

# Opportunities and challenges for modeling the clinical impact (i.e. systemic exposure) of formulation and manufacturing changes

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Current State and Future Expectations of Translational Modeling Strategies  
to Support Drug Product  
Development, Manufacturing Changes and Controls (FDA/CERSI)

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College Park, MD



# Outline

- Introduction and Background
  - Drug product journey
  - Biopharmaceutics risk assessments
- Model Based Approaches
  - Role of mechanistic biopharmaceutics modeling
  - Bridging formulation and manufacturing attributes
  - Opportunities and challenges
- Case Studies
- Summary

# What is Biopharmaceutics

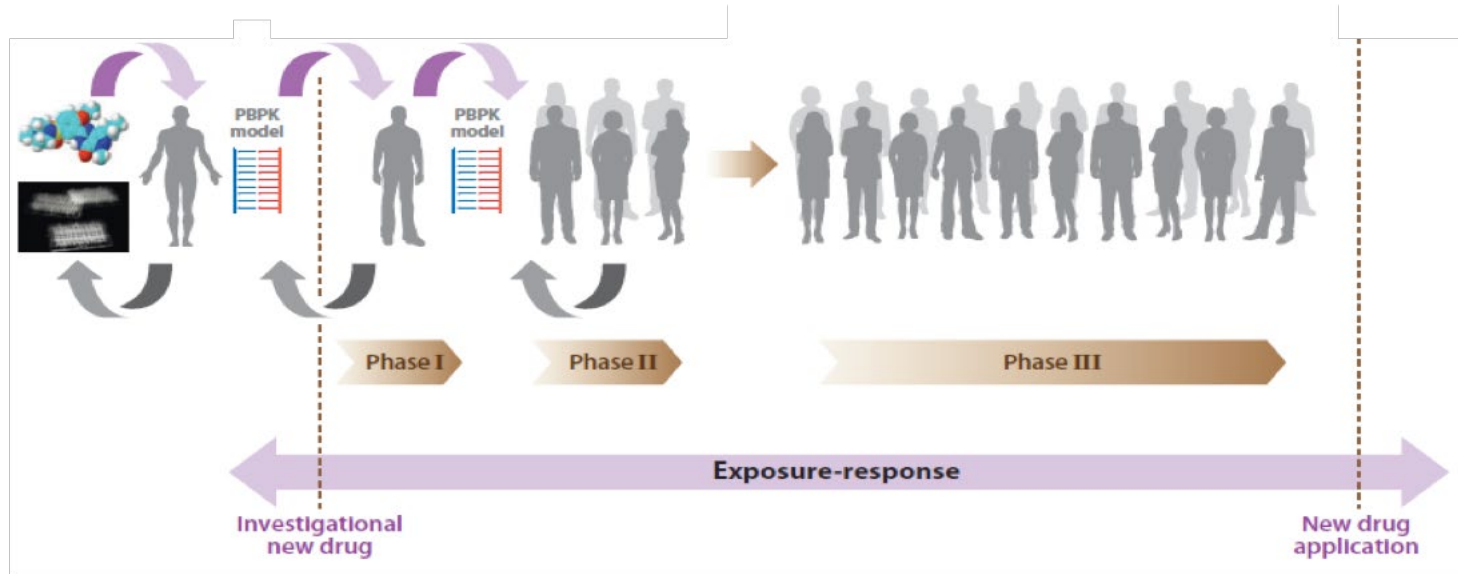
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The study of the physical and chemical properties of drugs and their dosage as related to the pharmacokinetics, onset, duration, and intensity of drug action.

## Involves:

- Selection of API physical form where appropriate
- Selection of dosage form for intended route of administration
- Maximizing their utility and limiting risks in vivo:
  - Meets desired PK profile
  - Maximizes exposure, minimize variability
  - Minimal patient compliance issues

# Overview of Drug Product Journey



Rowland, M. *Annu. Rev. Pharmacol. Toxicol.* 2011. 51:45-73

*Clinical performance considerations necessary to reach the right patients during development (SAD/MAD, ADME, absBA, Ph3 pivotal efficacy, etc.)*



Iterative product changes from pre-IND to NDA/LCM

Multiple unique presentations (solution, suspension, solid dosage form, etc) and processes (on site pharmacy compounding to commercial batch/CM) are necessary



# Biopharmaceuticals Risk Assessments

*Imbedded within all development stages (end-to-end)*



- During early stages the goal is to assess developability and enable discovery and clinical development
- During advanced stages the goal is to make commercially viable formulations

# Biopharmaceutics Risk Assessment (RA) Strategy

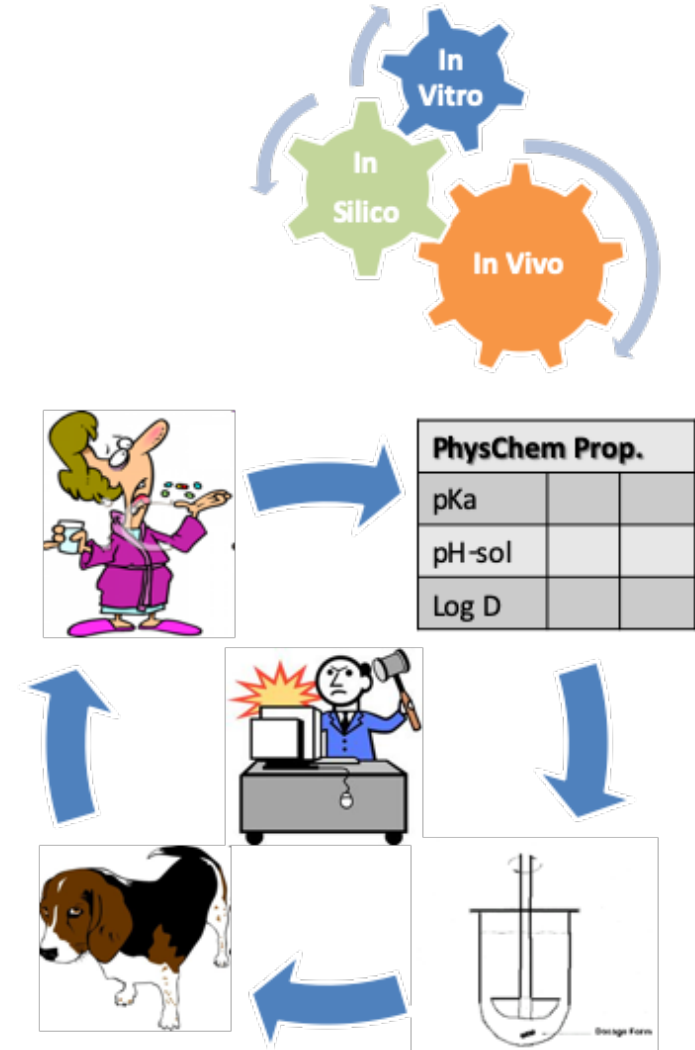
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- Goal:
  - To assess the bioperformance risks of APIs and drug products (exploratory and commercial), recommend mitigation strategies, provide mechanistic knowledge and regulatory input for oral drugs in the clinical development pipeline
- Mechanism:
  - Use an integrated approach: in vitro, in vivo, and in silico (IV-IV-IS) methodologies to identify and quantify the risks
  - Provide a holistic knowledge of the biopharmaceutics properties
  - Recommend the best options to mitigate the biopharm risks

