FDA's Experience on IVIVC-New Drug Products

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Outline

- The Purpose of IVIVC
- FDA's Experience in IVIVC
  - Type of submissions
  - Type of dosage form
  - Type of correlations
  - Type of modeling approaches
- Key Aspects on the Development of an IVIVC
- Examples of Common Causes of IVIVC Failure
- Regulatory Applications of IVIVCs
- Overall considerations on IVIVC and Conclusions

The Purpose of IVIVC

- Reduction of regulatory burden: IVIVC in lieu of required *in vivo* studies, leading to:
  - Time/Cost savings during product development
    - Less testing in humans
- Permits setting wider than standard (±10%) *in vitro* release acceptance criteria

Integration of IVIVC into QbD

IVIVC can provide:

- Supports approval of a design space
  - Prediction/determination of the clinical impact of "movements" within the design space without the need for additional *in vivo* studies
- Enhanced significance of *in vitro* testing
  - Permits the setting of acceptance criteria based on targeted clinically relevant plasma concentrations
- Wider drug product acceptance criteria resulting in regulatory flexibility

Why is the Use of IVIVC Relevant During QbD Implementation?

- IVIVC enhances drug product understanding during development because without it, it would be impractical to define the *in vivo* impact of each component and manufacturing step through *in vivo* studies

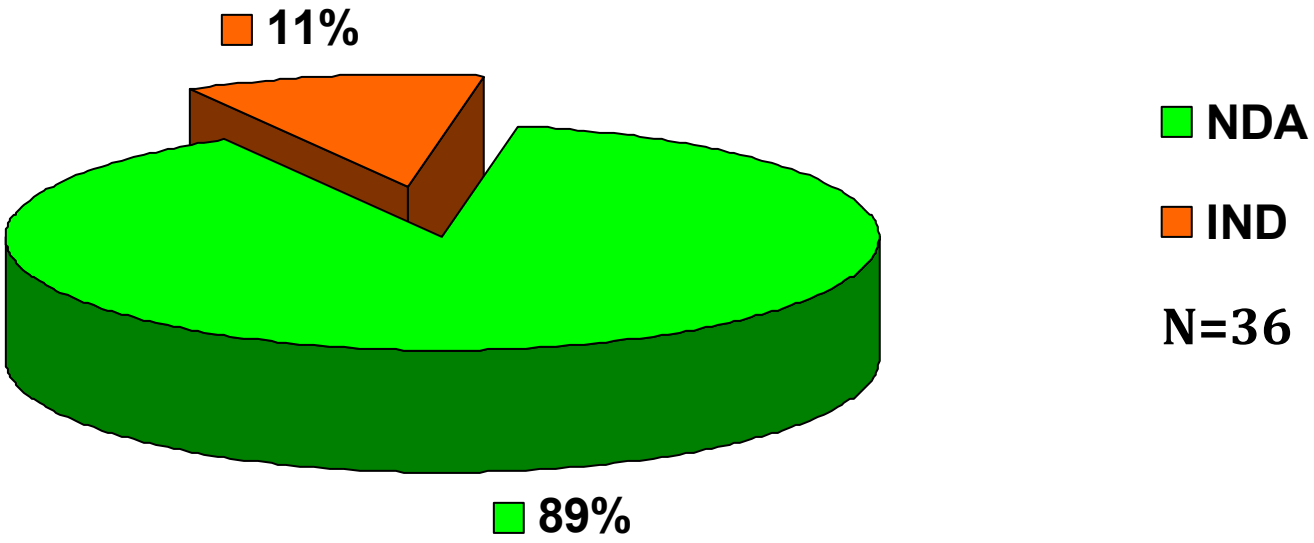
- Dissolution testing and plasma drug concentrations are identified as the most successful surrogate for safety and efficacy

