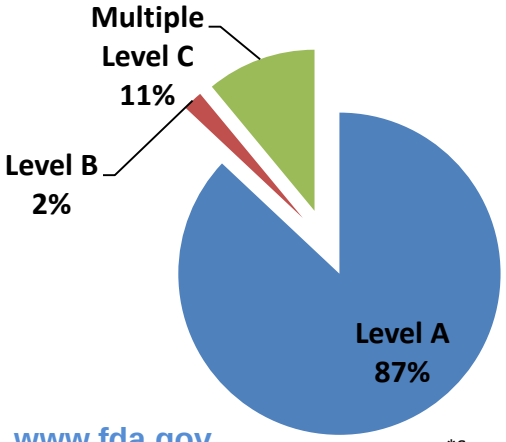
Current Status of IVIVC Studies in the NDA and IND Submissions

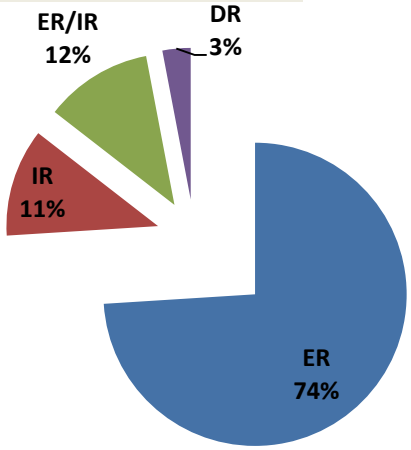
- Submission rate is very low

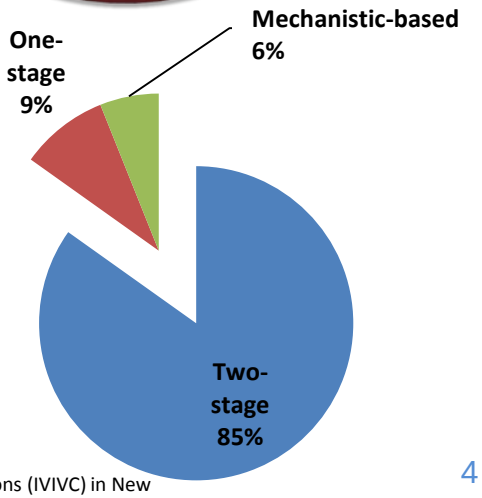


Success rate is low









*Suarez-Sharp S, Li Min, Duan J, Shah H, Seo P. Regulatory Experience with In Vivo In Vitro Correlations (IVIVC) in New Drug Applications. AAPS J. 2016 Nov;18(6):1379-1390.

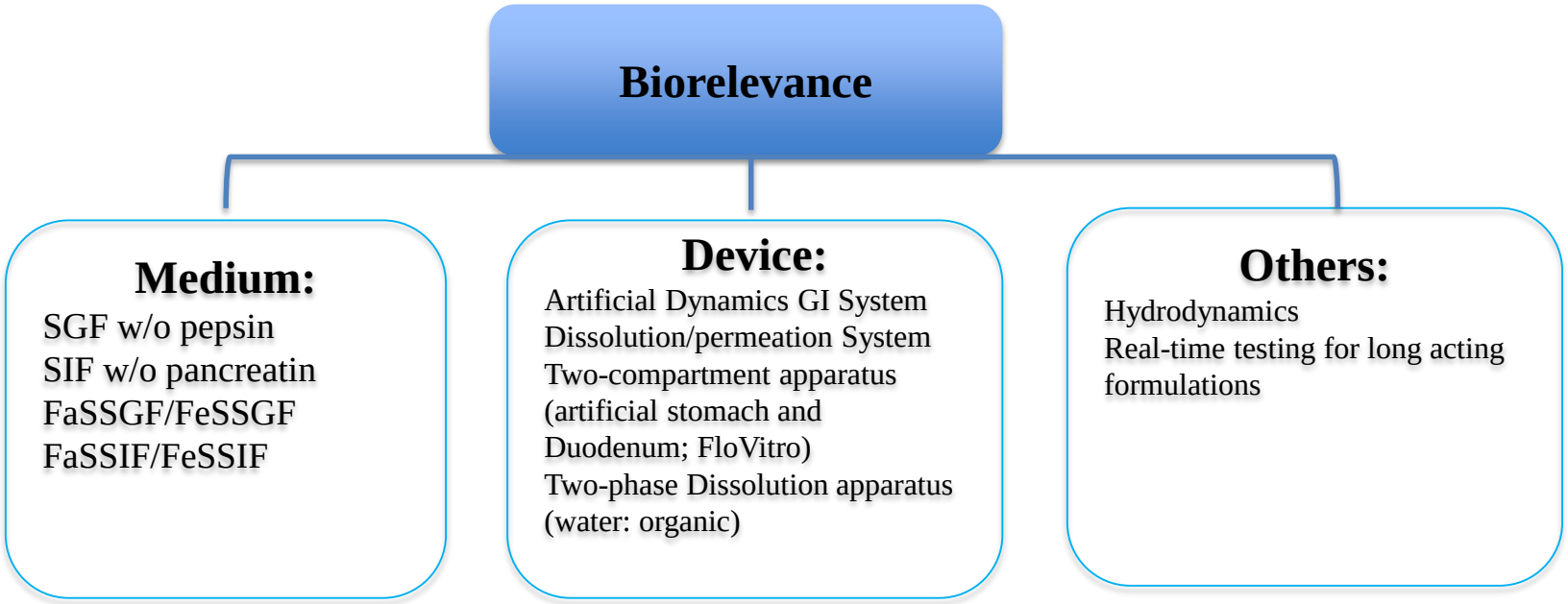
Analyzing Root Causes for Underutilized Status/Low Success Rate of IVIVC/R

