# The Utility of in silico PBPK Absorption Modeling and Simulation as a Tool to Increase the Success of Developing Bio-Predictive Dissolution Methods: Success and Limitations (Case Studies from Regulatory Perspective)

May 16, 2017

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# Disclaimer

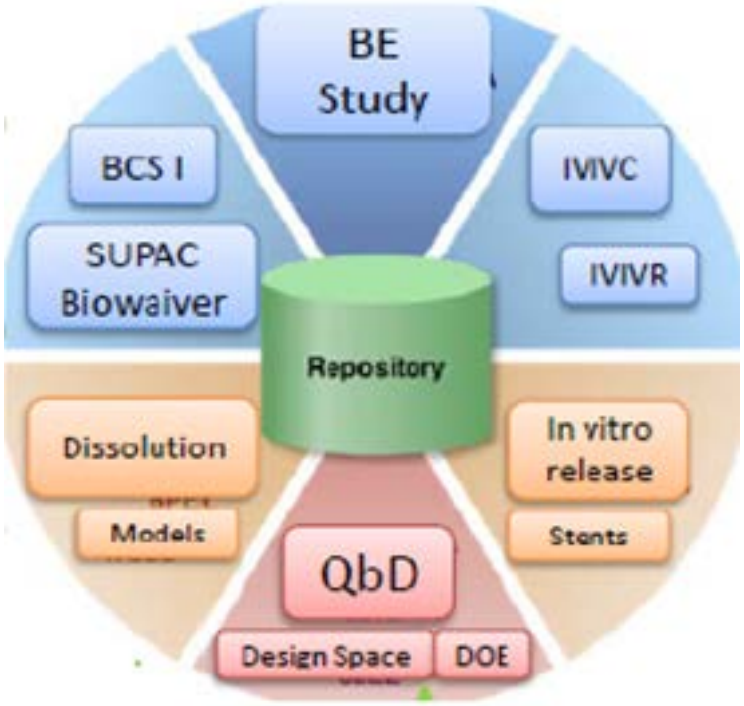
This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

# Outline

- A Retrospective Analysis of PBPK Modeling and Simulation in Biopharmaceutics Assessment
- Impact of PBPK Modeling and Simulation on linking product quality to clinical outcome
- Case Studies: The Use of in PBPK Absorption Modeling and Simulation as an Aid in Developing a Bio-predictive Dissolution Method
- Challenges and Opportunities
- Overall summary