The USFDA IVIVC Guidance*

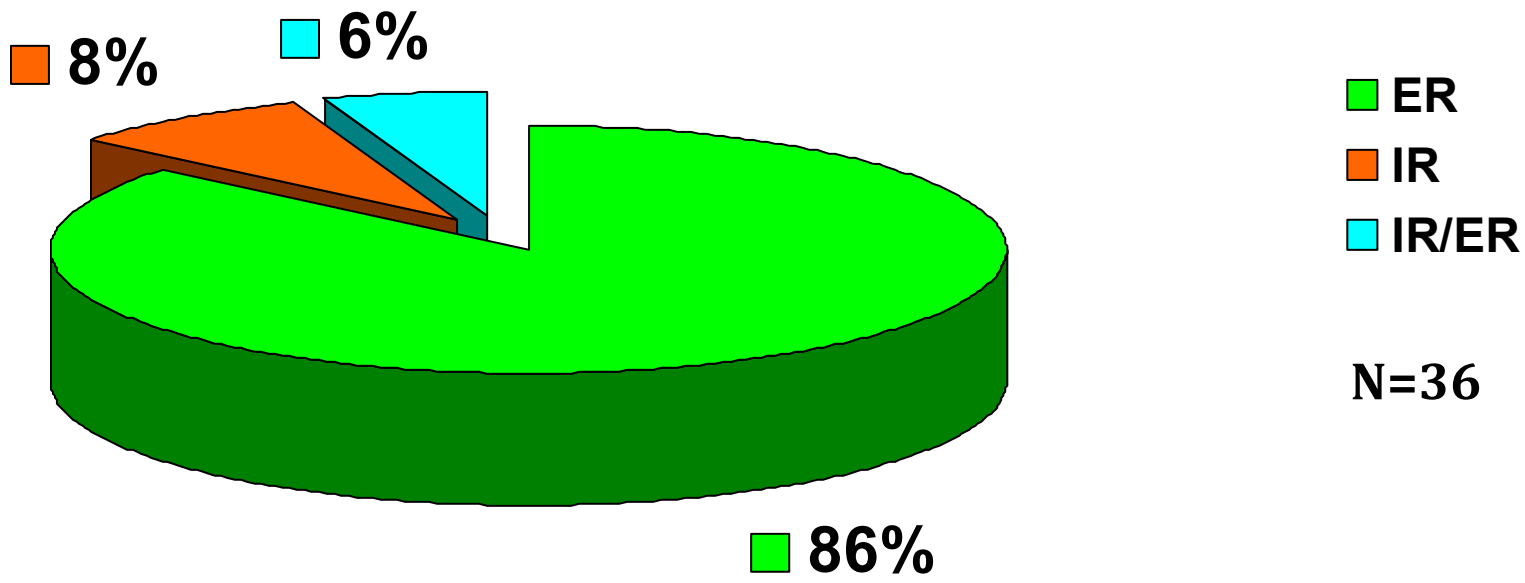
- Describes the characteristics of the raw data needed for the construction of an IVIVC (e.g., study design)
- Gives recommendations on model development
- Describes the evaluation of model predictability
- Describes which manufacturing changes can be filed with an IVIVC

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

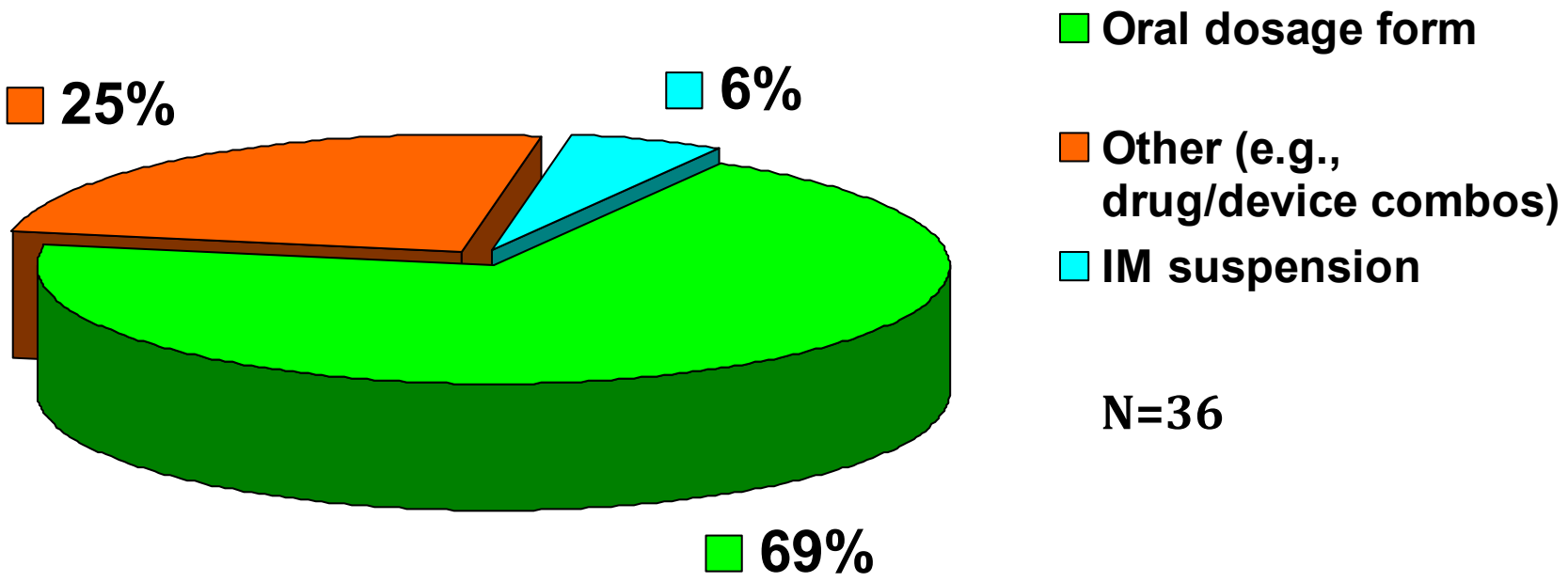
Type of Regulatory Submissions Containing IVIVC Models (2009- 2012)



Type of Formulations Containing IVIVC Models (2009- 2012)

