Hot Topic N: Introduction and Case Study on MR PBBM applications

August 31, 2023

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DISCLAIMER

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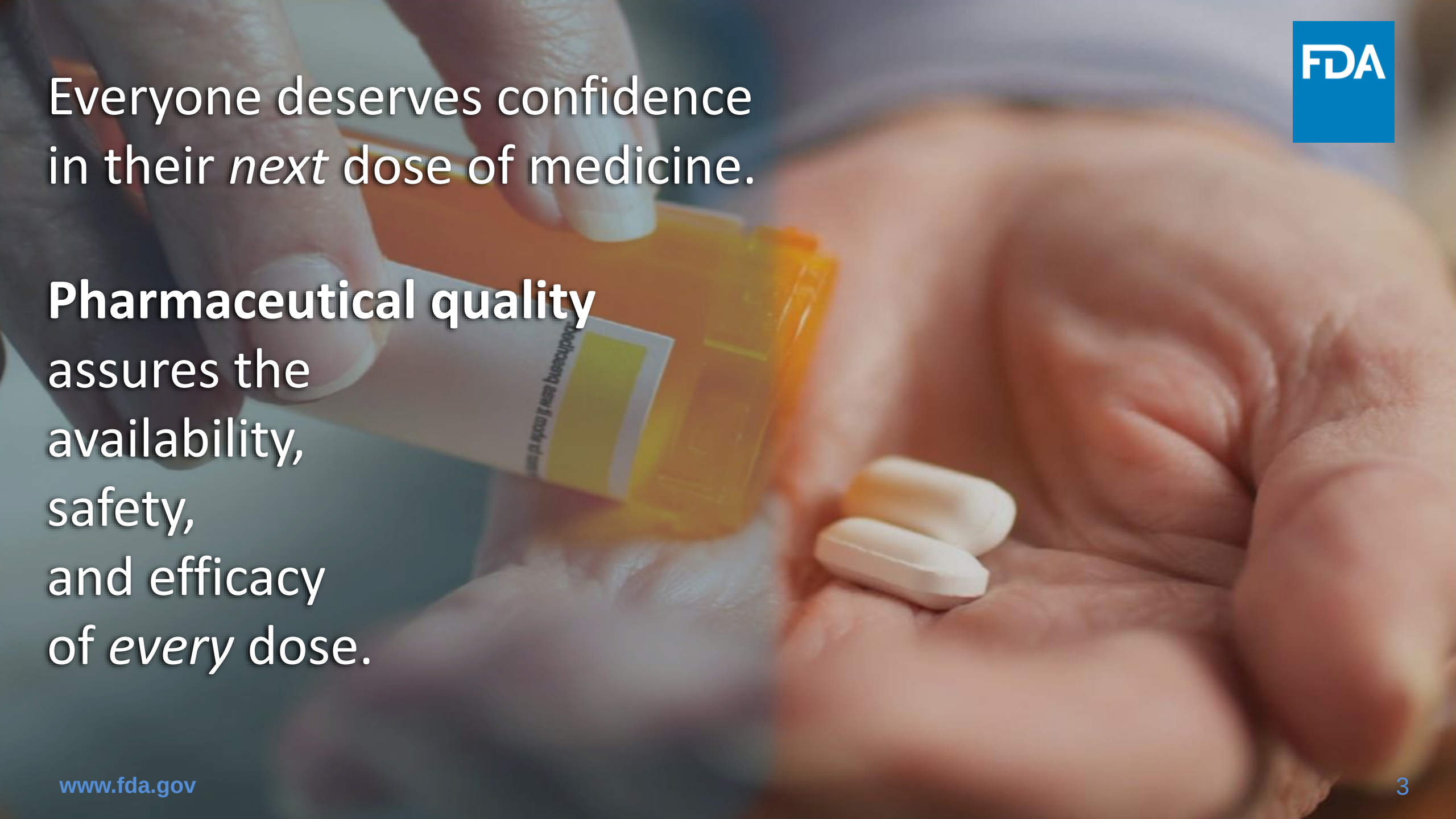
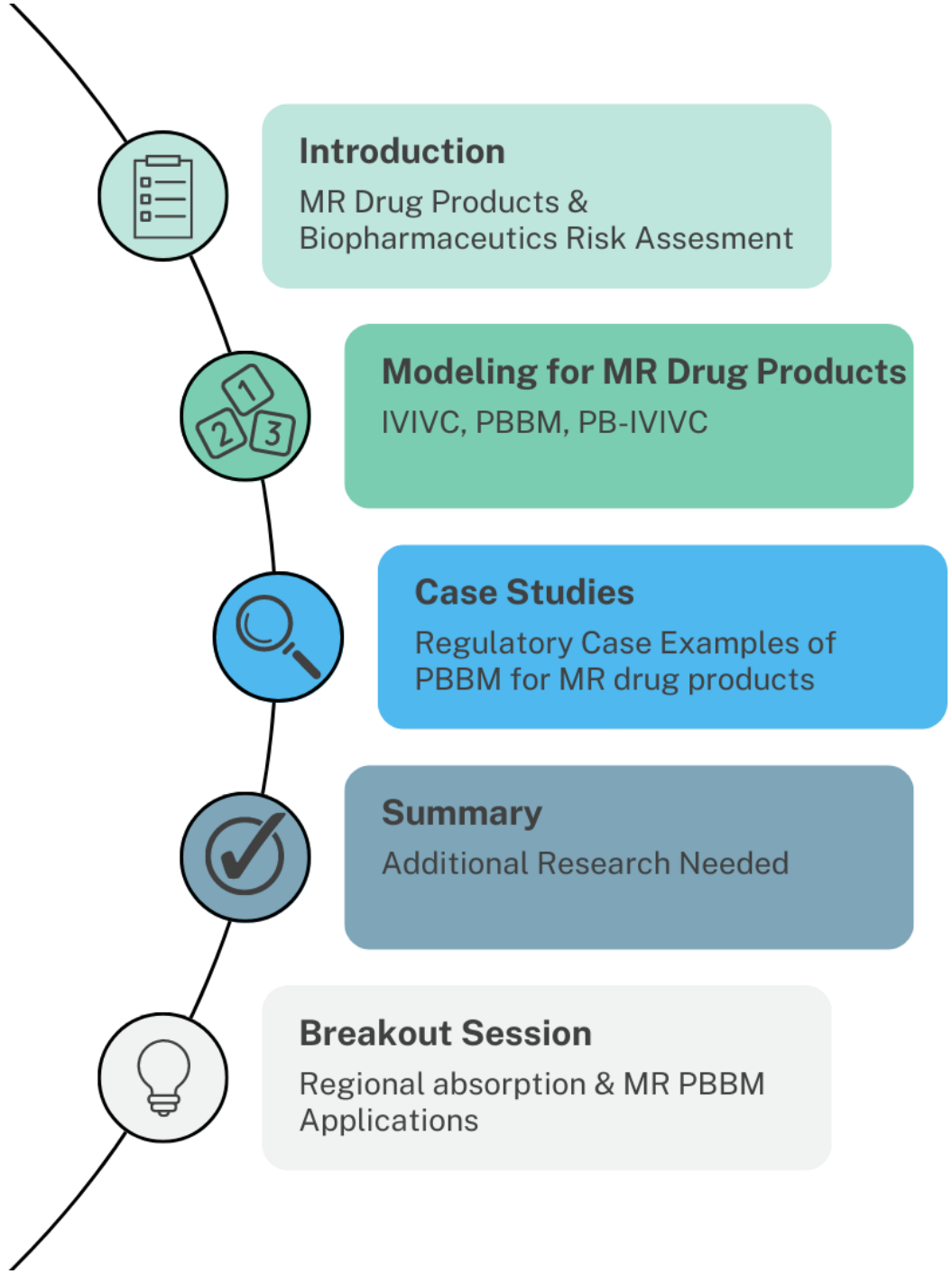


Everyone deserves confidence in their *next* dose of medicine.