- It is very challenging for IVIVC development meeting regulatory requirements (e.g., 3 release rates; cross-over studies; fasted conditions)

- Low success rate of IVIVC studies is discouraging
  - It could be very challenging to correlate in vitro dissolution vs in vivo absorption which is a complex integration of in vivo dissolution, GI transition, degradation, GI absorption, first-pass metabolism etc.)
  - The conventional IVIVC methodologies (e.g., two-stage) take insufficient considerations on drug in vivo dissolution and absorption mechanisms under physiological state
  - The compendial in vitro dissolution test may not be bio-predictive

Biorelevant Dissolution Testing

A biorelevant dissolution test can be defined as an in vitro test that reflects physiological environment in the test conditions with a purpose of correlating in vitro with in vivo drug absorption



Opportunities and Challenges of Biorelevant Dissolution

- **Opportunities: streamline product development and lead to time and cost savings during product development**
  - Pre-clinical development: screen active pharmaceutical ingredient; select/ develop formulation selection; guide quality control method development
  - Clinical development: correlate with in vivo dissolution; support clinical trial design; investigate food effect; explore IVIVC/R; assess the risk and impact of CMC on the in vivo performance; clinically relevant specifications and control strategies; bridging formulations; etc.
  - Lifecycle: support post-approval changes (via IVIVC/R)

- **Challenges:**
  - Complex medium/device/procedures
  - Unrealistic for quality control purposes
  - May not guarantee a correlation with the in vivo