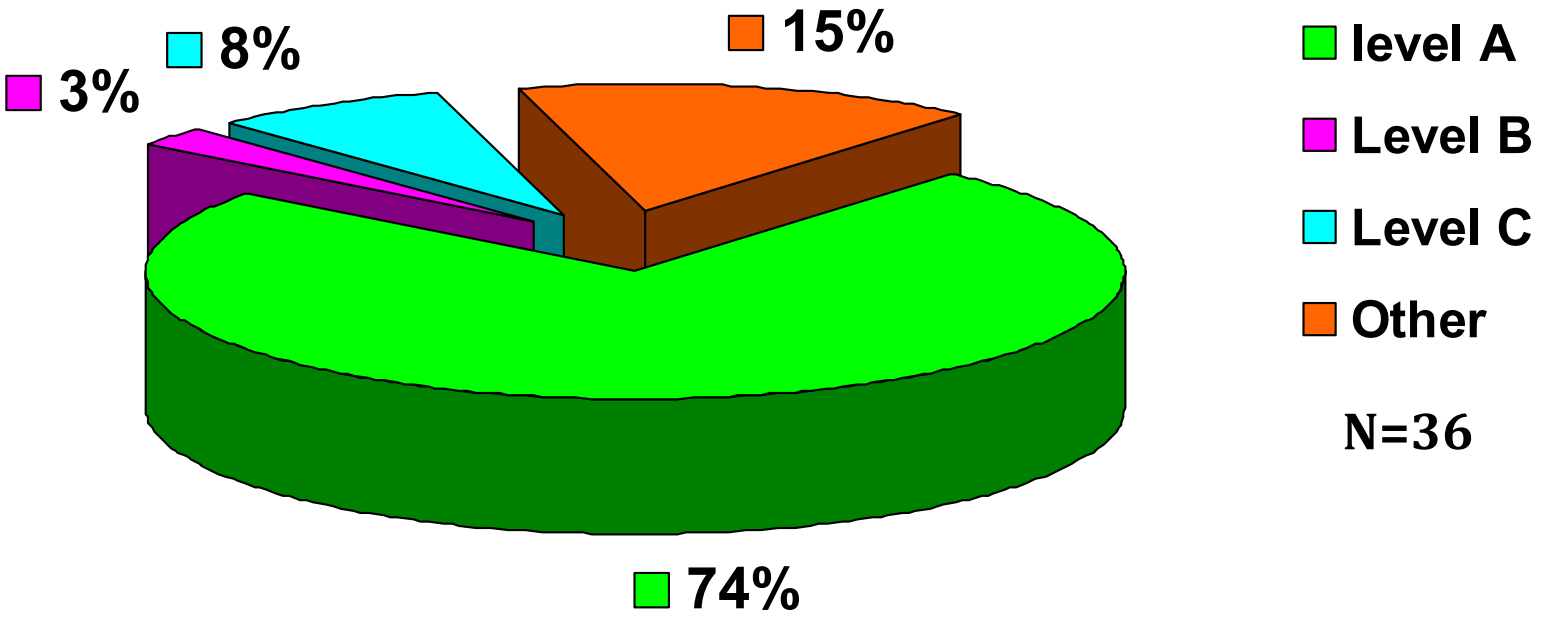


Type of Dosage Form Containing IVIVC Model (2009- 2012)