# Tools to Predict the Risk

Criteria: Need predictive, biorelevant, mechanistic

- **Types of data/systems:**
  - Physicochemical properties
  - *In vitro* dissolution data
  - Animal PK data
  - Clinical PK data
- **Vastly different test systems:**
  - Volumes, compositions, pHs, transit times, hydrodynamics, mechanics
- **Do they connect, collectively?**
- **Can we enable decisions?**
  - Formulation and manufacturing strategy
  - Clinical & regulatory strategy



# Tools to Predict the Risk

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Criteria: Need predictive, biorelevant, mechanistic

- In vitro biorelevant dissolution:
  - Mitigate low BA: formulation development, enabling technology selection (amorphous, lipid)
  - Food effect model, pH-transfer model
  - 2-stage USP model
  - Specialized models: pediatric, lipolysis
- In vivo PK models:
  - Dog model (BA risk, pH-effect, FE models)
  - Rat model (BA risk, site of absorption, permeability assessment)
  - Non-oral, non-invasive alternate route of administration models
  - Other animal models: cyno and mini-pig models (CRO)
- In-silico: GastroPlus, SimCyp for PBPK modeling and prediction





# Biopharm Risk – Example Threshold Levels

Risk	In Vitro (Dissolution)	In Silico (G+)	In Vivo PK
Low BA (Form, DP, equivalence)	High:<0.5 (rel. to CTRL) Low-to-Moderate: 0.5- 0.8 (if, p<0.05)	Exposure (AUC, Cmax) impact +/- >30% to initiate in vivo PK study  (Specific justification for alternative threshold required. Input from Clinical Pharmacology regarding target populations, PK variability, etc.)	High:<0.5 (rel. to CTRL) Low-to-Moderate: 0.5- 0.8 (if, p<0.05)
Food-effect <sup>1</sup>	Positive: >1.5 No FE: 0.8-1.5 Negative: <0.8		Positive: >1.5 No FE: 0.8-1.5 Negative: <0.8
pH-Effect <sup>2</sup>	High: <0.2 Mid: 0.2-0.5 Low: >0.5		High: <0.5 Mid: 0.5-0.8 Low: >0.8
API Particle size	High:<0.5 (rel. to CTRL) Low-to-Moderate: 0.5- 0.8 (if, p<0.05)		High:<0.5 (rel. to CTRL) Low-to-Moderate: 0.5- 0.8 (if, p<0.05)

<sup>1</sup> FE team efforts: IVIVR link to clinical data – Mathias et al., AAPS J. 17: 988-998, 2015

<sup>2</sup> pH-effect team (BMS-BRI) efforts: IVIVR link to clinical data – Mathias et al. Mol. Pharm. 10: 4063-4073, 2013.

# Degree of Formulation or Process Change

SUPAC defines specific levels and mitigations in the context of post approval changes

- Not targeted for early development
- Guidance for IR and MR products
- Covers only limited biopharmaceutics tools (dissolution testing and clinical evaluation)

Example:

**EXTENDED RELEASE SOLID ORAL DOSAGE FORMS  
RELEASE CONTROLLING COMPONENTS AND COMPOSITION**

LEVEL	CLASSIFICATION	THERAPEUTIC RANGE	TEST DOCUMENTATION	FILING DOCUMENTATION
I	-< 5% W/W CHANGE BASED ON TOTAL RELEASE CONTROLLING EXCIPIENT (e.g., controlled release polymer, plasticizer) CONTENT -NO OTHER CHANGES	ALL DRUGS	-STABILITY -APPLICATION/COMPENDIAL REQUIREMENTS -NO BIOSTUDY	-ANNUAL REPORT
II	-CHANGE IN TECHNICAL GRADE AND/OR SPECIFICATIONS -<10% W/W CHANGE BASED ON TOTAL RELEASE CONTROLLING EXCIPIENT (e.g., controlled release polymer, plasticizer) CONTENT -NO OTHER CHANGES	NON-NARROW	-NOTIFICATION & UPDATED BATCH RECORD -STABILITY -APPLICATION/COMPENDIAL REQUIREMENTS PLUS MULTI-POINT DISSOLUTION PROFILES IN THREE OTHER MEDIA (e.g., WATER, 0.1N HCL, AND USP BUFFER MEDIA AT pH 4.5 AND 6.8) UNTIL >80% OF DRUG RELEASED OR AN ASYMPTOTE IS REACHED <sup>1</sup> -APPLY SOME STATISTICAL TEST (F2 TEST) FOR COMPARING DISSOLUTION PROFILES <sup>2</sup> -NO BIOSTUDY	-PRIOR APPROVAL SUPPLEMENT
		NARROW	-UPDATED BATCH RECORD -STABILITY -APPLICATION/COMPENDIAL (PROFILE) REQUIREMENTS -BIOSTUDY OR IVIVC <sup>1</sup>	-PRIOR APPROVAL SUPPLEMENT
III	->10% W/W CHANGE BASED ON TOTAL RELEASE CONTROLLING EXCIPIENT (e.g., controlled release polymer, plasticizer) CONTENT	ALL DRUGS	-UPDATED BATCH RECORD -STABILITY -APPLICATION/COMPENDIAL (PROFILE) REQUIREMENTS -BIOSTUDY OR IVIVC <sup>1</sup>	-PRIOR APPROVAL SUPPLEMENT

<sup>1</sup> IN THE PRESENCE OF AN ESTABLISHED IN VITRO/IN VIVO CORRELATION ONLY APPLICATION/COMPENDIAL DISSOLUTION TESTING SHOULD BE PERFORMED.

<sup>2</sup> IN THE ABSENCE OF AN ESTABLISHED IN VITRO/IN VIVO CORRELATION.

# Clinical Impact of Formulation and Manufacturing Changes

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## Opportunities

1. Apply clear framework for biopharmaceutics risk assessments
2. Integrate in vitro, in vivo, and silico data
3. Establish mechanistic knowledge of in vivo performance through all development stages (end-to-end)
  - Discovery: Developability assessment (preclinical PK, toxicology, and pharmaceutics studies)
  - Exploratory Development: Advance multiple unique formulations to establish/confirm key biopharmaceutics risks
  - Full Development and LCM:
    - Integrate PBPK/popPK/PD models
    - IVIVR/C, controls, and specifications for CQAs, CMAs, and CPPs to ensure target PK performance
    - Enable direct clinical use for range of expected materials and process conditions/methods (de-risked by prior biopharm RAs)
    - Biowaivers. Avoidance of unnecessary clinical studies.