# Review Tasks at Division of Biopharmaceutics

- Clinically Relevant Specifications




- Patient-centric Product Quality

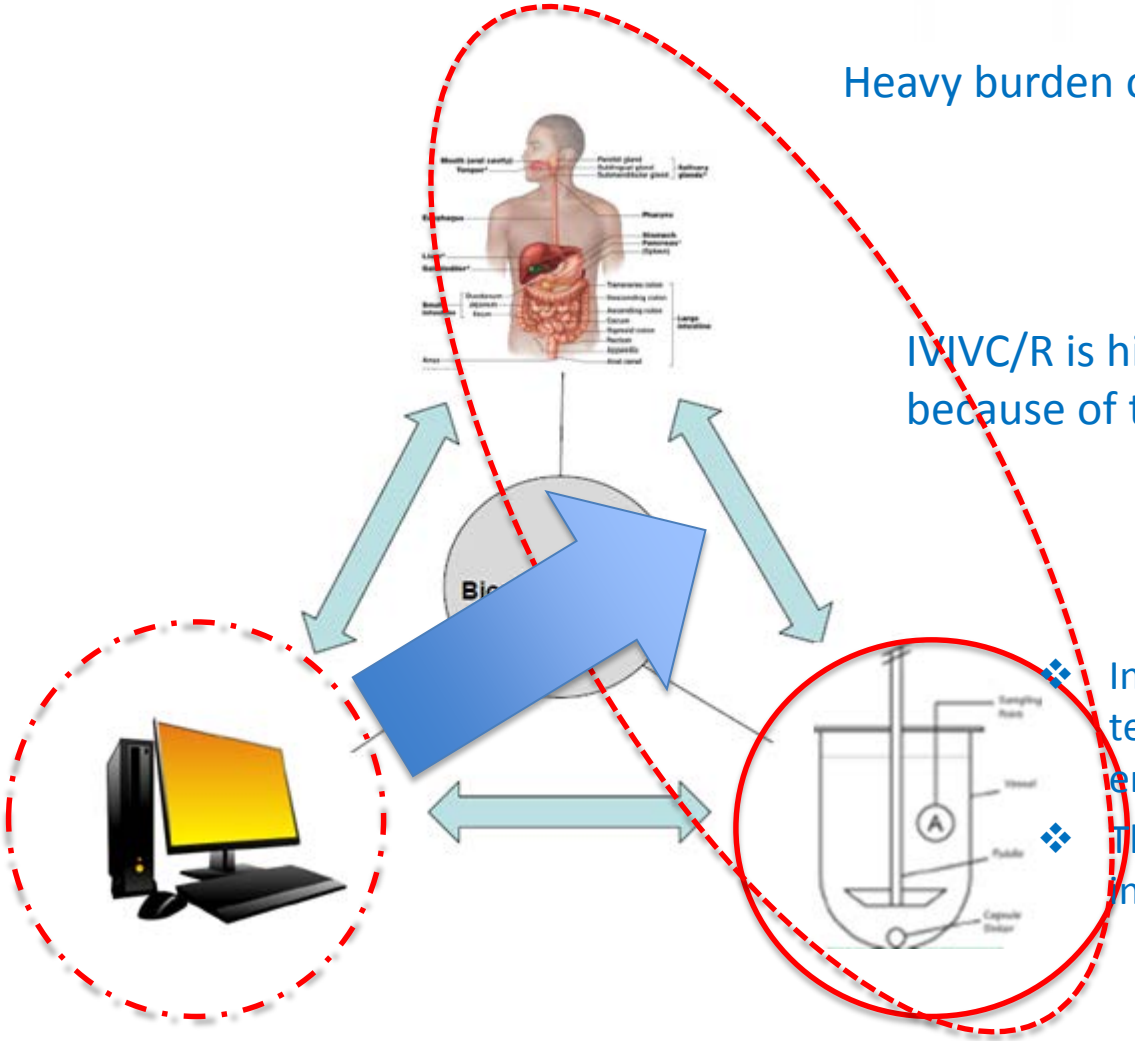
Courtesy of John Duan

# Submissions with mechanistic absorption modeling for Biopharmaceutics review

| | Potential Applications | Current Status |
|---|---|---|
| Dissolution Method and Acceptance Criteria | *Justify/support bio-predictive dissolution method* | • *Use the verified PBPK/absorption model combined with bioequivalence clinical study and dissolution profiles generated to show that the proposed dissolution method can reject non-BE (bioequivalence) batch* |
| | *Set clinically relevant dissolution acceptance criteria* | • *Allow dissolution acceptance criteria to go beyond target ±10% range*<br>• *Additional evidence (data) needed to validate model and confirm predictive performance* |
| Set clinically relevant drug product specifications for CMAs and CPPs | *CMAs (particle size, polymorphic form)* | • *Predict particle size distribution (PSD) limits which would result in similar in vivo performance to the target (clinical batch)*<br>• *Predict the effect of polymorphic form on in vivo performance of drug product* |
| | *CPPs (milling method, pressure force/hardness)* | • *Predict the effect of milling method on the bioequivalence of drug product (e.g. pre- and post-change of milling method)*<br>• *Used to justify specification range of compression force based on the predicted in vivo performance* |
| Risk assessment | *Evaluation of the risk* | • *Quantitative assessment* |

modified from presentation: "Application of Mechanistic Oral Absorption Model in Biopharmaceutics Review." by John Duan. http://www.fda.gov/Drugs/NewsEvents/ucm488178.htm . Courtesy of Fang Wu, Heta Shah and John Duan.

# *Current Status of Biopharmaceutics Assessment Towards Clinical relevance*



Heavy burden on the clinical trials

IVIVC/R is highly underutilized because of the low success rate

- In vitro dissolution/release testing is one of the primary endpoints of quality
- The clinical relevance of the in vitro method is unclear