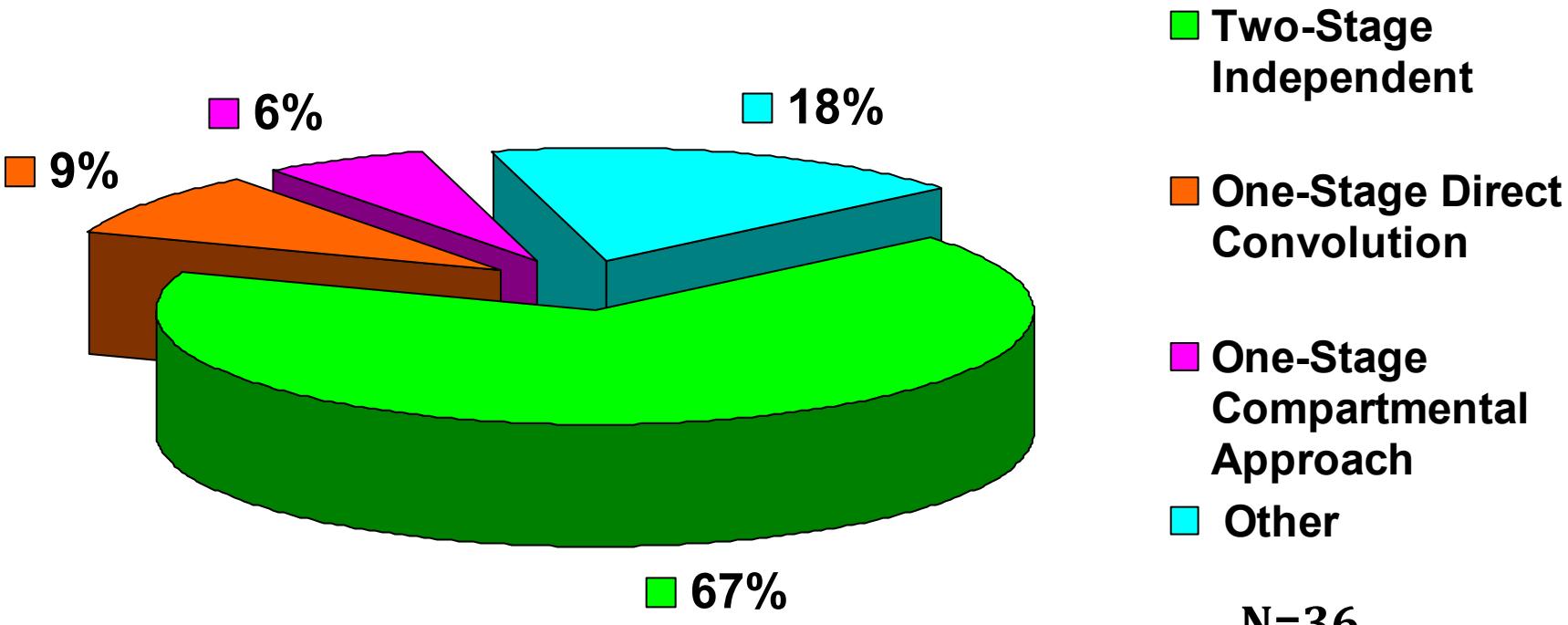


Principles described in the IVIVC guidance are applicable to other dosage forms

IVIVC Categories: NDA/IND Submitted (2009- 2012)



Types of Modeling Approaches Included in Regulatory Submissions (2009- 2012)



Types of Dissolution Media Used in IVIVC (2009- 2012)

- pH 1.2 Buffer, Simulated Gastric TS (without pepsin)
- 0.01N HCL with 0.05% SLS and 0.7% NaCl
- 0.04 M sodium phosphate buffer pH 6.8 containing 2% SLS
- Water (drug product has condition independent dissolution)
- 0.05 M Sodium Citrate and 0.09 N NaOH, pH 4.8. At 5 hours, pH is adjusted to 6.6 with addition of 100 mL media: 0.05M sodium phosphate and 0.46N NaOH
- Ethanol/water 90/10 v/v (%)

Successful IVIVC models are also possible when simple dissolution methods (USP listed) are used

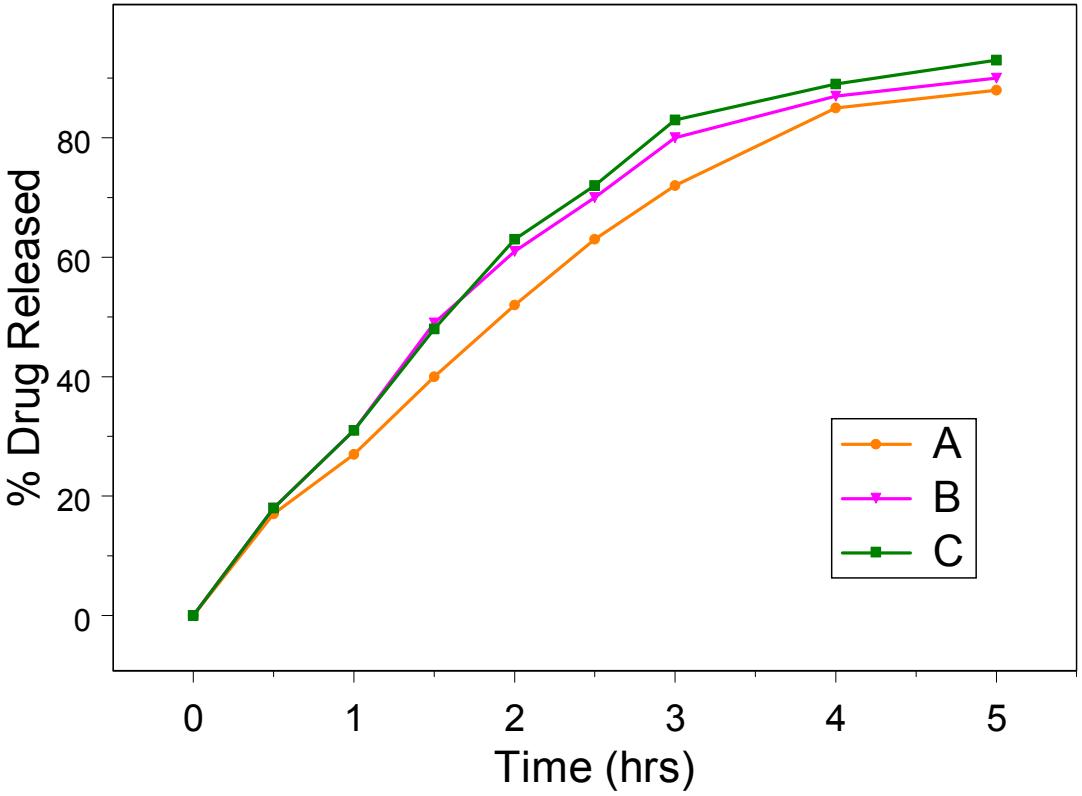
What Are the Key Aspects of the Development of an IVIVC?