Current Status of Biorelevant Dissolution Testing in the Submissions of IVIVCs

- **5 out of 53 IVIVCs used biorelevant media in the dissolution testing**

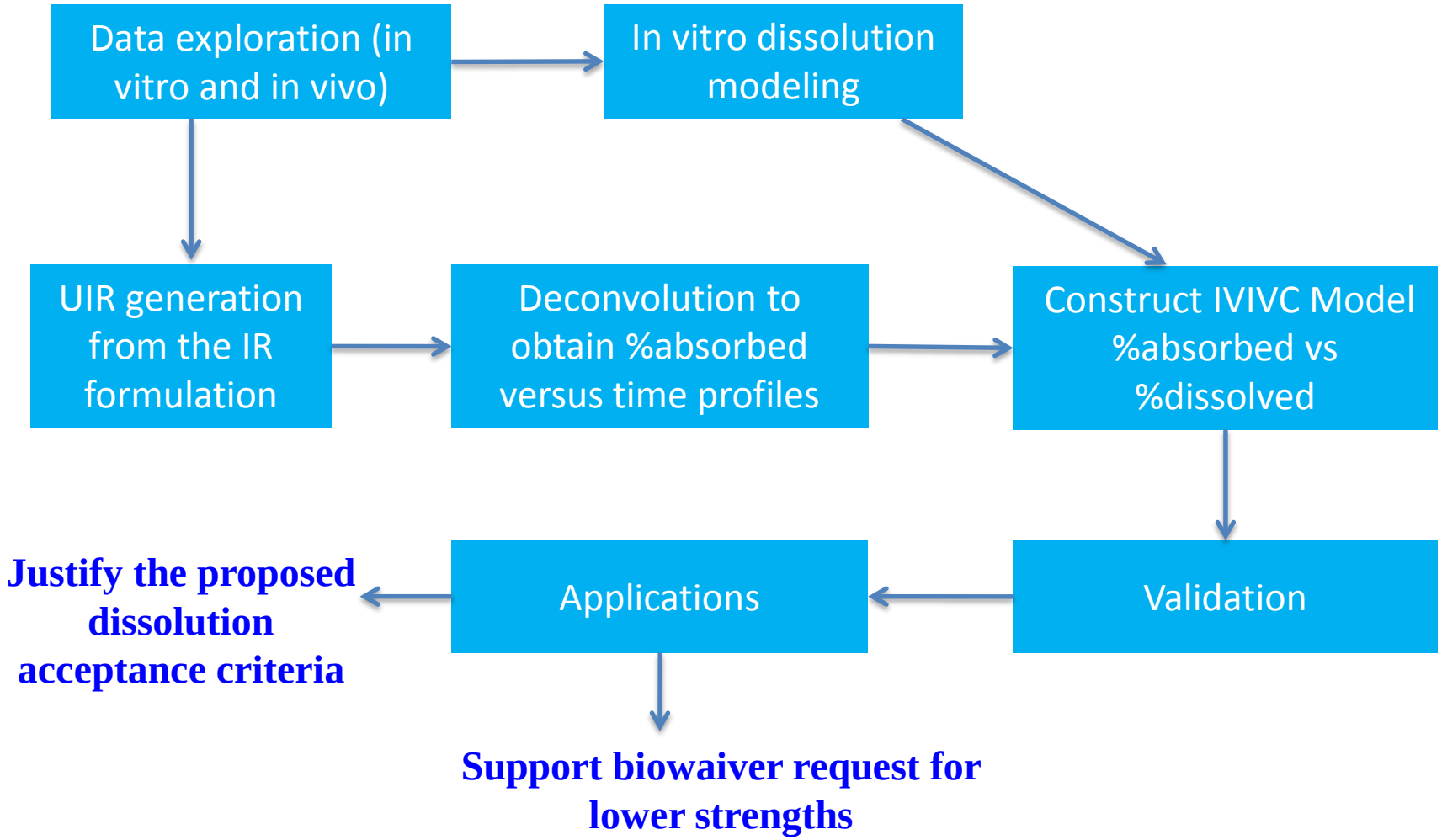
Drug product	Dosage form	Dissolution method	Development strategy	Accetable or not	Deficiencies
A	IR tablet	Apparatus I; rpm 100; pH1.2 mSGF without pepsin; 900 mL	Two-Stage	No	1. In vivo studies were conducted in fed condition while food has significant effect on drug absorption; 2. Excluding 4 subjects' in vivo data from a total 16 subjects without acceptable justifications; 3. inconclusive predictability
B	ER tablet	Apparatus II; rpm 100; pH 6.8 SIF without pancreatin; 900 mL	One-Stage	No	1. Non-mechanistic term was included in the model without reasonable justification; 2. Mean in vivo data instead of individual data was used
C	ER capsule	Apparatus I; rpm 75; SGF for 2 hrs followed by pH7.0 buffer for 4 hrs; 900 mL	Two-Stage	No	1. No difference in the in vitro release rate between formulations; 2. In vitro and in vivo data were not from the same batch
D	ER tablet	Apparatus II; 50 rpm; SGF without pepsin, pH 1.2; 900 mL	Two-Stage	No	No submissions of the in vivo/vitro data, model files and IVIVC study report
E	ER capsule	Apparatus I; rpm 100; pH1.2 SGF without pepsin; 900 mL; 12 hrs	Two-Stage	Yes	N/A

- **Use of biorelevant medium alone may not lead to increased success rate of IVIVCs**
- **The failure of IVIVC models was due to common deficiencies in IVIVC development**