Courtesy of Min Li

# *Questions of interest*

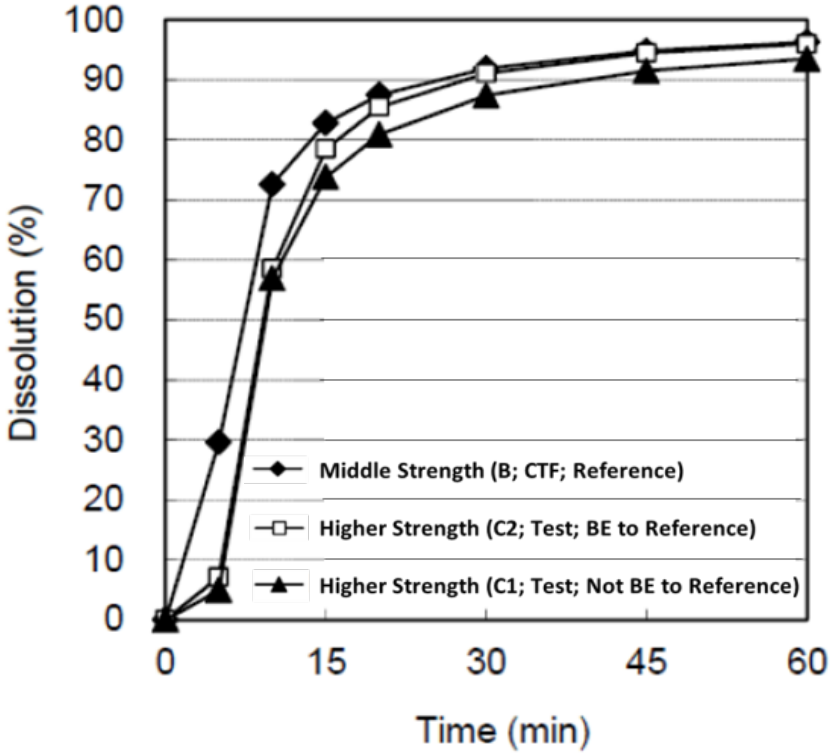
**Bio-relevant Dissolution = IVIVC/R ?**

Can PBPK Absorption modeling make this correlation easier ?

# Case Study 1

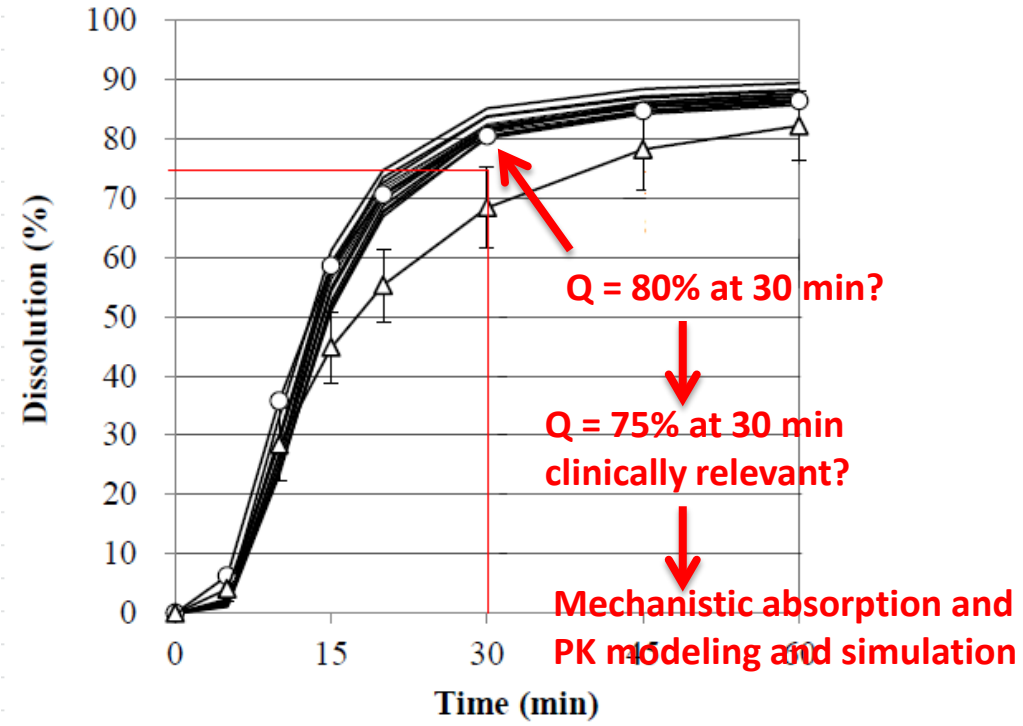
## PBPK Absorption Modeling and Simulation for Drug Product B

- Immediate release tablet
- BCS class 4 drug substance
  - (low solubility and low permeability)
- Three Strengths
  - A (lower), B (middle), and C (higher)
  - A and B studied in phase 3 clinical trials
  - A pivotal BE study comparing
    - Higher strength C (C1 and C2) to middle strength B
- Dissolution method: Atypical behavior and under-discriminating
  - For changes in drug substance and product attributes
  - Did not reject batch that was not BE to the phase 3 clinical batch
- Development of a new dissolution method