Key Aspects of an IVIVC

- Robustness of the correlation as proven by:
  - Meeting the criteria for internal and external predictability
- Meeting the criteria for *in vitro*, *in vivo* experimentation
  - Number and in vitro release rate characteristics of formulations used in the construction of the model
  - Rank order correlation
  - Fasting conditions
- The use of individual concentrations in the deconvolution process (model independent approach)

Examples of Common IVIVC Issues

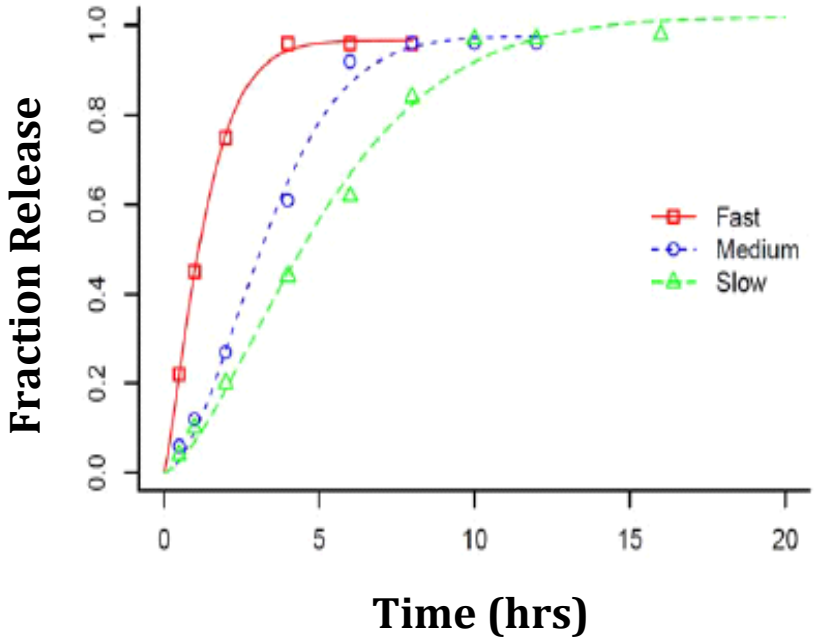
No Difference in the in Vitro Release Rate Characteristics



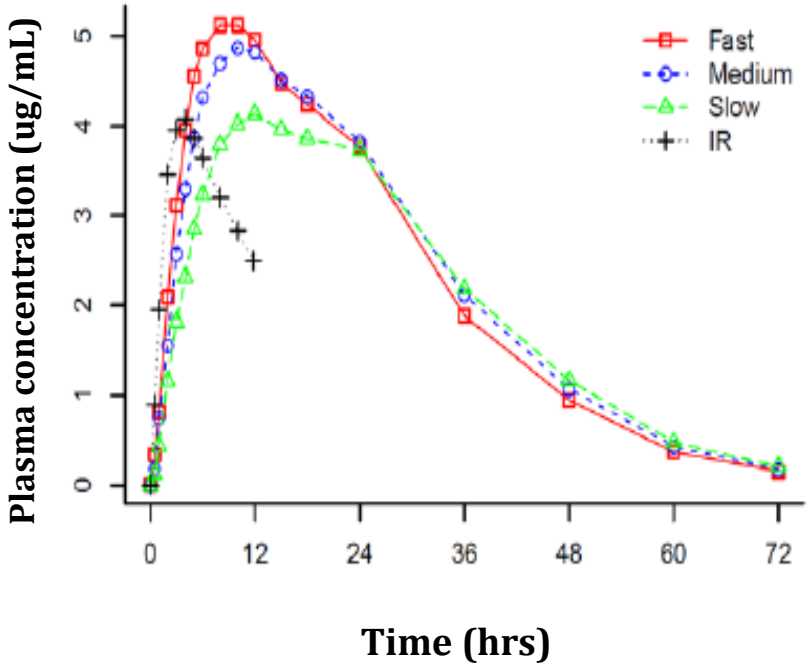
Formulations		*f2*
A	**B**	52
A	**C**	55
B	**C**	84