Pharmaceutical quality assures the availability, safety, and efficacy of *every* dose.

Outline

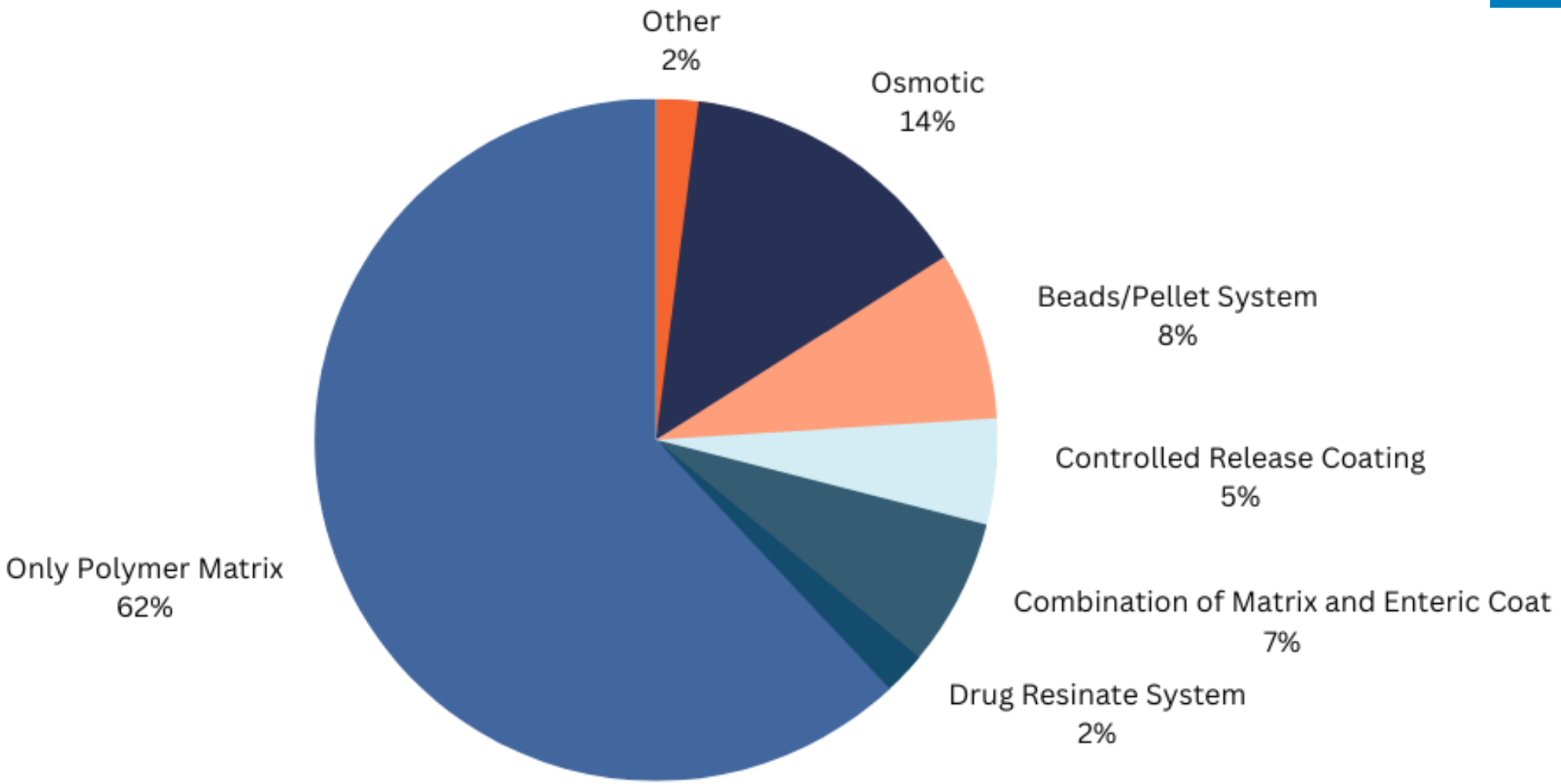

Introduction
MR Drug Products &
Biopharmaceutics Risk Assesment
Modeling for MR Drug Products
IVIVC, PBBM, PB-IVIVC
Case Studies
Regulatory Case Examples of
PBBM for MR drug products
Summary
Additional Research Needed
Breakout Session
Regional absorption & MR PBBM
Applications

Introduction

Purpose for Modified Release Product Development:

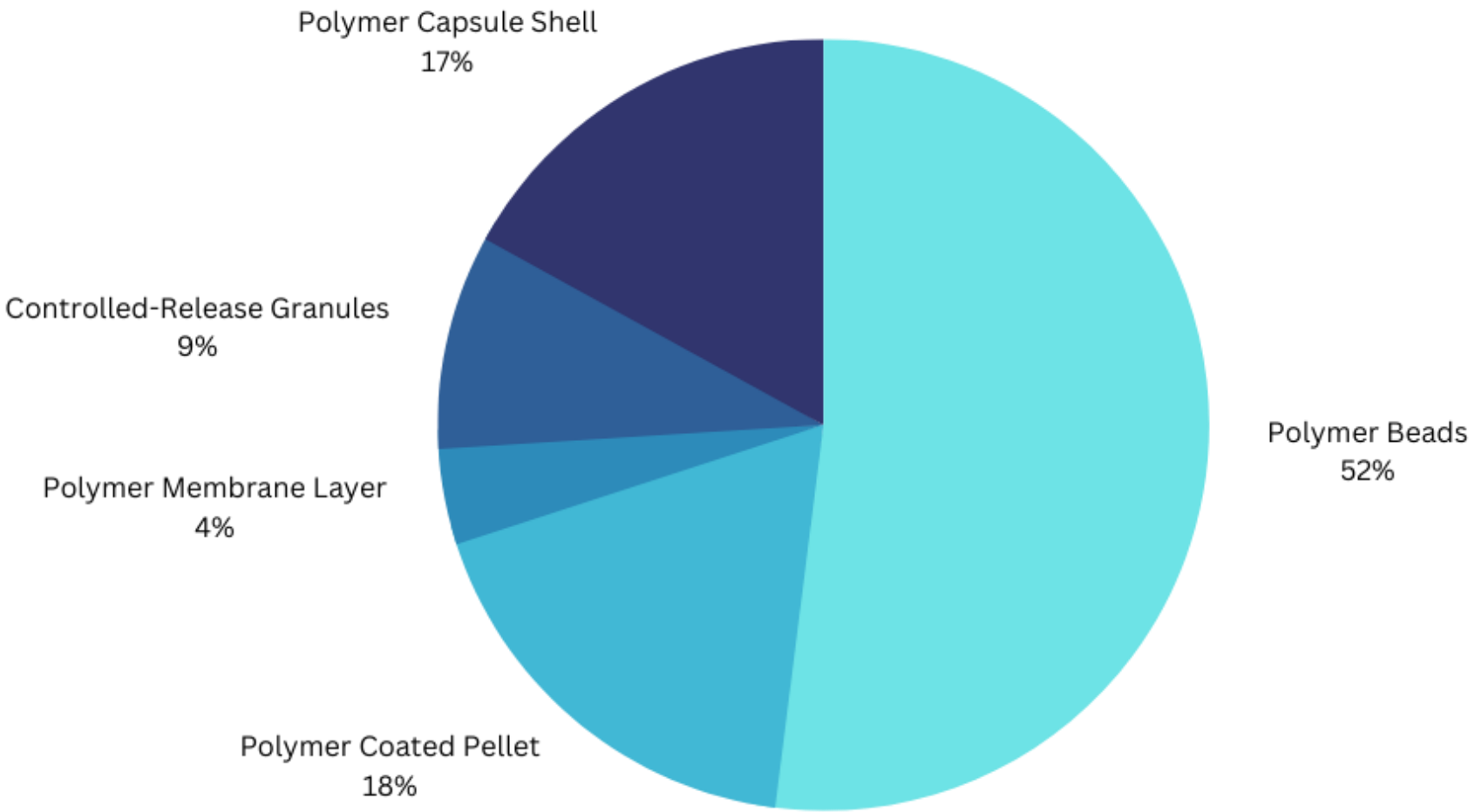
- Reduce dosing frequency for better patient compliance
- Better controlled plasma drug levels with reduced overdose risk or lower incidence of side effects
- Enhance bioavailability to reduce total drug intake