# Setting of Clinically Relevant Dissolution Acceptance Criteria

- Dissolution acceptance criteria based on new dissolution method:
  - Commercial and registration stability batches
  - BE and Non-BE batches
- Proposed dissolution acceptance criteria
  - Q = 75% at 30 min

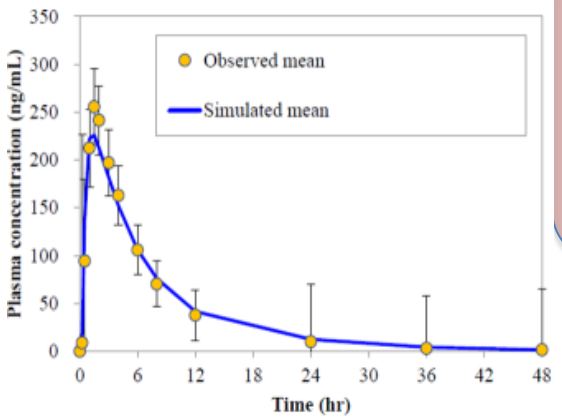



O Higher strength C2 (BE Batch)
Δ Higher strength C1 (Non-BE Batch)
Other Profiles (Commercial batches of higher strength C2)

# Mechanistic Modeling and Simulation Strategy for Drug Product B

**MODEL BUILDING**

- I.V. PK Data
- Oral PK Data of Strength B (CTF)
- Physicochemical properties, absorption parameters, and PK parameters
- Dissolution Profiles (Discriminating dissolution method)




Strength B

**MODEL VALIDATION**

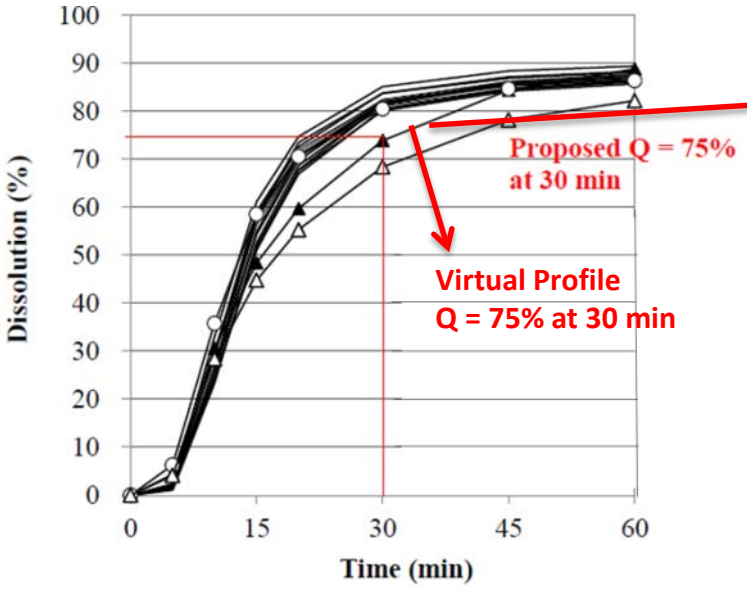
- Internal Validation (Strength B)
- External Validation (Strength C – C1 and C2)
- Repeated Virtual BE Trials (C1 is not BE to B; C2 is BE to B)
- ***Accurate predictions for all of the above***