Formulations should have different release rate characteristics

Lack of Rank Order Correlation



Medium and fast were BE

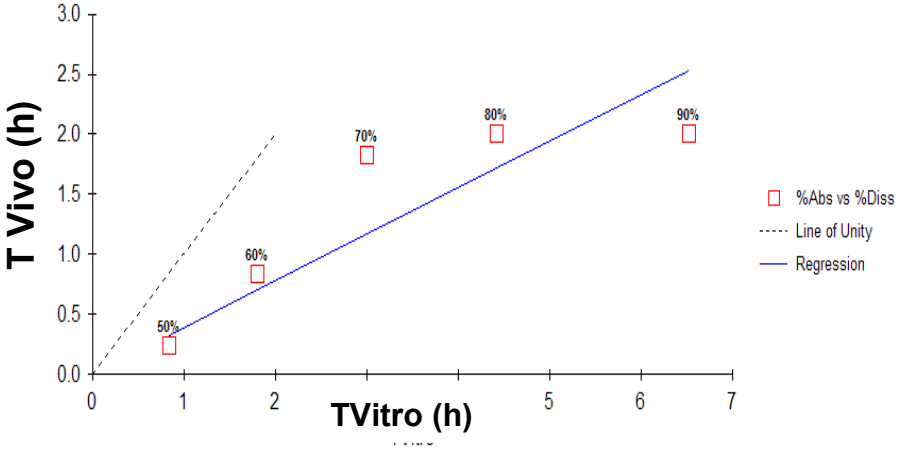


Formulations		*f2*
Fast	medium	30
Fast	slow	25
medium	slow	47

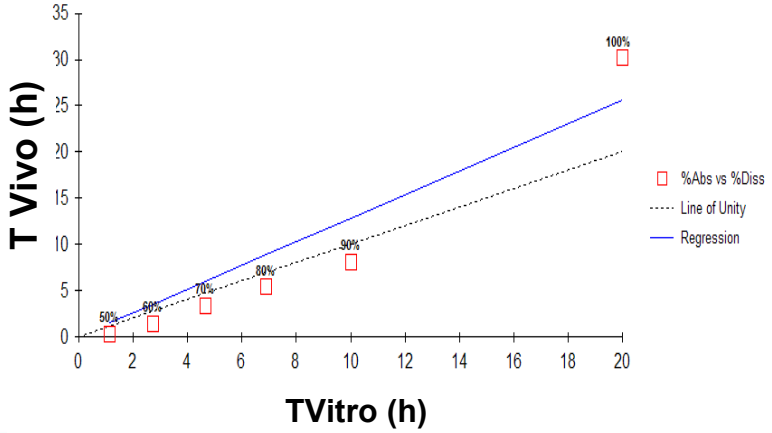
Data should show a rank order correlation

Formulations Do Not Have the Same Scaling Factor

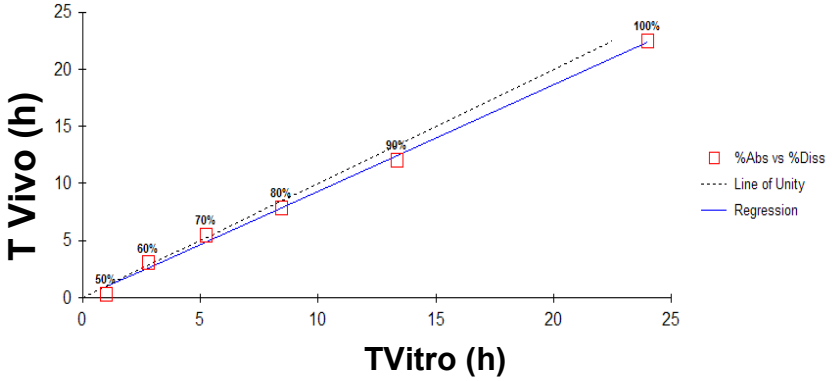
Form A, sl=0.39



Form B , sl=1.3



Form C, sl=0.93



All formulations should use the same Scaling factor

Other Causes for IVIVC Failure

- IVIVC model did not meet validation criteria
- Use of mean-based deconvolution instead of individual-based deconvolution
- Model developed under fed conditions for a drug that exhibits substantial food effect
  - Fed conditions should only be used when safety
- Model is over-parameterized and not fully mechanistic

What Are the Regulatory Applications of an IVIVC?