Product Design - ER Tablets



Nadia Ahmed et al. Retrospective Analysis of the Biopharmaceutics Characteristics of solid oral Modified-Release Drug Products in Approved US FDA NDAs. Submitted.

Product Design - ER Capsules



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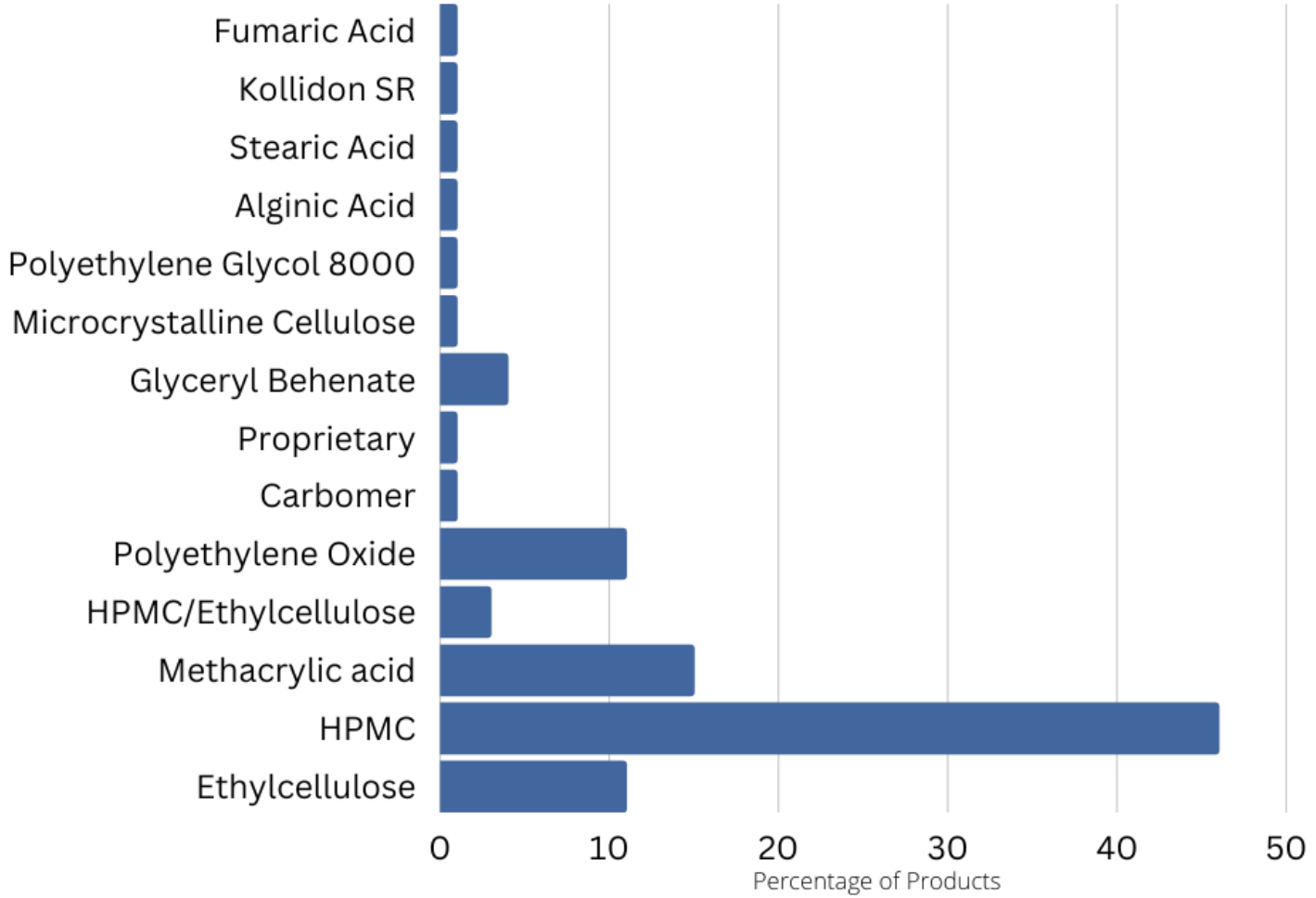
Polymer Components of ER Products



Nadia Ahmed et al. Retrospective Analysis of the Biopharmaceutics Characteristics of solid oral Modified-Release Drug Products in Approved US FDA NDAs. Submitted.

Biopharmaceutics Risk Assessment

Table II Initial Biopharmaceutics Risk Assessment Matrix Based on API and Formulation Properties

API	Formulation					
	Immediate release				Modified release	
	Standard		Enabled			
	Innovator composition	Alternative composition	Innovator composition	Alternative composition	Innovator composition	Alternative composition
BCS I	Very Low	Very Low	Very Low	Low	Medium	Medium-High
BCS III	Very Low	Low	Low	Medium	Medium	Medium-High
BCS IIa (weak acid)	Medium	Medium-High	Medium	High	Medium	Medium-High
BCS IIb (weak base)	Medium	High	High	Very High	Medium	High
BCS IIc (neutral)	Medium	High	High	Very High	Medium-High	Very High
BCS IV	High	Very High	Very High	Very High	High	Very High

Note:

- Standard formulations include capsule, tablet dosage forms made with same API form as that of innovator
- Enabled formulations examples are solid dispersions, microemulsions, nano-suspensions/emulsions, micronized API/different salt forms
- Along with API and formulation aspects, considerations also to be made for process controls