# Clinical Impact of Formulation and Manufacturing Changes

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## Challenges

1. Establish proper channels for integrating information accumulated by multiple functions
  - Discovery, clinical pharmacology, product development, manufacturing, etc.
  - Need to share and track many data sets and key findings that impact risk assessments
2. Implementing risk balanced approaches
3. Detailed mechanistic description of certain CMAs, CQAs, CPPs

# Developing and bridging a target level of exposure

- If two drug products, containing the same drug, have the same concentration profile at the intestinal membrane surface then they will have the same rate and extent of absorption.
- If two drug products have the same in vivo dissolution profile under all luminal conditions, they will have the same rate and extent of drug absorption.

# Role for Biopharmaceutics Models in CMC

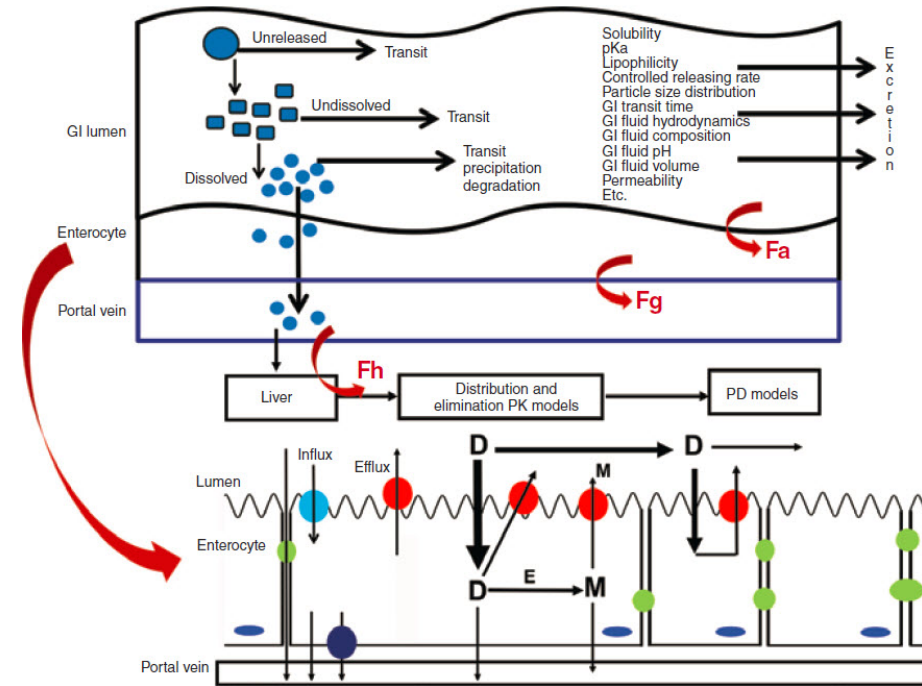
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- In vivo performance is critical to implementing Quality by Design (QbD) in drug development
- Well validated predictive PK absorption models provide missing link to in vivo performance... facilitate QbD implementation
  - Identify Critical Process Parameters (CPPs), Critical Quality Attributes (CQAs) by linking material attributes, process parameters, and in vivo performance.
  - More meaningful controls – Impact to PK. Provides operational flexibility
  - Compare process or material variability against clinical variability (virtual bioequivalence studies)
- Mechanistic risk analysis: Identify what to test for CMC development/validation
  - Does API physical form/purity/particle size impact exposure?
  - Does tablet disintegration impact bioavailability?
  - What dissolution range is clinically acceptable?

# Mechanistic Modeling as Tool for QbD Implementation

“Mechanism-based modeling approaches, particularly those used during the formulation development stage, can be of great help for development .... Drug applicants are encouraged to adopt such approaches to guide formulation development and set product specifications.”

“Predictive biopharmaceutical models also have great potential uses in CMC review. For example, when there is a large difference in particle size distribution... a predictive absorption model could be employed to identify the risks in having a significant difference in particle size distribution. Another important application is to define biorelevant dissolution specifications”



**Figure 1** Schematic describing the absorption process of oral solid dosage forms and factors affecting oral absorption. D, drug; E, enzymes; Fa, fraction of drug absorption from the gastrointestinal tract; Fg, fraction of drug that escapes the gut extraction; Fh, fraction of drug that escapes the liver extraction; GI, gastrointestinal; M, metabolites; PD, pharmacodynamics; PK, pharmacokinetics.

X Zhang and RA Lionberger (FDA Office of Generic Drugs)  
Clinical pharmacology & Therapeutics | VOLUME 95 NUMBER 5 | MAY 2014

# PBPK Modeling of Formulation and Manufacturing Changes

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## Examples of Opportunities

### 1. Minimize dependence on clinical and animal PK studies

- Fewer iterations to establish key formulation/process risk elements wrt clinical exposure
- Reduce study size. Confirmatory in nature based on mechanistic assessment
- Smaller and earlier PK observations to guide development in place of late stage changes

### 2. Facilitate design of in vitro dissolution methods

- For development purposes and long-term quality applications (e.g. CRS)
- Less likely to be over/under discriminating

### 3. Extend knowledge from accumulated clinical PK/PD

### 4. Allow focus on subjects/patients with most discriminating physiology (i.e. greatest risk level)

### 5. Overcome limitations with patient access (e.g. special populations)



# PBPK Modeling of Formulation and Manufacturing Changes

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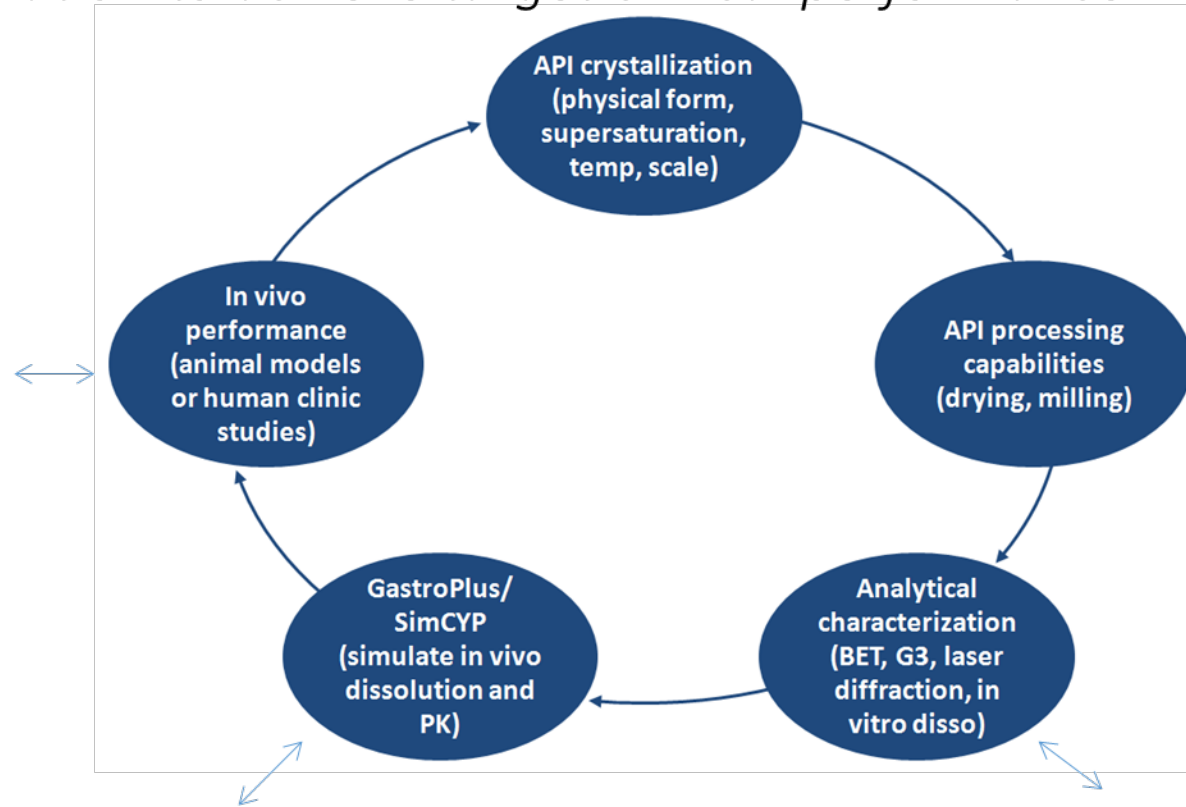
## Examples of Challenges