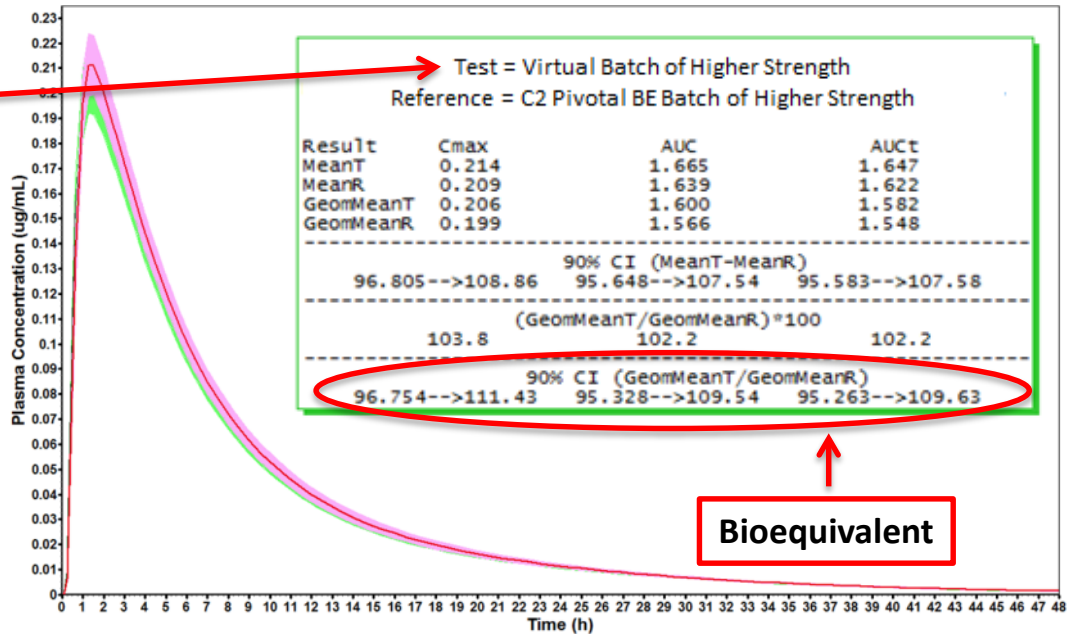
**Use of Virtual Dissolution Profiles**

**MODEL APPLICATION**

- Support bio-predictive nature of the new in vitro dissolution method
- Set dissolution acceptance criteria

# Dissolution Acceptance Criteria for Higher Strength (C)

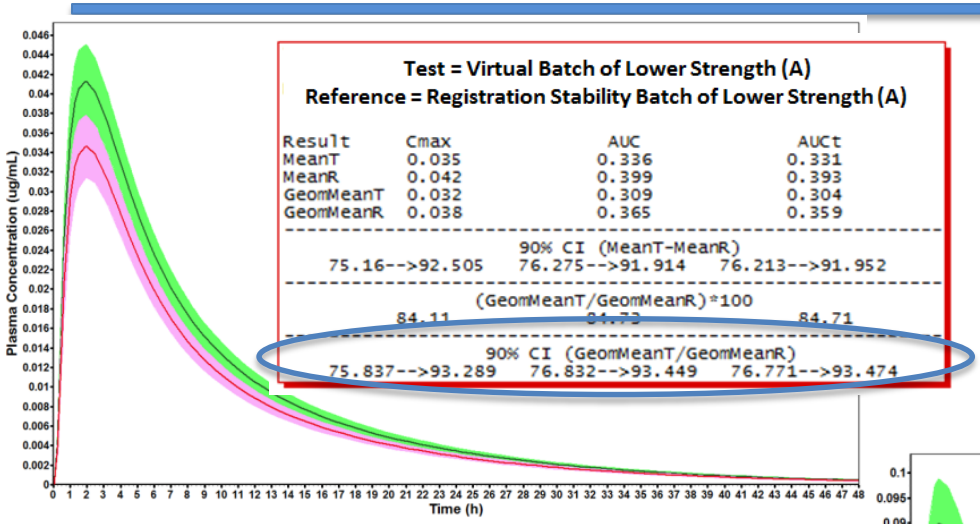



**Q = 75% at 30 min**
**Clinically relevant for higher strength**

**Q = 75% at 30 min**
**Clinically relevant for other strengths (A and B) ?**

# Dissolution Acceptance Criteria for Lower (A) and Middle (B) Strengths




Test = Virtual Batch of Lower Strength (A)
Reference = Registration Stability Batch of Lower Strength (A)

| Result | Cmax | AUC | AUCt |
|---|---|---|---|
| MeanT | 0.035 | 0.336 | 0.331 |
| MeanR | 0.042 | 0.399 | 0.393 |
| GeomMeanT | 0.032 | 0.309 | 0.304 |
| GeomMeanR | 0.038 | 0.365 | 0.359 |

90% CI (MeanT-MeanR)

| Cmax | AUC | AUCt |
|---|---|---|
| 75.16-->92.505 | 76.275-->91.914 | 76.213-->91.952 |