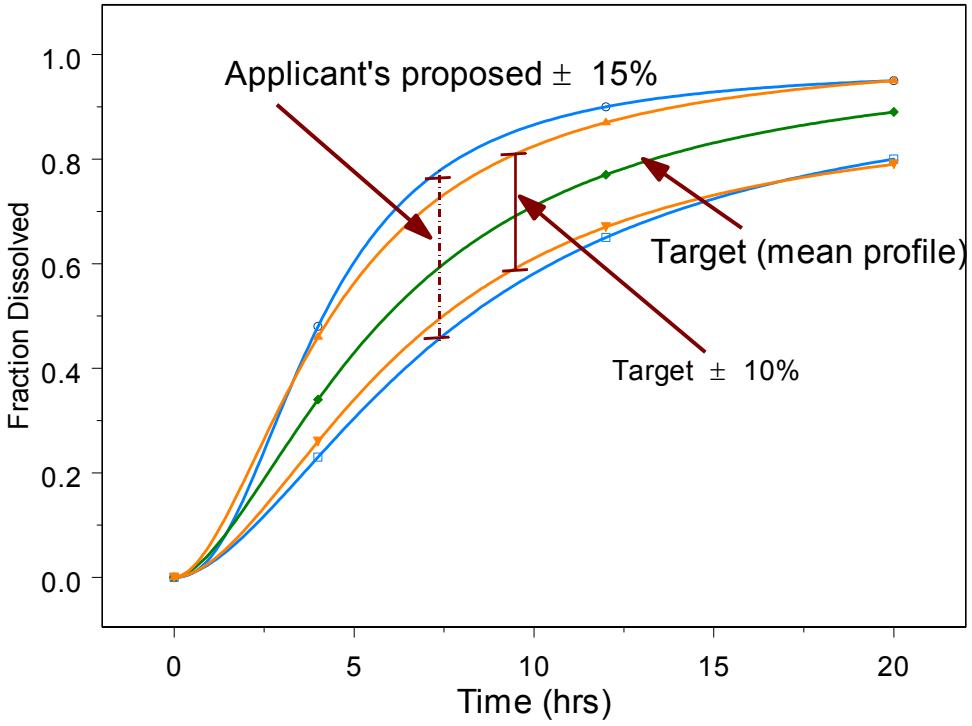
Regulatory Applications*

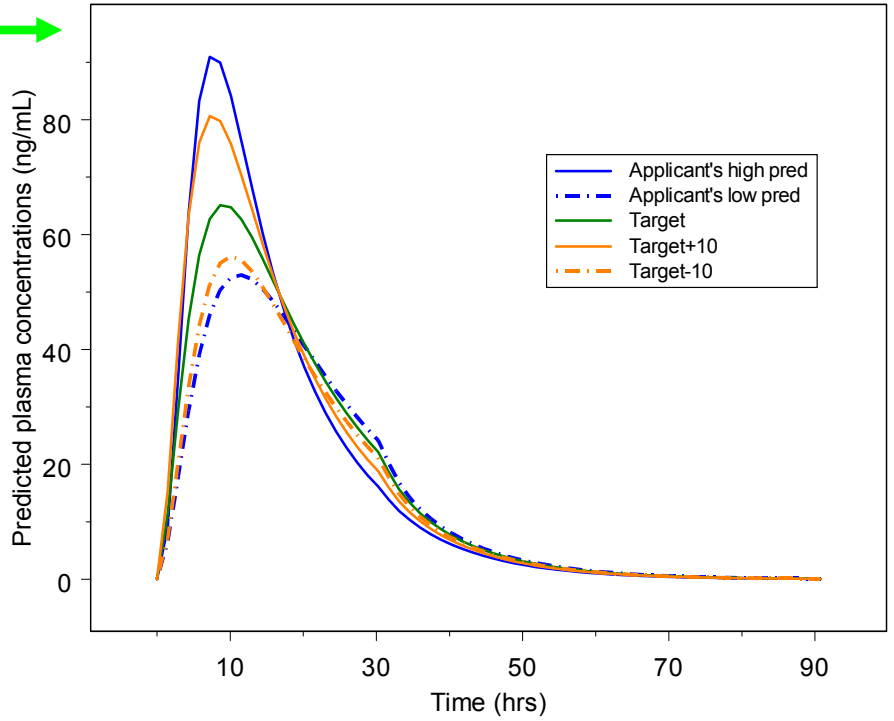
- Waiver of required *in vivo* BA/BE studies:
  - Pre-approval manufacturing changes
  - Post-approval changes
  - Approval of lower strengths
- Wider than standard (±10%) *in vitro* release acceptance criteria
  - The difference in predicted means of Cmax and AUC from upper and lower release limits are no more than 20%
- Evidence for biorelevant and discriminating dissolution method
  - Setting of clinically relevant drug product acceptance criteria
  - Wider drug product acceptance criteria resulting in regulatory flexibility

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

Wider than Standard (±10%) in vitro Release Limits

Convolution





Wider than Standard (±10%) in vitro Release Acceptance Criteria, cont.

	Cmax (ng/mL)	**AUC (ng*hr/mL)**
	% difference (high vs. low)	**% difference (high vs. low)**
Target - 10%	17 %	15%
Target +10%		
Applicant's low	19%	17%
Applicant's high		

- Dissolution acceptance criteria were set based on the mean dissolution values for the biobatch and stability batches ± 15% variation

Support of Post-Approval Changes Requiring BE studies

Batch #	Site	Mean Predicted Cmax (ng/mL)	Mean predicted AUC (ng*h/mL)	% Difference (Current vs. New)	
				Cmax	AUC
A11	New	275	4359	1	0.2
A12	New	277	4328	2	-1
A13	New	270	4383	-3	-3
B00	Current	274	4356	---	---

Criteria

- Predicted profiles from pre- and post change are within 20% range of AUC and Cmax
  - Supersedes f2 similarity testing

Common Mistake in the Application of the IVIVC

- Prediction of Cmax and AUC defined by the upper and lower dissolution acceptance criteria boundaries
  - If predicted values meet the acceptance criteria (less than 20% difference), then the CMC change is acceptable
- Instead, the PK predicted profiles ***from pre- and post change*** should be within 20% range of AUC and Cmax

Clinically Relevant Drug Product Specifications: A possibility even without IVIVC

Drug Product Z

- BCS 2 Drug Substance
- Immediate Release Tablet
- Single strength
- Proposed Level C and A IVIVCs