Initial Biopharmaceutics Risk Categories

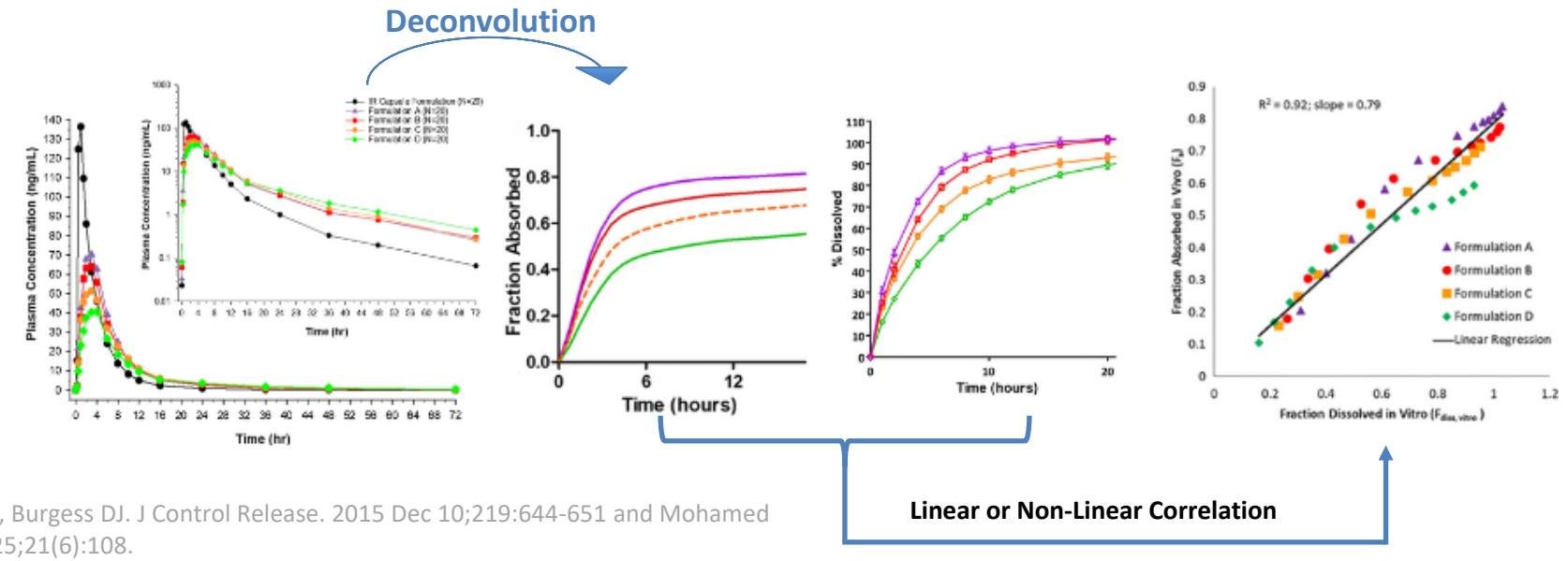
Biopharmaceutics Risk Level	Examples of Biopharmaceutics Risk Mitigation Approaches
Very Low	Standardized dissolution test
Low	Adequate method development to justify dissolution method and acceptance criterion
Medium	In vitro approach is used to mitigate the biopharmaceutics risk. Dissolution test should target to detect meaningful changes in identified critical bioavailability attributes to provide insight into the in vivo performance
High	IVIVR is used to support patient-centric dissolution test (Based on available in vitro/in vivo data and/or PBBM)
Very High	In vivo studies are used to develop IVIVC/R to support patient-centric dissolution test

Initial Risk of Modified Release Drug Products is *at least* Medium

Ahmed T, et al., AAPS J. 2023 Jul 27;25(5):77.

Conventional IVIVC

- "Gold Standard." Has well-established regulatory pathway
- Simplifies drug product development.
- Established by deconvolution and convolution methods.



Internal/external predictability

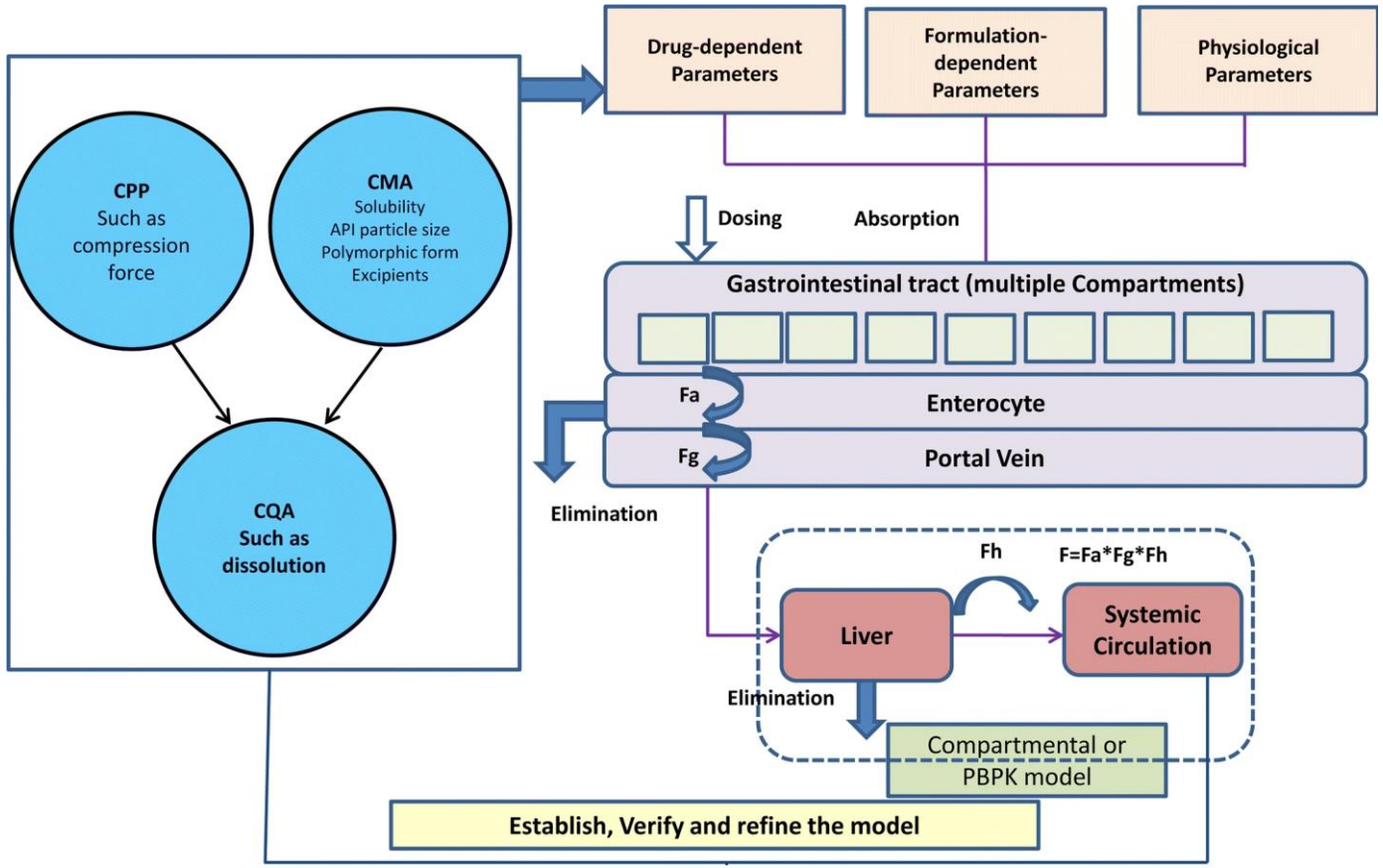
%PE < 10% for Cmax and AUC

Figure Modified from Shen J, Burgess DJ. J Control Release. 2015 Dec 10;219:644-651 and Mohamed MF, et al. AAPS J. 2019 Oct 25;21(6):108.

Physiologically Based Biopharmaceutics Modeling

Integration of physicochemical properties of drug substance and formulation characteristics with system physiological parameters to predict the absorption and pharmacokinetics (PK) of a drug product.