(GeomMeanT/GeomMeanR)*100

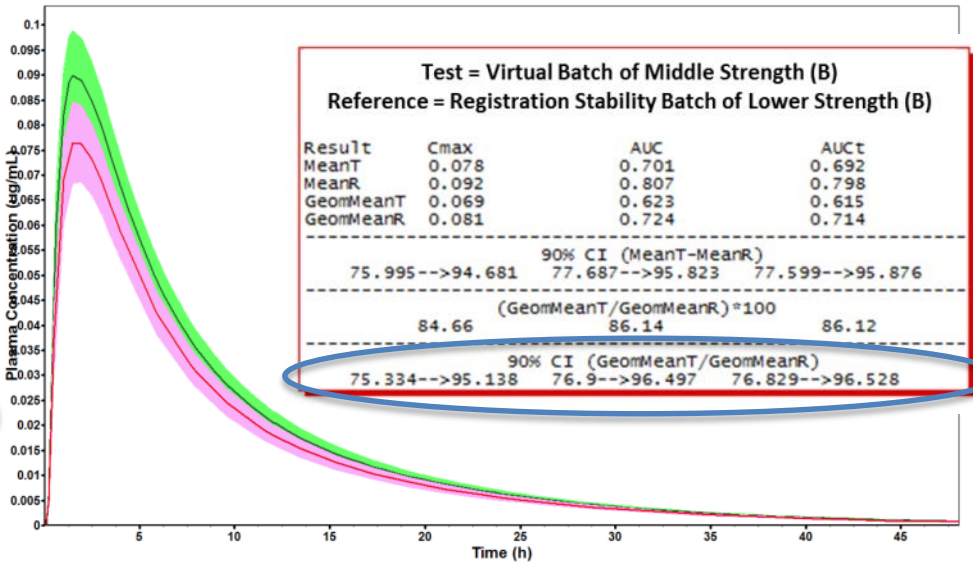
| Cmax | AUC | AUCt |
|---|---|---|
| 84.11 | 84.73 | 84.71 |

90% CI (GeomMeanT/GeomMeanR)

| Cmax | AUC | AUCt |
|---|---|---|
| 75.837-->93.289 | 76.832-->93.449 | 76.771-->93.474 |

**Lower (A) and Middle (B) Strengths**
**Q = 75% at 30 min**
***Not clinically relevant***

**Lower (A) and Middle (B) Strengths**
**Q = 80% at 30 min**
***Clinically relevant***
***(data not shown)***




Test = Virtual Batch of Middle Strength (B)
Reference = Registration Stability Batch of Lower Strength (B)

| Result | Cmax | AUC | AUCt |
|---|---|---|---|
| MeanT | 0.078 | 0.701 | 0.692 |
| MeanR | 0.092 | 0.807 | 0.798 |
| GeomMeanT | 0.069 | 0.623 | 0.615 |
| GeomMeanR | 0.081 | 0.724 | 0.714 |

90% CI (MeanT-MeanR)

| Cmax | AUC | AUCt |
|---|---|---|
| 75.995-->94.681 | 77.687-->95.823 | 77.599-->95.876 |

(GeomMeanT/GeomMeanR)*100

| Cmax | AUC | AUCt |
|---|---|---|
| 84.66 | 86.14 | 86.12 |

90% CI (GeomMeanT/GeomMeanR)

| Cmax | AUC | AUCt |
|---|---|---|
| 75.334-->95.138 | 76.9-->96.497 | 76.829-->96.528 |