Case Study: Drug Product E

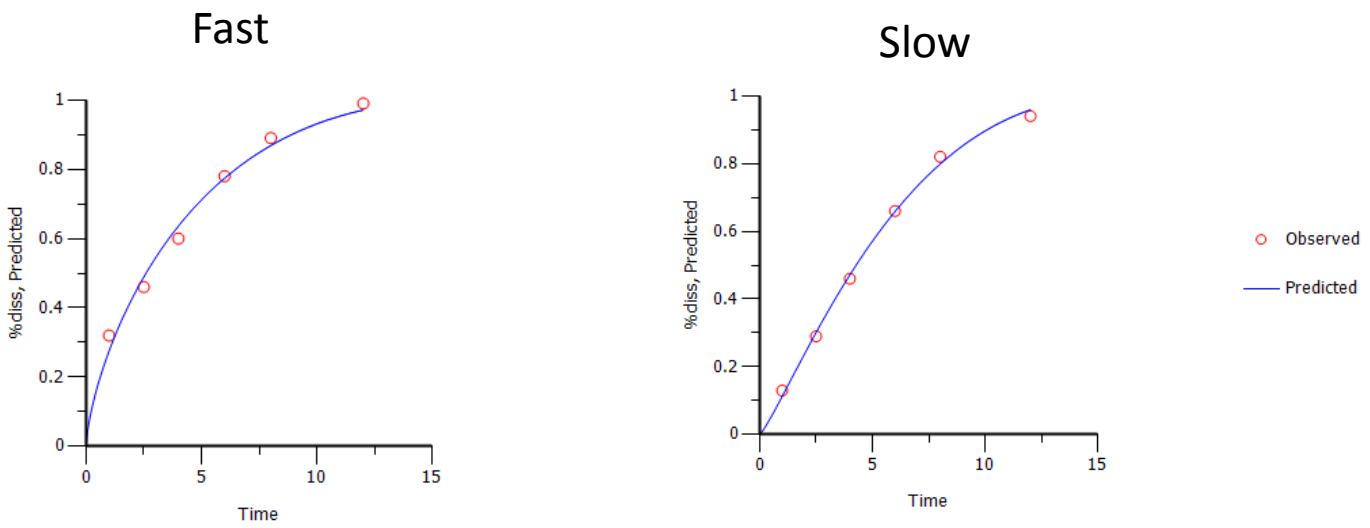
- **Drug product information:**
  - ER capsules: polymer-based delivery system
  - BCS Class I
  - Multiple strengths: compositionally proportional
- **Objectives of the IVIVC study**
  - To request the waiver of the in vivo BE for the lower strengths (the four strengths are dose proportional)
  - To support dissolution specification
- **Formulations for IVIVC development**
  - Different release rates were produced by varied ratio of coated ER beads

Level A Two-Stage IVIVC Flow Chart



In Vitro Dissolution Data and Modeling

- **In vitro dissolution method (same as the QC method):**
  - USP Apparatus I
  - rpm 100
  - 900 mL Simulated Gastric Fluid without pepsin, pH 1.2
  - Drug dissolution was demonstrated condition independent (pH 1.2, 5.0 and 6.8; rpm 50, 100, and 150), indicating one release rate for IVIVC model development may be sufficient per IVIVC Guidance



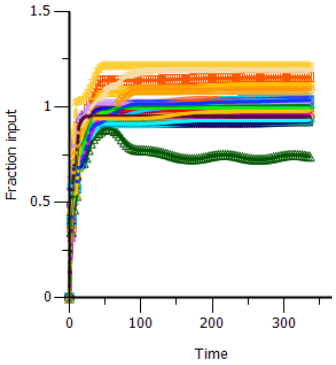
Makoid Banakar model was selected based on AIC, CV%, residual plot, predicted vs. observed plot

In Vivo Data and IVIVC Model Development

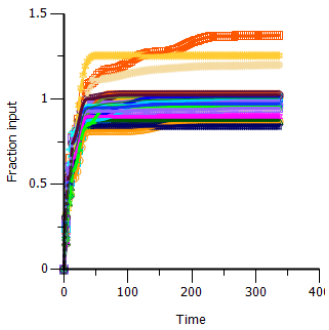
- **In vivo data from a single dose cross-over study including:**
  - Unit impulse response (UIR) generated from IR tablet
  - Slow and fast release formulations used for model construction (deconvolution-based) and internal validation
  - To-be-marketed formulation was used for external validation
- **Individual deconvolution**
- **Linear IVIVC model**: Fabs = AbsScale*Diss(Tscale*Tvivo)

% Absorbed vs Time

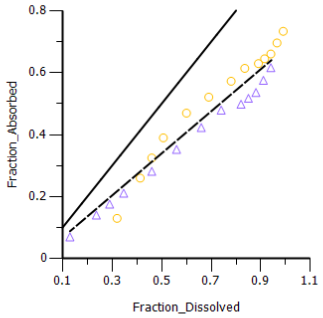
Fast



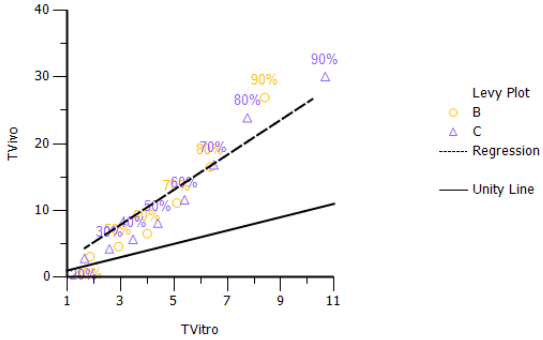
slow



% Absorbed vs % Dissolved



Tvivo vs Tvitro



Model Validation

Formulation	Parameter	% P.E.
Fast release	AUC	0.71
	Cmax	5.27
Slow release	AUC	1.71
	Cmax	8.22
Avg Internal	AUC	1.21
	Cmax	6.75
External	AUC	8.4
	Cmax	0.8