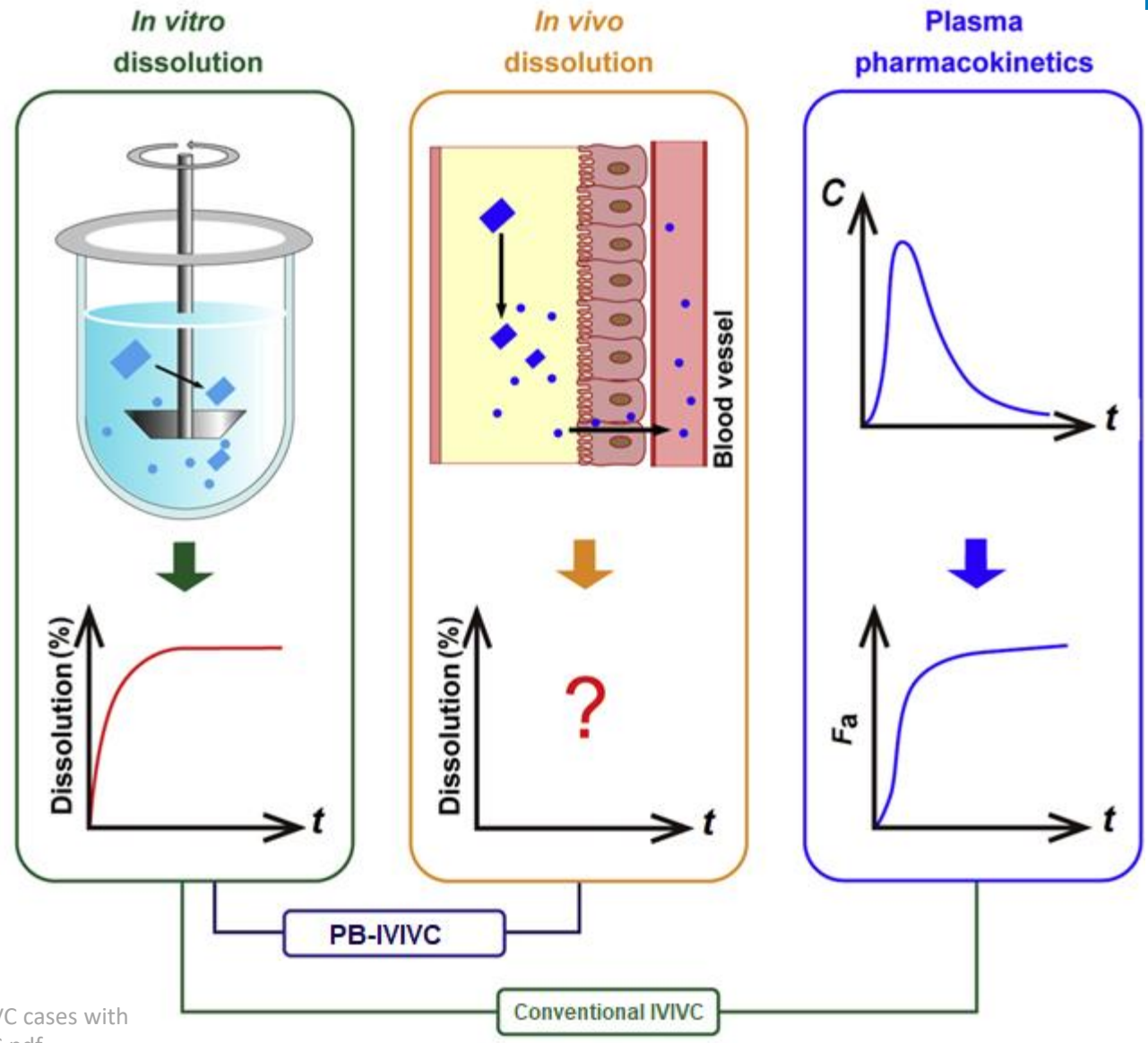
Not limited to IVIVC



Wu, D., Li, M. *Pharm Res* **40**, 321–336 (2023). Wu F. et al., AAPS J. 2021 Feb 22;23(2):31

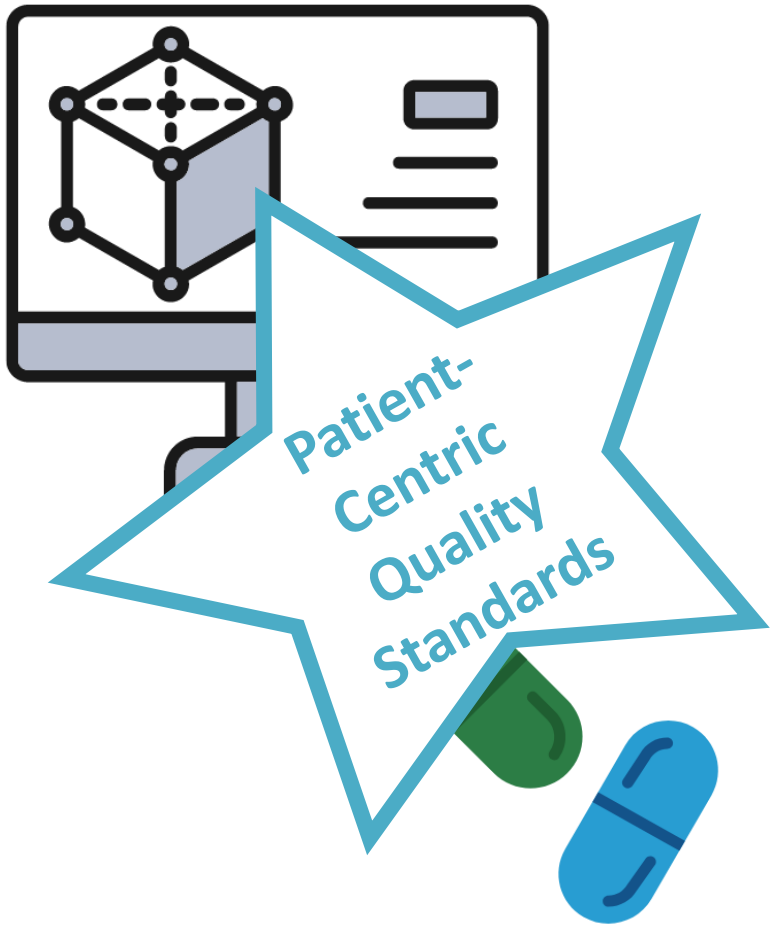
Advantages of PB-IVIVC over conventional IVIVC for MR Products

- Can be as mechanistic as our knowledge of physiology
- Can account for population variability
- Flexible in formulation changes
- Can handle complex drug delivery mechanism
- Can answer DDI questions
- Adaptable to new technologies
- Safe space built using mechanistic approach wider than conventional approaches?