1. Determination of stage appropriate verification or validation for modeling approach(es).
  - Aided by clear guidance (regulatory and sponsor organizations) – facilitate early dialogue (e.g. end of Ph2 meetings)
2. Not all clinical PK/PD data is of equal quality
  - PK sampling (sparse PK, timepoints)
  - Summary demographics vs detail physiological elements
3. Evolve mechanistic descriptions of critical formulation and process elements
  - Inherent focus on dissolution methodologies and IVIVR/C
  - Improve how mechanisms related to CMAs, CQAs, and CPPs can be integrated

# Integrated View of DS, In Vitro, In Silico, and In Vivo Characterization

*Routine collaboration to achieve target clinical performance*

- Progress in clinic by identifying behavior (exposure and variability)
- Confirm performance of materials/formulations (oral – dissolution and permeability)
- Accumulated biopharmaceutics experience drive final material specifications. Includes observed clinical data (central) as well as non-clinical and PBPK models.



- Early models developed for non-clinical species that can be validated
- Establish TMP (particle size distribution, morphology, solubility) and revise with accumulated in vitro and in vivo experience/validation
- Drive selection of processes and materials to validate in vivo. Predict limit for exposure and integrate to exploratory materials/formulation PK studies.
- Image based PSD methods for early stages (prior to validation of suitable release method)
- Biorelevant in vitro dissolution and SSA for compounds with predicted sensitivity (additional characterization).

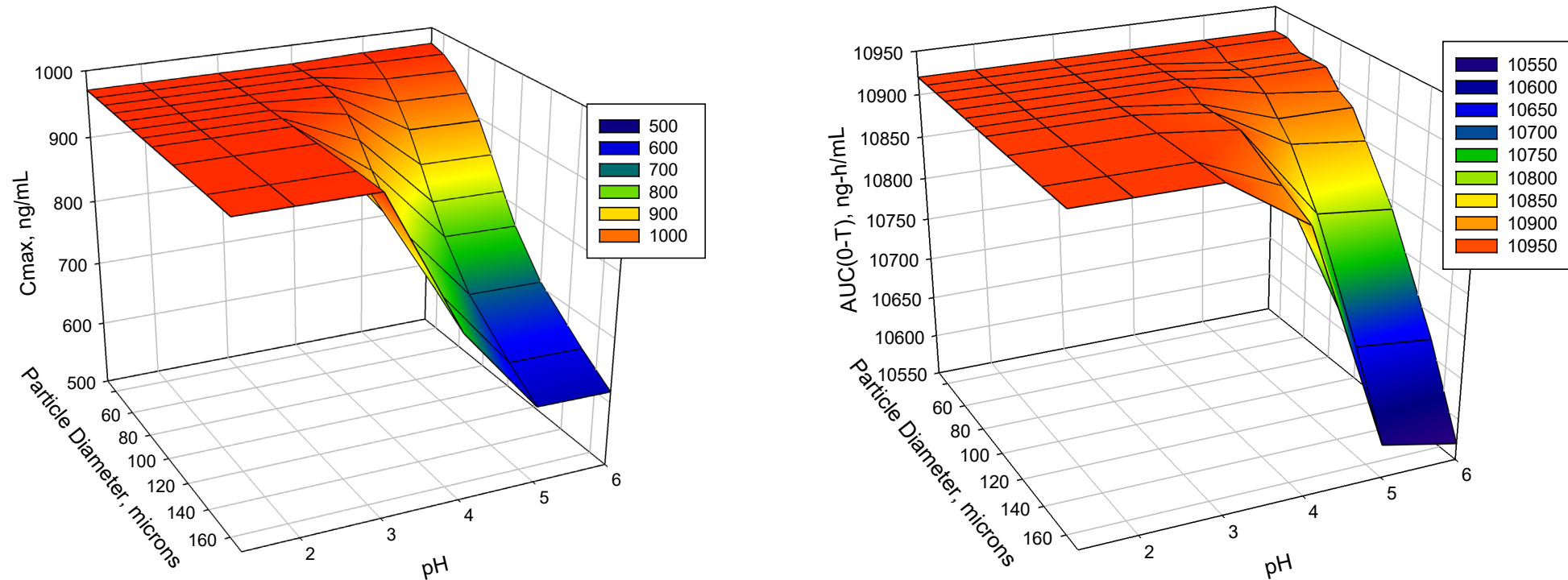
# Case Studies: Particle Size Limits

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- Simulate plasma concentration vs time profiles for a range of particles sizes to identify particle size specifications
- Use PBPK model to correlate in vitro dissolution to in vivo dissolution
  - Simulate the plasma concentration for a range of particle sizes and pH dependent solubilities to create a biopharmaceutics design space to support formulation decisions.
- Advantage: Mechanistic
  - Allows formulator to understand and quantify how the drug release from the formulation can impact the plasma concentration vs time profile

# Example 1: Identify Acceptance Criteria for API

This Scenario: The drug is BCS Class 2 weak base with high solubility at low pH values, therefore the formulator needs to identify a particle range that will not impact bioavailability