# Case Example 1 - Summary

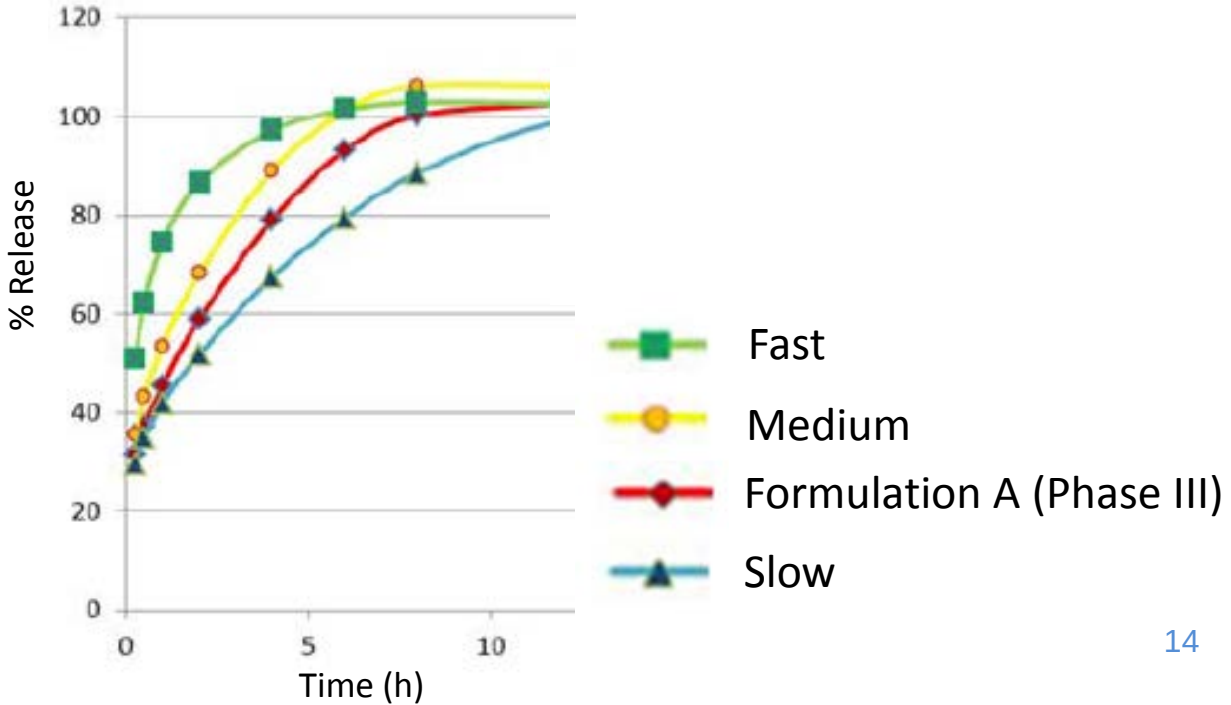
- Successful application of validated mechanistic model
  - Supported bio-predictive nature of the developed dissolution method
  - Establishing clinically relevant dissolution acceptance criteria

- Application of biopharmaceutics principles and integration of *in silico* tool, and *in vitro* and *in vivo* data for establishing clinically relevant dissolution acceptance criteria

# Case Study 2

## Support of Bio-relevant dissolution method by virtual BE studies

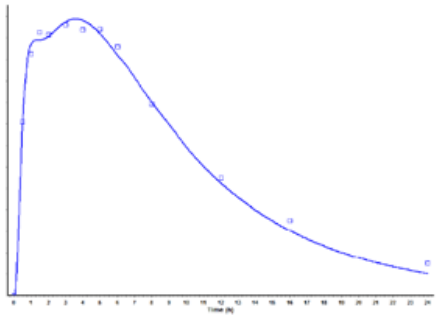
- (25%IR+ 75%ER) tablet
- BCS class I drug substance
  - (high solubility and high permeability)
- Single strength
- Discriminatory dissolution method



# Mechanistic Modeling and Simulation Strategy

**MODEL BUILDING**

- I.V. PK Data
- Oral PK Data (formulation A, 1X dose)
- Physicochemical properties, absorption parameters, and PK parameters
- Dissolution Profiles

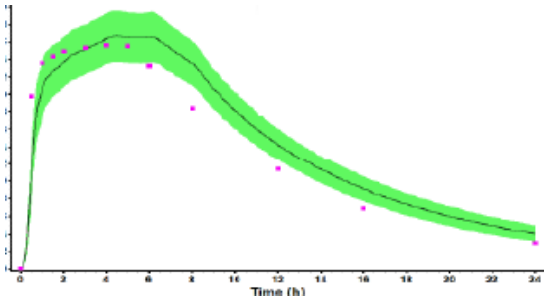


**MODEL VALIDATION**

- External Validation (formulation A, 2X dose)

  A. Population simulation vs. observed mean PK

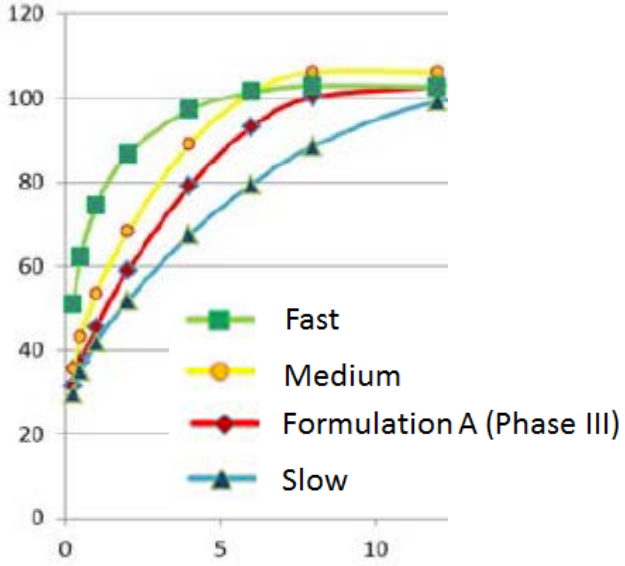
  B. Population simulation is BE to observed PK