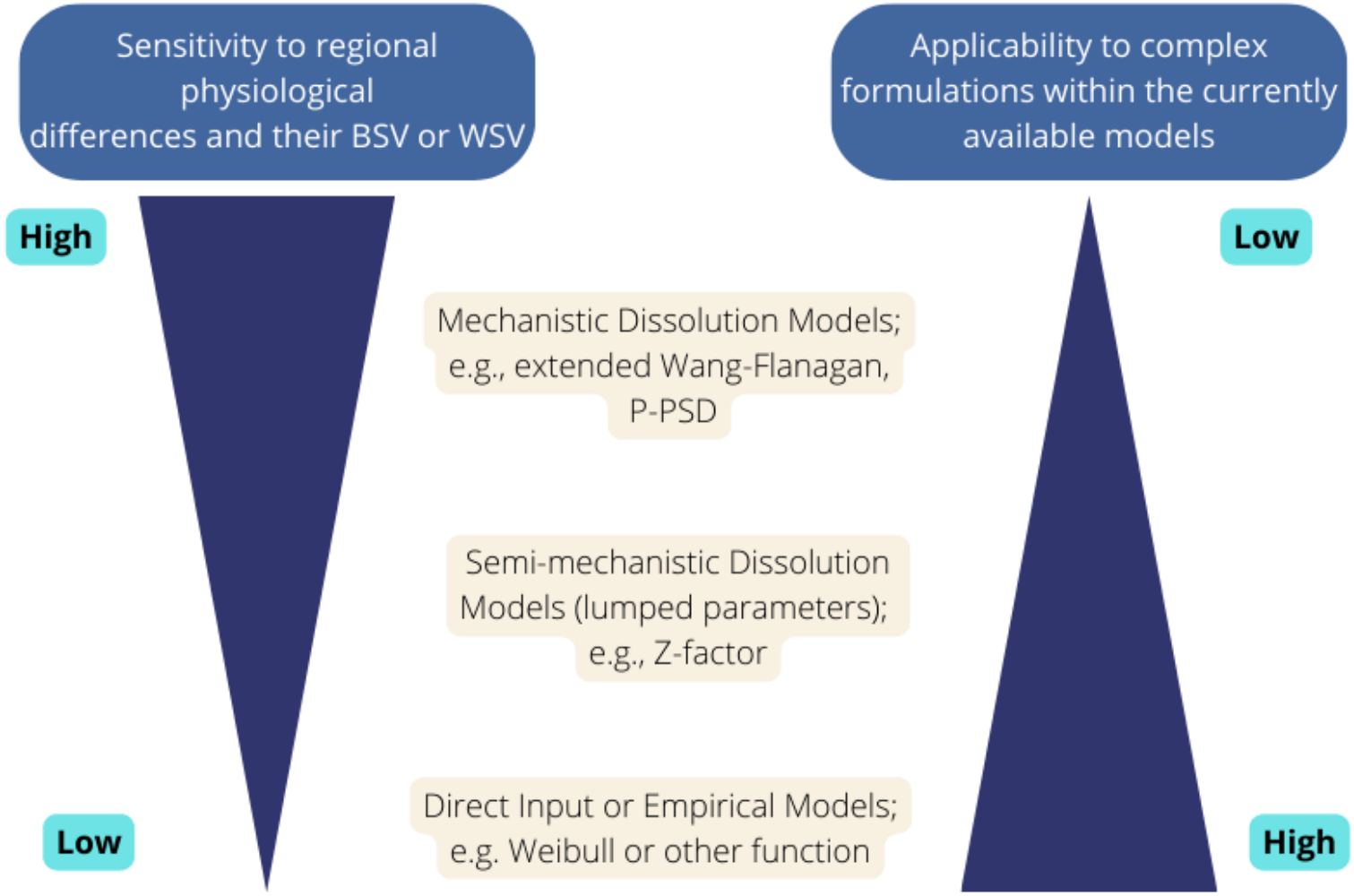
Yinqian Yang et al. Acta Pharmaceutica Sinica B, Volume 11, Issue 4, 2021, Pages 1056-1068.
Nikunj Patel et al. Conventional vs. PB-IVIVC: Revisiting some successful and failed conventional IVIVC cases with PB-IVIVC Poster at https://certara.com/app/uploads/Resources/Posters/Patel_2014_PBPWM_IVIVC.pdf

Use of Modeling for MR formulations



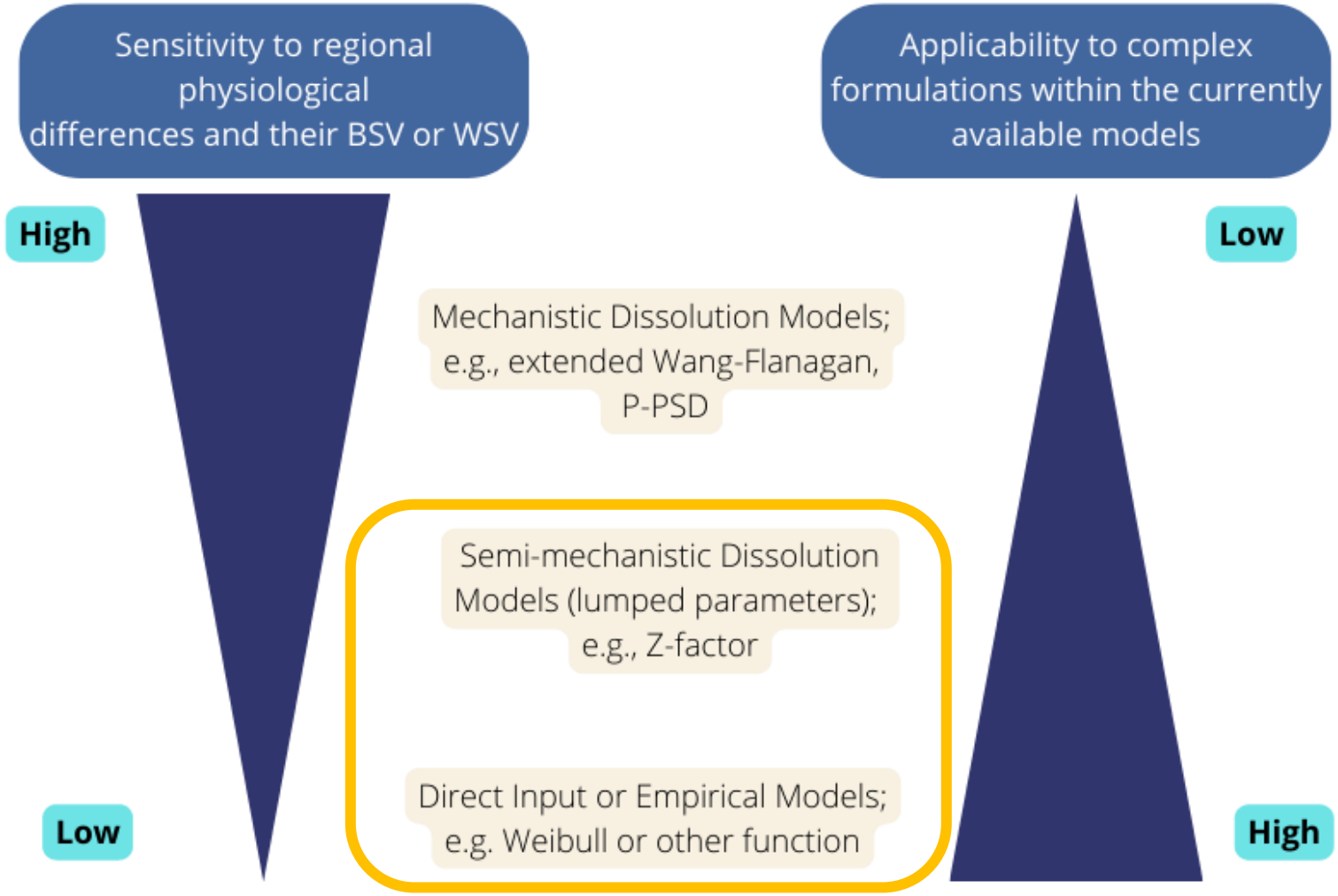
- ☐ Biowaiver
- ☐ Major Manufacturing Changes (SUPAC)
- ☐ Formulation Selection during Drug Development
- ☐ Wider Dissolution Acceptance Criteria
- ☐ Understanding Design Space
- ☐ Risk Assessment: CMAs and CPPs
- ☐ Setting Clinically Relevant DP Specifications

Dissolution Modelling Approaches



Nikunjkumar Patel et al. Oral Drug Delivery for Modified Release Formulations, First Edition, 2022, Pages 355-374.

Dissolution Modelling Approaches



Dissolution Input Options for MR Formulations

Nikunjkumar Patel et al. Oral Drug Delivery for Modified Release Formulations, First Edition, 2022, Pages 355-374.