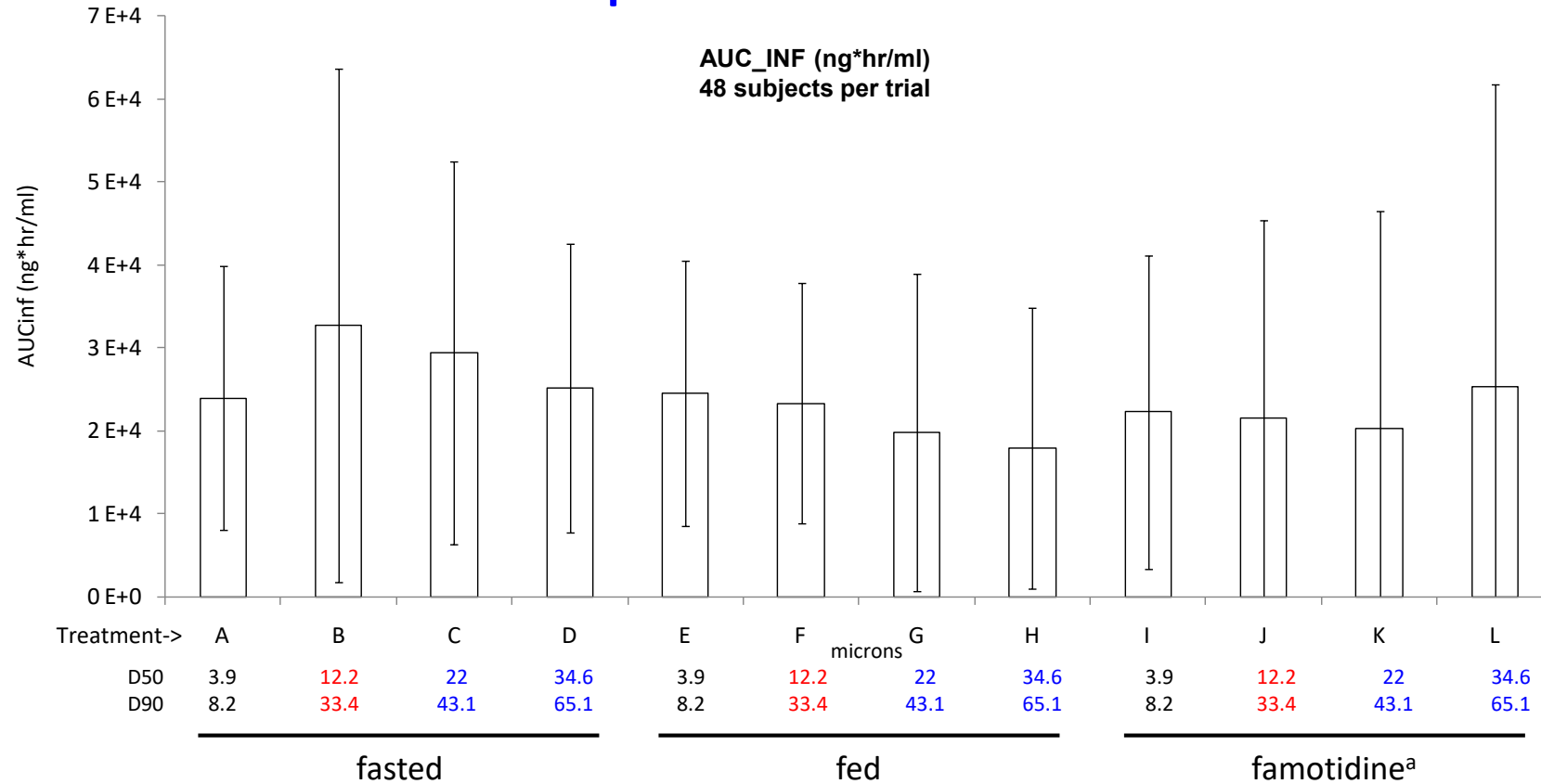


- Both particle size and pH affect Cmax and AUC
- Predictions show that particle size >100-120  $\mu\text{m}$  can have significant impact on performance – useful in setting acceptance criteria limits for API powder
- Furthermore, high pH does not critically affect *in vivo* performance if particle size is kept below 100  $\mu\text{m}$ .

# Example 2: Eliminate Micronization after Ph1&2 Studies

- Initial particle size target: D50<5 micron (D90<10 microns)
  - Based on preliminary BCS classification
  - Challenging during processing and handling for drug product (High drug loading tablet formulation)
  - Dust explosivity risk – Engineering controls needed at commercial site to handle drug product manufacturing.
- Development team needs to explore alternate approaches
  1. Increase particle size for commercial formulation (keep process)
  2. Alternative granulation process
- PBPK absorption model simulations, and analysis of non-clinical and clinical data supports revision to increase limits for target particle size

# PBPK Population Simulations



<sup>a</sup> No exposure difference observed for patients in Ph 1 taking PPIs (~half of subjects enrolled)

All PSD input as actual distributions from API lots (16bin/channel resolution) including:

- Jet milled API (representative lot)
- Wet milled (representative lot)
- Wet milled (two largest PS lots from lab scale screening)

*Suitable PSD can be achieved by other milling/crystallization processes  
(jet mill not required)*

# Observed Summary Exposure of Prototype Formulations Against Reference (dry granulated, jet milled API)

Treatment	Cmax (% of reference capsule)	AUC (% of reference capsule)	N
Dry granulation large PSD (B/A)	105	100	10
Wet granulation small PSD (C/A)	84	76	9
Wet granulation large PSD (D/A)	79	68	10

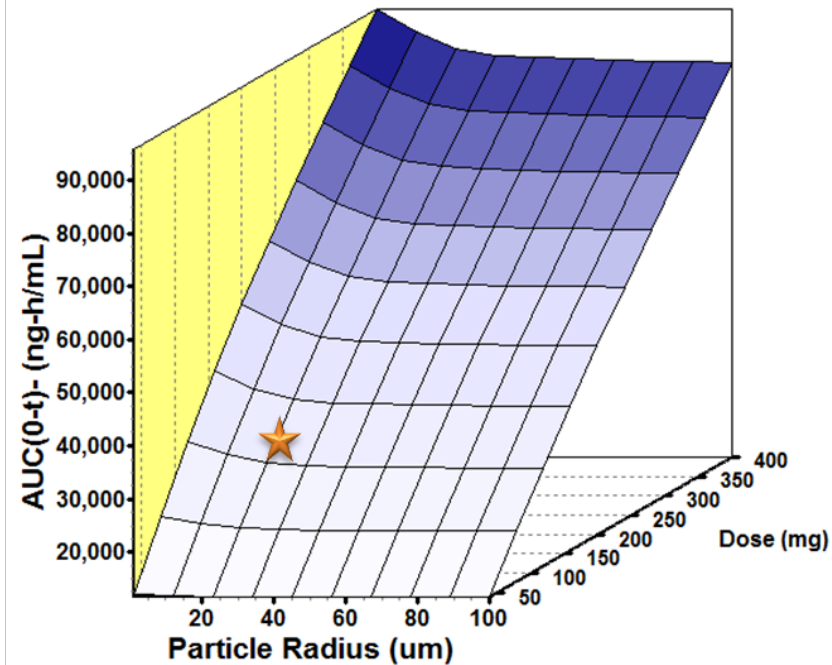
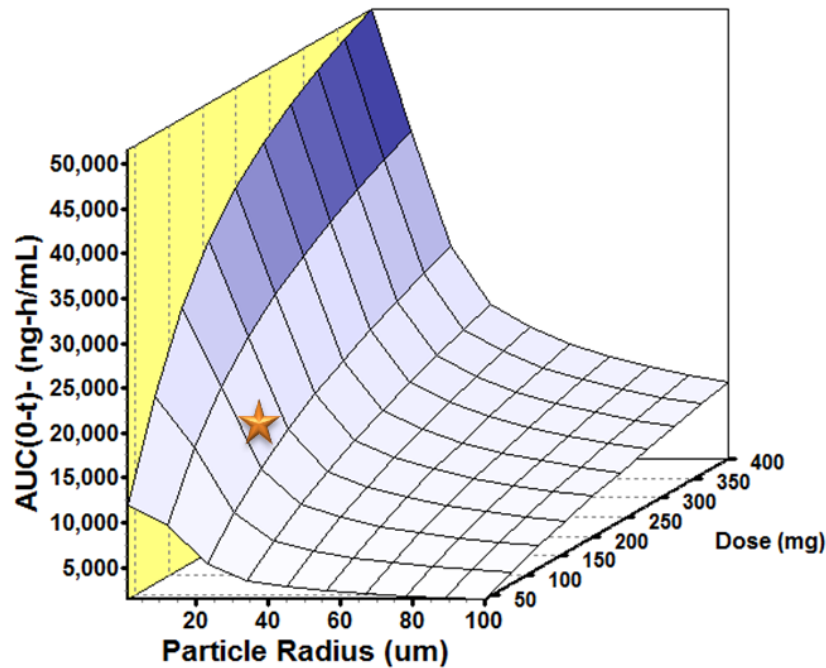
*No apparent particle size effect (consistent with G+ predictions)*