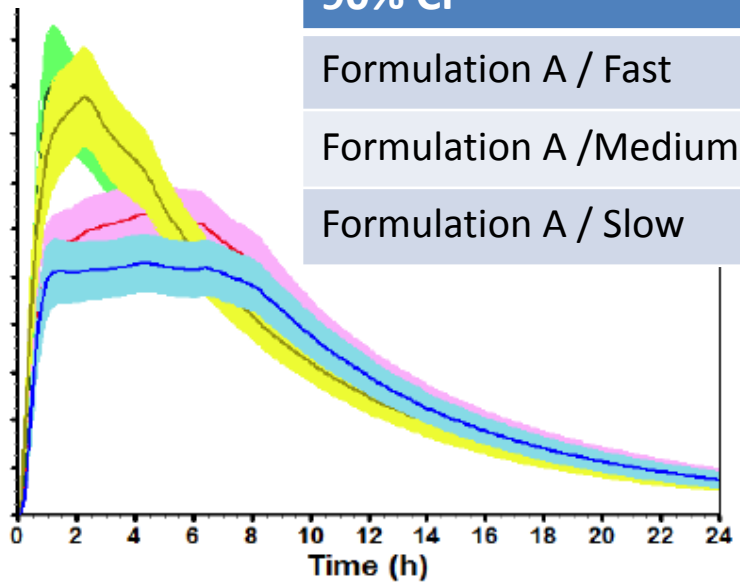



| 90% CI | Cmax | AUCt |
|---|---|---|
| Simulated/ Observed | 87-110 % | 88-113 % |

# MODEL APPLICATION: Justify/Support Bio-relevant dissolution method

Virtual BE studies:
clinical batch (Formulation A) against 3 test formulations (fast, medium, slow)




| 90% CI | Cmax | AUCt |
|---|---|---|
| Formulation A / Fast | 61-79 % | 88-111 % |
| Formulation A /Medium | 65-84 % | 88-112 % |
| Formulation A / Slow | 100-129 % | 100-127 % |

Bio-relevant dissolution method was claimed, based on:

1. Correlation between in vitro drug release profiles and PK data
2. Correlation between dissolution profiles and virtue BE results
3. In vitro dissolution tests performed could be used to differentiate the in vivo drug performance using virtual BE studies)

# “Bio-relevant” was not granted

The relationship was established based on model **predicted values** from three formulations with different release characteristics rather than on **observed values**.

# Case Example 2 - Summary

- To justify bio-relevant dissolution through IVIVC or IVIVR:

The process typically consists on the evaluation of formulations with at least three different release formulations correlating in vitro release with in vivo PK

# Challenges and Opportunities

**CHALLENGES**

- *In vitro in vivo* correlations (IVIVC) success rate is low
- *In vivo* link to quality is challenging (especially for poorly soluble drugs (BCS class II and IV drug products)~~)~~

**OPPORTUNITIES**

- Leverage the use of bio-relevant media which closely mimic the fluids of the human stomach and intestine allowing for better simulated conditions of the gastrointestinal tract.
- Use of *in silico* absorption modeling to assess the impact of *in vitro* dissolution on *in vivo* performance

Courtesy of Min Li

# *Summary*

- The Office of New Drug Products and the Division of Biopharmaceutics is patient focused and uses unique tools to link product quality to in vivo (clinical) performance
- PBPK modeling is a promising approach for promoting clinically relevant risk assessment and specifications
- Bio-relevant dissolution method are essential elements for setting clinically relevant product design space and specifications
- Proper model building and validation is essential for bridging dissolution and PK characteristics and establishing confidence in bio relevancy of the dissolution method

# *Acknowledgments*

***(arranged alphabetically by last names)***


Dr. Poonam Delvadia

Dr. Min Li

Dr. Sandra Suarez-Sharp

Dr. Fang Wu

Dr. John Duan

Dr. Kimberly Raines

Dr. Paul Seo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