Common Deficiencies MR PBBM

- Insufficient data to support model development and validation
- Lack of justification for changes to physiological parameters
- Lack of discriminative ability of dissolution method/Insufficient link between in vitro dissolution and in vivo outcome (lack of clinical relevance)
- Model not challenged by available or theoretical non-BE batch

Case Studies:

1. PBBM to derisk alcohol dose dumping
2. PBBM to support Clinically Relevant Specifications
3. Internal Research Project

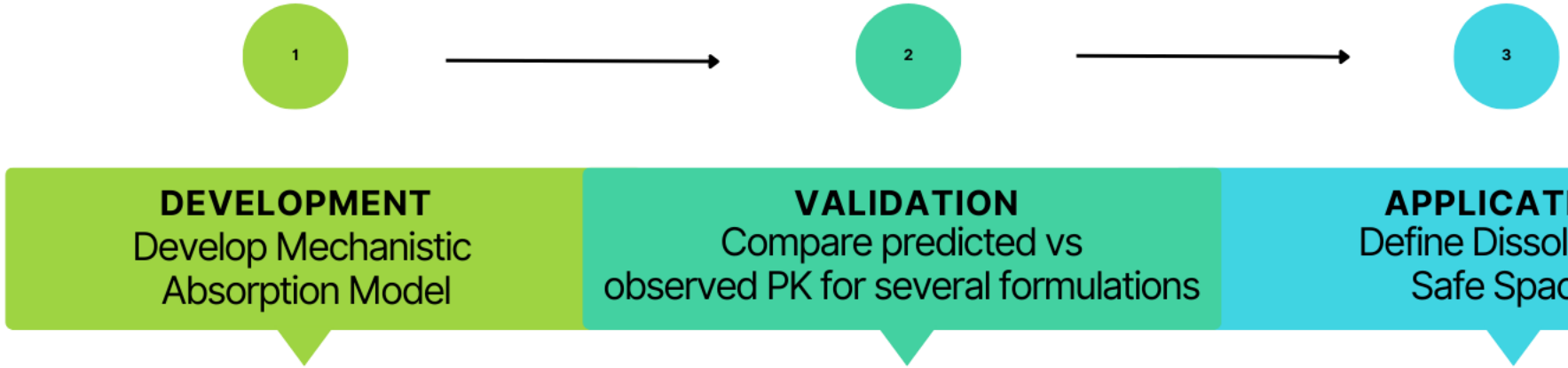
Case Studies:

1. **PBBM to derisk alcohol dose dumping**
2. **PBBM to support Clinically Relevant Specifications**
3. **Internal Research Project**

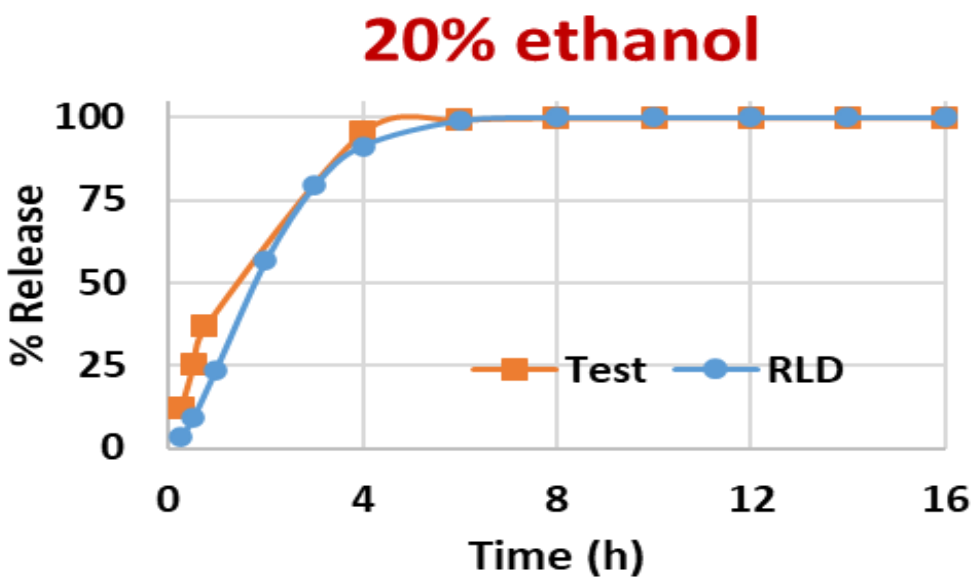
Background & Model Objective

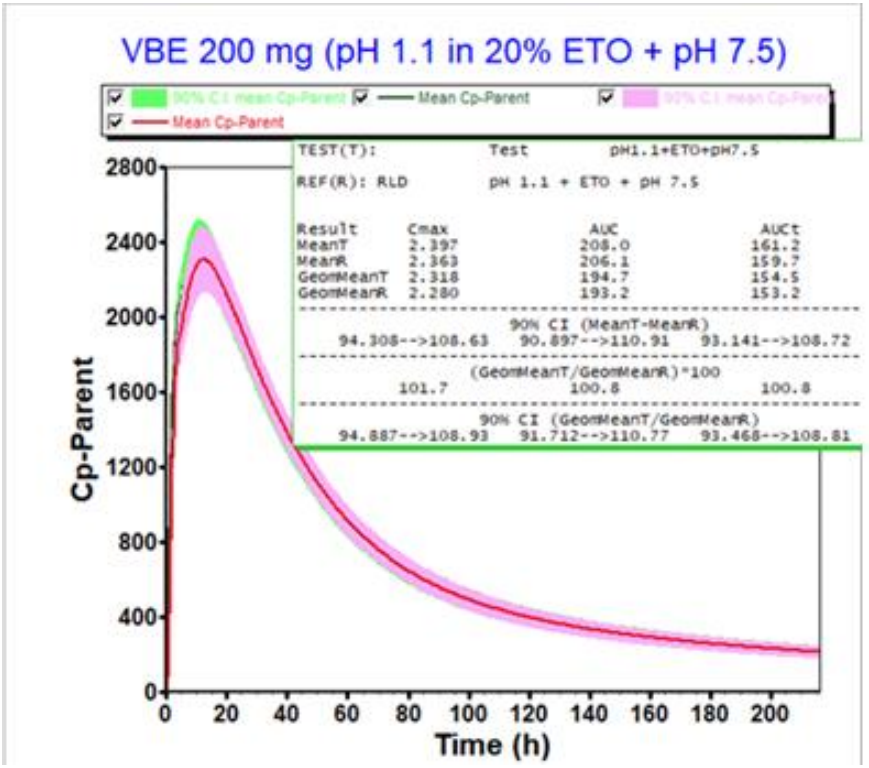
- Drug Product is a generic Extended-Release Capsule.
- Test product had increased in vitro release in 0.1N HCl with 20% ethanol in comparison to RLD.
- Mechanistic absorption model developed by reviewers to answer: Would different release observed between Test and RLD in alcohol dose dumping study result in different systemic exposure?

Model Strategy



Model Application & Summary





- Used Biphasic dissolution profiles (dissolution at pH 1.1 for 1 hour and then dissolution at pH 6.8 or 7.5) to mimic drug release in different GI segments as input for PBBM.
- Increased release of Test Product at pH 1.1 with 20% ethanol unlikely to result in significant differences in systemic exposure compared to RLD.

Case Studies:

1. PBBM to derisk alcohol dose dumping
2. **PBBM to support Clinically Relevant Specifications**
3. Internal Research Project

Background & Model Objective

- Drug Product is a generic Extended-Release Tablet.
- Mechanistic absorption model was developed to justify proposed dissolution specifications for both strengths of drug product.

Model Strategy

Disposition Model

- Literature data for IV infusion used to build disposition model.
- Three compartment model selected to define elimination.