Probability that exposure would fall outside 80-125 limits for BE

(% probability 0-100)

Treatment	Cmax		AUC	
	<80	>125	<80	>125
Dry granulation large PSD (B)	7	17	19	19
Wet granulation small PSD (C)	39	2	58	3
Wet granulation large PSD (D)	54	1	74	1

# Example 3: Combined Particle Size, Dose Sensitivity, and Food-Effect



*Star indicates clinical experience; Mean particle radius can be roughly equated to D50 (32 μm)*

- **Fasted administration shows strong sensitivity to particle size and dose**
  - Steep drop across dose range for particles with radius <40 μm (diameter <80 μm)
  - Very large particles (diameter >120 μm) show relatively less sensitivity
- **Fed-state lessen particle size sensitivity across dose range (light or standard meal)**



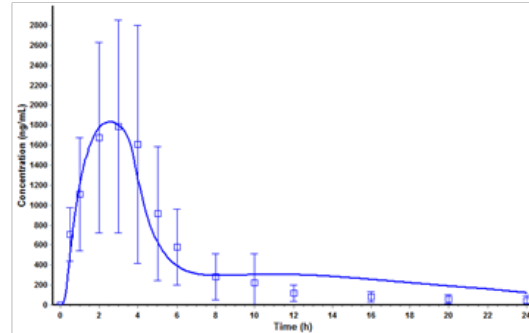
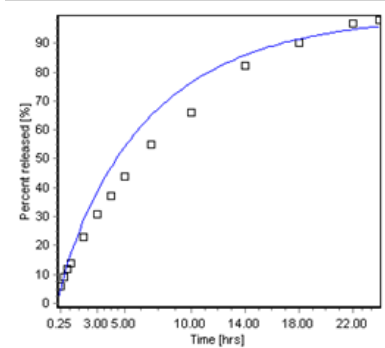
# Modified Release Tablet (Adult and Pediatric)

Formulation Attribute	Biopharmaceutics assessment (In silico, in vitro, in vivo)	Outcome/Significance
Release rate IVVC/R	<ul style="list-style-type: none"><li>▪ In vivo matrix tablet release has positive deviation from in vitro</li><li>▪ In vitro release from hydrophilic matrix has shear sensitivity</li></ul>	<ul style="list-style-type: none"><li>▪ Prototype compositions with more diffusion controlled release for clinical assessment</li><li>▪ Refine in vitro to understand shear sensitivity</li></ul>
Dosage form (tablet/multi-particulates)	<ul style="list-style-type: none"><li>▪ Multi-particulate technology has release lag time and more disperse GI transit time</li><li>▪ Multi-particulate must release faster for equivalent exposure</li></ul>	<ul style="list-style-type: none"><li>▪ Adaptive clinical trial to verify release target for new dosage form/mechanism</li><li>▪ Can new release kinetics achieve same exposure profile?</li></ul>
Dose levels	<ul style="list-style-type: none"><li>▪ Demonstrated XR release rate and manufacture is drug load specific (+ dose size limitations)</li></ul>	<ul style="list-style-type: none"><li>▪ Set critical design element for prototype formulations</li><li>▪ Use PBPK and allometry to ID target for development</li><li>▪ GastroPlus aligned for exposure predictions</li></ul>

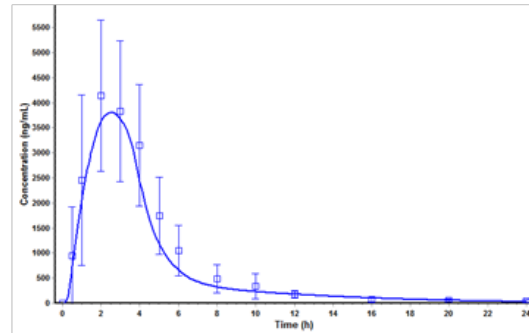
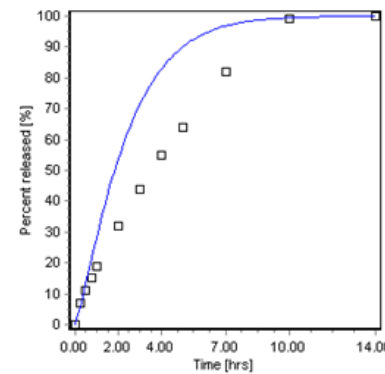
# Example 1: IVIVC/R MR Dosage Form Design

Release rate:

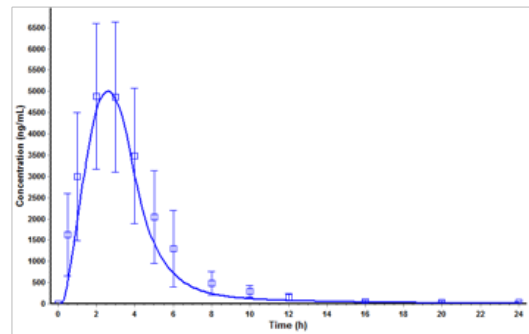
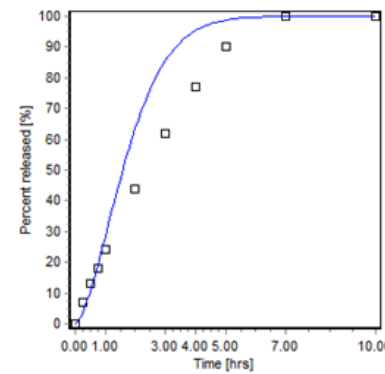
Slow