Validation acceptance criteria (per IVIVC guidance):

Internal validation: average absolute percent prediction error (% PE) of 10% or less for Cmax and AUC and the % PE for each formulation should not exceed 15%
External validation:% PE of 10% or less for Cmax and AUC

IVIVC Application 1: Biowaiver

Step 1: Collect dissolution profiles of primary batches at lower strengths

Step 2: In vitro dissolution profile modeling (same model as IVIVC construction

Step 3: Predict plasma drug concentration time profiles for the lower strengths based on convolution using the IVIVC model

Step 4: Evaluate BE using predicted PK parameters (after dose normalization)

Biowaiver of all lower strengths were granted

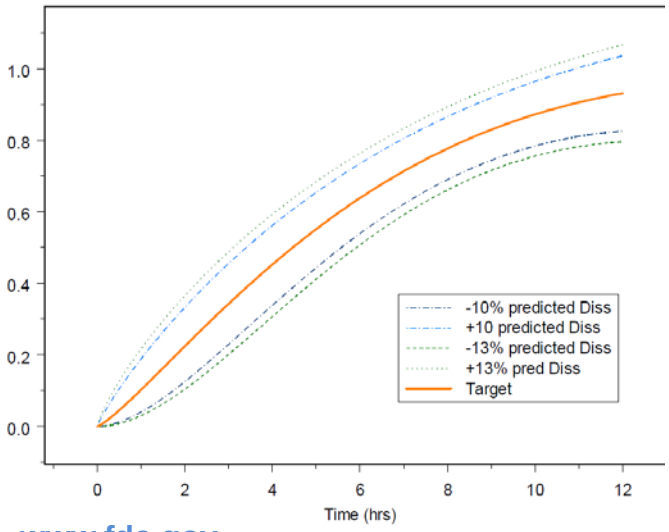
Strength	Parameter	Ratio of predicted to the target
S1	AUClast	1.19
	Cmax	1.05
S2	AUClast	1.18
	Cmax	1.04
S3	AUClast	1.18
	Cmax	1.04

IVIVC Application 2: Dissolution Acceptance Criteria

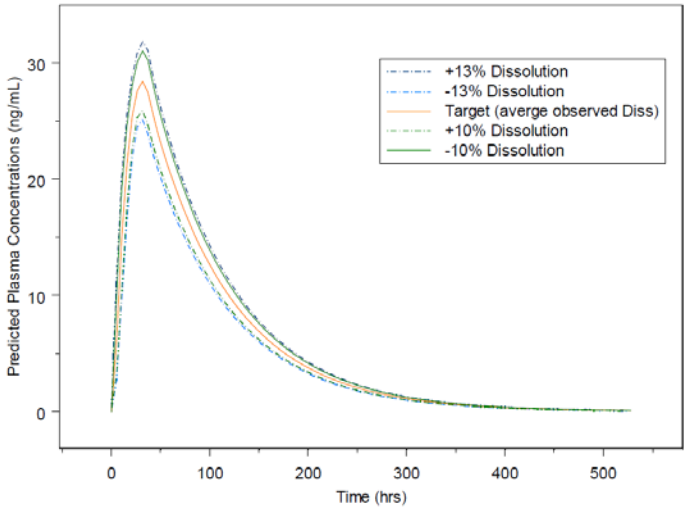
Current practice for ER products:

- at least three time points covering the initial, middle, and terminal phases of the complete dissolution profile
- the selection of acceptance criteria ranges is based on mean target value +10% and NLT 80% for the last specification time-point
- wider specification ranges may be acceptable if justified with IVIVC

In vitro dissolution



Predicted PK profile



Deviation from Target	Ratio of Predicted to Target	
	Cmax	AUC
-10%	0.90	0.96
+10%	1.06	1.17
-13%	0.87	0.93
+13%	1.08	1.17

Summary

- It could be very challenging for IVIVC/R development indicated by low submission/success rate of IVIVCs in the new drug applications
- Biorelevant dissolution method was not often considered in the IVIVC/R development
- The use of biorelevant medium alone may not lead to increased success rate of IVIVCs
- New modeling approaches are needed to guide bio-predictive dissolution method development and support IVIVC establishment (e.g., PBPK absorption modeling and simulation)

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