Oral Model Development

- Physiochemical parameters measured experimentally or gathered from literature.
- Optimization of gut transporter kinetics via IR data.
- Dissolution input via Weibull

Validation Part I

- Ability of model to predict observed clinical data for IR and MR formulations in fasting and fed conditions over wide dose range (sourced from literature)

Validation Part II

- Ability of model to predict observed clinical data for modified release formulations with different release rates

Application

- Virtual Bioequivalence trials run comparing dissolution profiles generated at upper and lower bounds of proposed specifications to pivotal test formulation

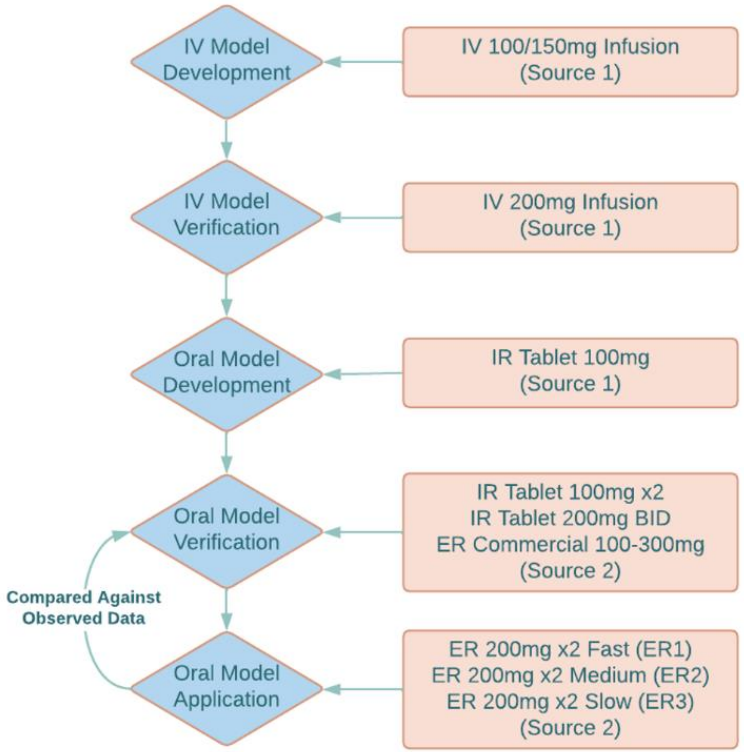
Model Summary

- Virtual BE trials indicated theoretical drug product batches with dissolution profiles at the upper or lower specifications were BE to the pivotal test formulation in fasting and fed state.
- Further, drug product batches having dissolution profiles at the upper or lower specification were predicted to be bioequivalent in the fed state.
- Proposed dissolution specifications were accepted for quality control of the drug product.

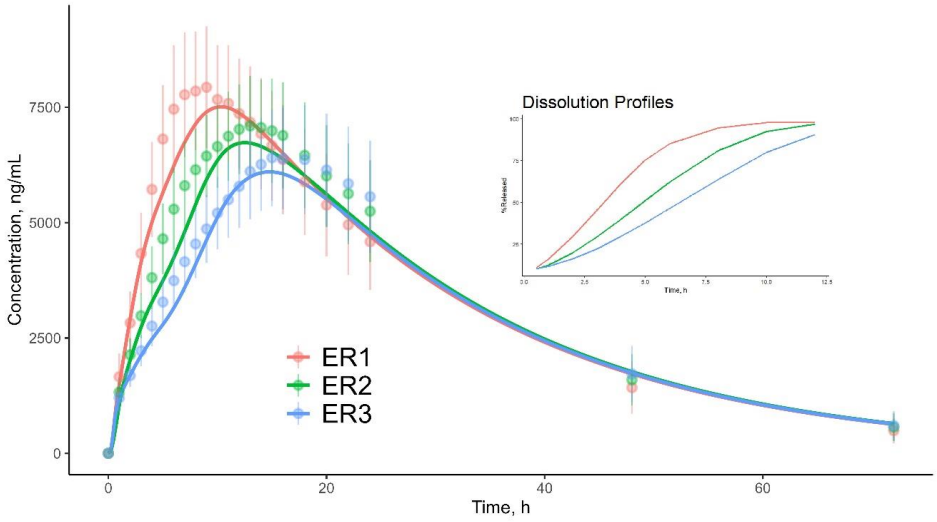
Case Studies:

1. PBBM to derisk alcohol dose dumping
2. PBBM to support Clinically Relevant Specifications
3. **Internal Research Project**

Exploring use of PBBM in predicting ER Drug Product exposure-Repurposing a Failed IVIVC

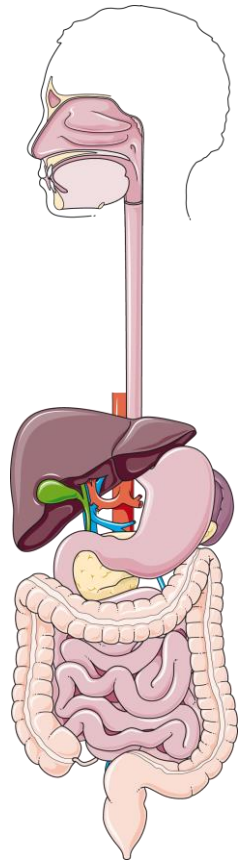


Formulation	Cmax Ratio	AUCi Ratio	Tmax Ratio	R^2
IV 200mg	-	1.03	-	0.97
IR 100mg x2	0.97	1.02	1.28	0.96
IR 200mg BID	1.09	1.10	0.96	0.88
ER Commercial 100mg	0.93	0.96	1.23	0.94
ER Commercial 200mg	0.9	0.93	1.08	0.92
ER Commercial 300mg	0.93	0.97	1.11	0.95



Additional research needed…

- Understanding complex interplay of polymers, drug, and GI components
- Biopredictive in vitro dissolution methods
- Impact of regional differences along the gastrointestinal tract



Acknowledgements

- Dr. Yunming Xu
- Dr. Kimberly Raines
- Dr. Bhagwant Rege
- Division of Biopharmaceutics
- DQMM
  - Dr. Sherin Thomas and Dr. Fang Wu

Thank you!

Questions for Discussion

Q1. Current applications of PBBM for MR formulations – Confidence & room for expansion?

a. What are the considerations when establishing PBBM for MR product? Does the release mechanism impact the strategy of building PBBM for MR products?

b. What is the usefulness/confidence of PBBM for alcohol induced dose dumping and food predictions for MR formulations? Waive in vivo studies?

Q2. How to account for regional/colon absorption in PBBM for ER formulations - Current status and how to improve

a. What factors impact regional absorption and should be incorporated in model development and validation?

Q3. Which modeling approach is more feasible for MR product, traditional IVIVC or PBBM?

a. How to best incorporate mechanistic absorption modeling with IVIVC, i.e., PB-IVIVC

Q4. What is the best approach for integrating in vitro dissolution data into PBBM for MR products?

a. What is the suitability of non-mechanistic vs mechanistic dissolution integration approaches (e.g., Weibull to Z-factor to extended Wang-Flanagan)?

b. What are the limitations in model applicability based on integration of in vitro dissolution (i.e., does empirical parameterization of the in vitro release rate decrease our confidence in the model's ability to predict/simulate population exposure in vivo?)

Q5. Considerations for higher quality of in vitro data inputs into PBBM for more reliable in vivo PK predictions and formulation performance comparisons e.g., bile salt solubilization ratio considerations for PBBM of Modified Release Dosage forms

Q6. What is an appropriate prediction performance for ER models?

a. What criteria should be evaluated (Cmax, AUC, Tmax, Partial AUCs, etc.) and how should it be evaluated (AFE, PE, AAFE, etc.)?