Medium



Fast



Deconvolute MR tablet formulations  
Simulated *in vivo* release – IVIVC/R

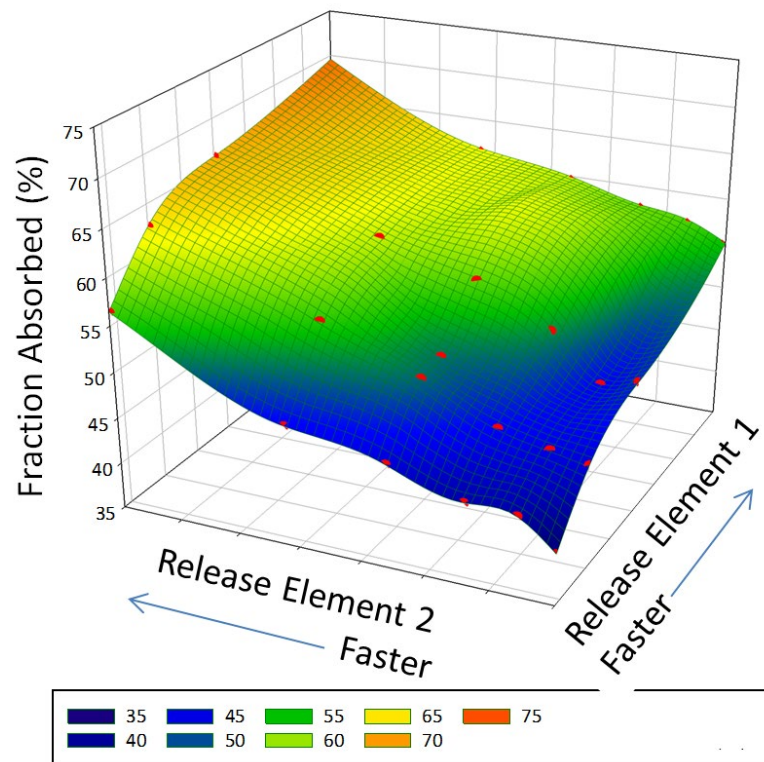
- All in vivo profiles track in vitro data for early time points (<~2-3hrs) and exhibit positive deviation for ~2-10hrs.
- Impact of hydrodynamics and in vivo motility.
- Diffusion and erosion for matrix tablet in vivo... minimal erosion in vitro

# Example 1 : IVIVC/R MR Dosage Form Design

Alter hydrophilic matrix tablet dimensions

- Requires new composition
- Model formulation space to design exploratory clinical studies and identify IVIVC/R

*in silico* simulations



*in vivo – in silico*

Treatment Release rate	Observed/Simulated	$C_{max}$ rel%	$AUC_{(0-t)}$ rel%	$AUC_{(0-inf)}$ rel%
Original MR tablet	Observed (target 100%)	87%	103%	102%
Fast	Observed	133%	125%	118%
	Simulated	138%	124%	118%
Medium	Observed	REF	REF	REF
	Simulated	REF	REF	REF
Slow	Observed	76%	80%	90%
	Simulated	80%	82%	84%

**Achieved IVIVC level A Correlation from Mechanistic PBPK model**

# Example 2: MR Dosage Form Design

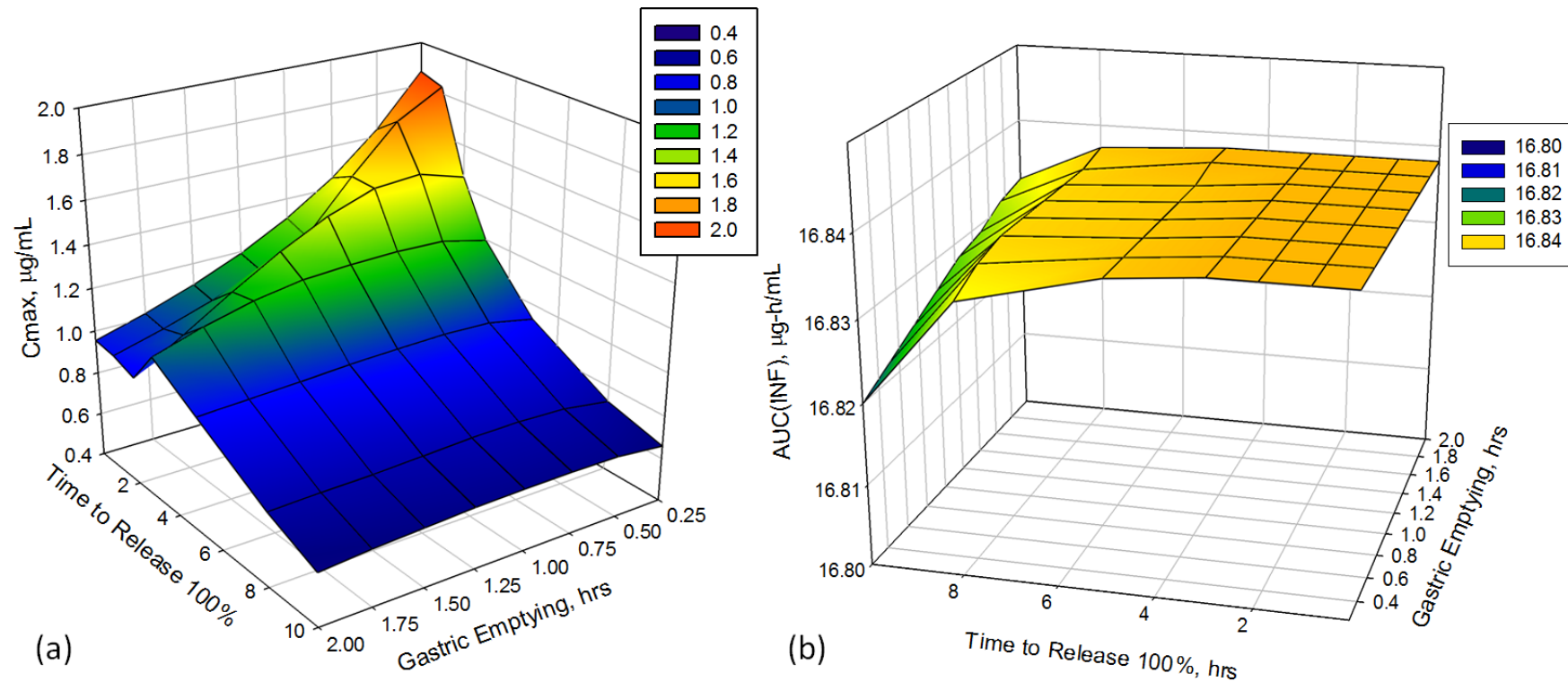


Table 2. Summary Exposure (AUC) from Solution Administration of BMS-914392<sup>a</sup>