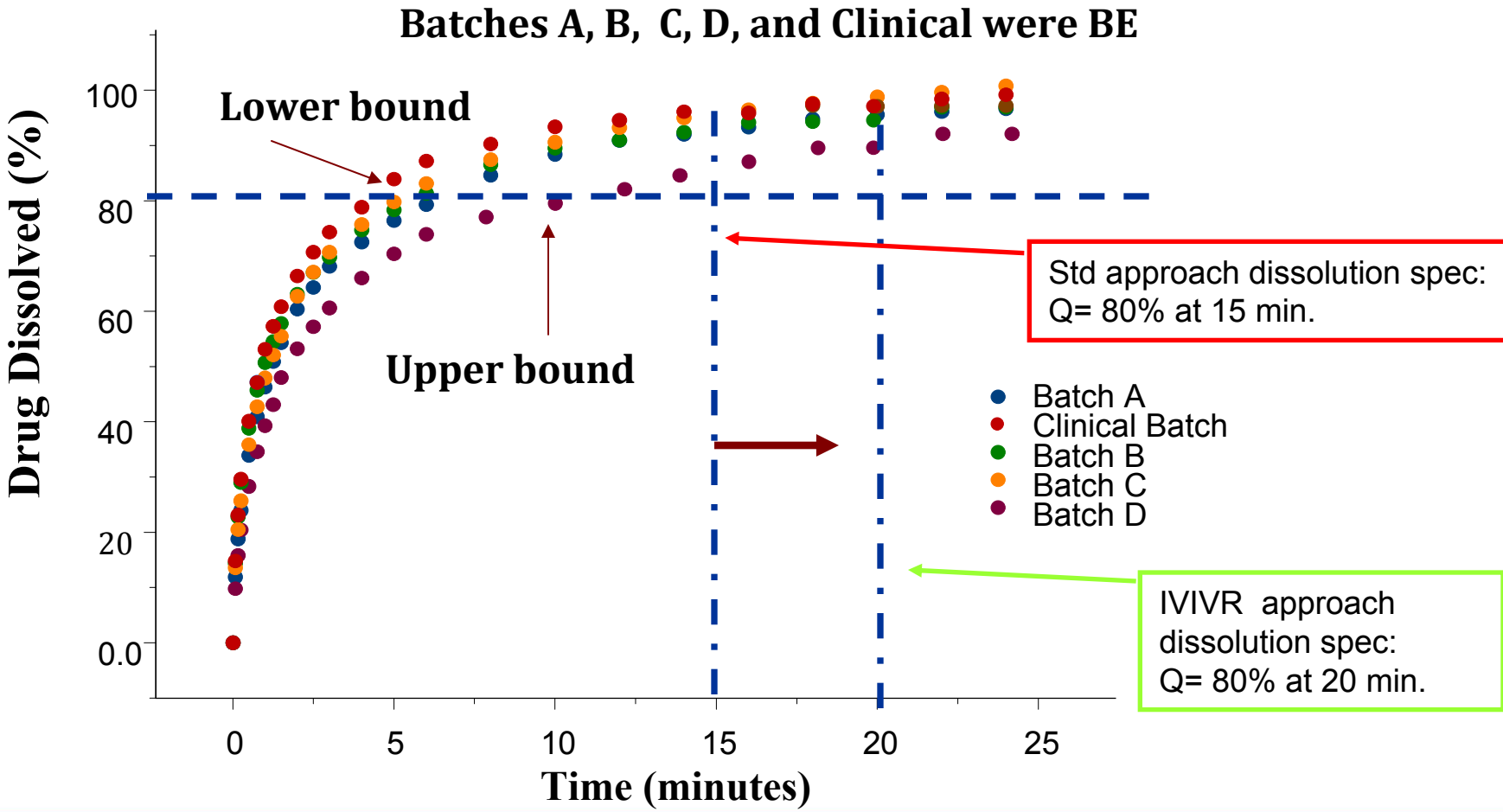
IVIVC Development/Evaluation

- *Dedicated PK study to determine the effect of particle size (PS) on dissolution and BA*
- Release rate was altered by changing the particle size of the drug substance
- Linear IVIVC model constructed was found not acceptable by the FDA

Making Sense of the Data

- Setting clinical relevant specifications can still be performed
  - The dedicated PK study provided enough information to determine which dissolution rates result in similar in vivo performance
    - Clinical relevancy is established for those changes whose dissolution profiles fall within the extremes of dissolution profiles for batches that were BE

Clinically Relevant PS Ranges



Overall Considerations for IVIVCs

- IVIVC can be possible for some IR formulations
- IVIVC can be possible for other routes of administration other than oral dosage forms
- FDA does not specify the kind of modeling approaches in the construction of IVIVCs
- Successful IVIVC models can be possible when simple dissolution methods are used

Overall Considerations for IVIVCs, cont.

- For an IVIVC with major impact on the approvability of the NDA submission, firms should submit the IVIVC model during IND stage
  - Changes implemented to the Phase 3 formulation requiring BE study

- IVIVC development should be planned a priori instead of being a *post-hoc* event
  - Ensures the use of robust/appropriate analysis of the data
  - Increases the outcome of a successful correlation

Overall Considerations for IVIVCs, cont.

- Once approved, the IVIVC should be used to support pre- and post approval manufacturing changes:
  - IVIVC supersedes f2 testing
  - Pre- and post-change dissolution data should be used to predict Cmax and AUC to determine acceptability

- Clinical relevancy of the specifications for material attributes/process parameters can still be determined in the absence of an IVIVC model
  - Clinical relevancy is assured for those changes whose dissolution profiles fall within the extremes of dissolution profiles for batches that were BE

Conclusions

- FDA encourages the inclusion of IVIVC models in regulatory submissions. IVIVC models provide:
  - A direct link to in *vivo* performance
    - Establishment of clinically relevant drug product specifications
  - Stronger link between *in vivo* and *in vitro* performance as compared to using F_2 testing
    - Regulatory flexibility within the QbD frame-work