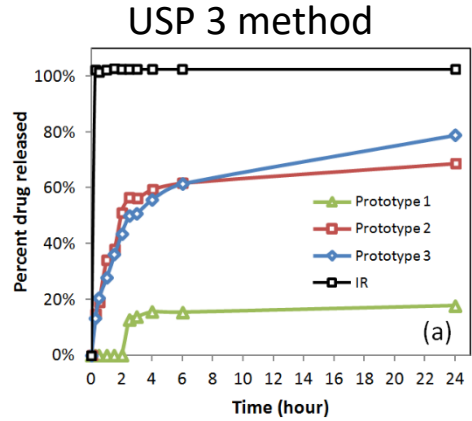
treatment (region of administration)	AUC <sub>(0-t)</sub> (ng·h/mL)
oral	702.0 (43.0)
proximal small intestine	664.7 (38.6)
distal small intestine	797.5 (37.3)
ileocecal/ascending colon	1004.1 (38.7)

<sup>a</sup>Values provided are geometric means and % CV.

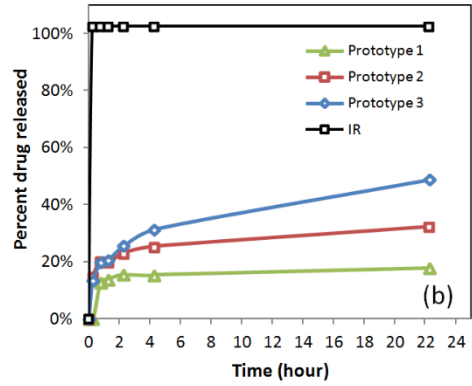
- Compound is well absorbed throughout GI tract
- Exposure (AUC and Cmax) are function of release time and gastric emptying time

# Example 2: MR Dosage Form Design

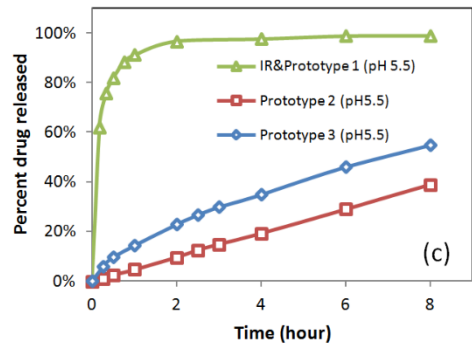
2 hr GE fasted pH



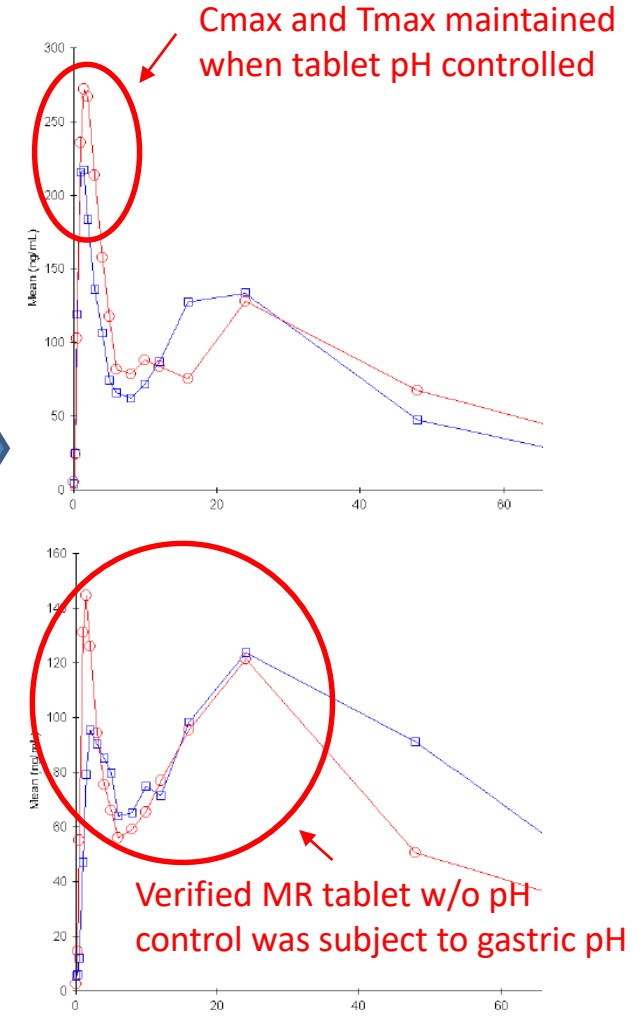
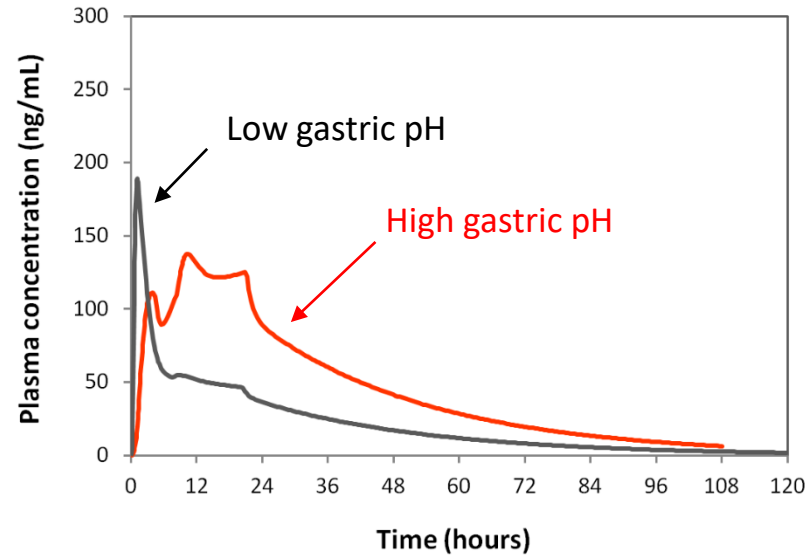
15 min GE fasted pH



pH 5.5



## PBPK Simulated Exposure



- Simulates demonstrated MR tablet release and exposure sensitivity to gastric pH
- Unique tablet formulation needed to control local pH and release rate

# Takeaway Messages: Clinical Impact of Product Changes

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- Biopharmaceutics risk assessments for all development stages (end-to-end approach)
  - Emphasis on clinical relevant product quality starts in early development and carried through to NDA/LCM
  - Valuable to understand complex mechanisms early in development
- Diverse methods (IVIVIS) and experience for multiple modalities and problem statements
- PK absorption modeling is a critical interface for clinical and product development
  - Central tool to establish and quantify risk. Establish formulation strategy
  - Identify target performance attributes, boundaries, and control strategies
  - Opportunities for high quality medicines to reach patients faster and avoidance of unnecessary clinical studies
- Opportunities to advance the parameterization of process/formulation elements within PBBM

# Acknowledgements

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*Thank you for your attention*

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