Dissolution Methodologies from Biorelevant to Quality Control – The Challenges and Gaps

Xujin Lu[1], Jian-Hwa Han[2], Danna Mattocks[3]

[1] Analytical Science, DPST, Bristol-Myers Squibb Company

[2] NCE-Analytical R&D/Dissolution Group, AbbVie

[3] Product Development and Manufacturing, TherapeuticsMD

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Outline:

- **Functions and roles of dissolution testing**
  - Dissolution as a tool for formulation development
  - Dissolution as a tool for drug product quality control
- **Dissolution methodology: biorelevant vs. QC**
- **From biorelevant to QC – gaps and challenges**
- **From biorelevant to QC - bridging**
  - Phase relevant dissolution consideration
  - From biorelevant to QC – when it works?
  - Case studies for QC method optimization
- **Summary**

Functions and roles of dissolution testing

Dissolution as a tool for formulation development

- Biopharmaceutics risk assessment around TPP
- Speed up evaluation of biorelevant performance of formulations
- Save animal resources by screening out poor-performing prototypes
- Evaluate more prototypes and variations to enhance lead formulation quality
- Potential IVIVR to guide further formulation development

Dissolution as a tool for drug product quality control

- Used to confirm the batch-to-batch consistency
- Highly Discriminating to formulation and process differences that affect the drug product quality
- Support stability studies to set meaningful dissolution specification
- Establish IVIVC for BE and biowaiver in later stage and DP lifecycle

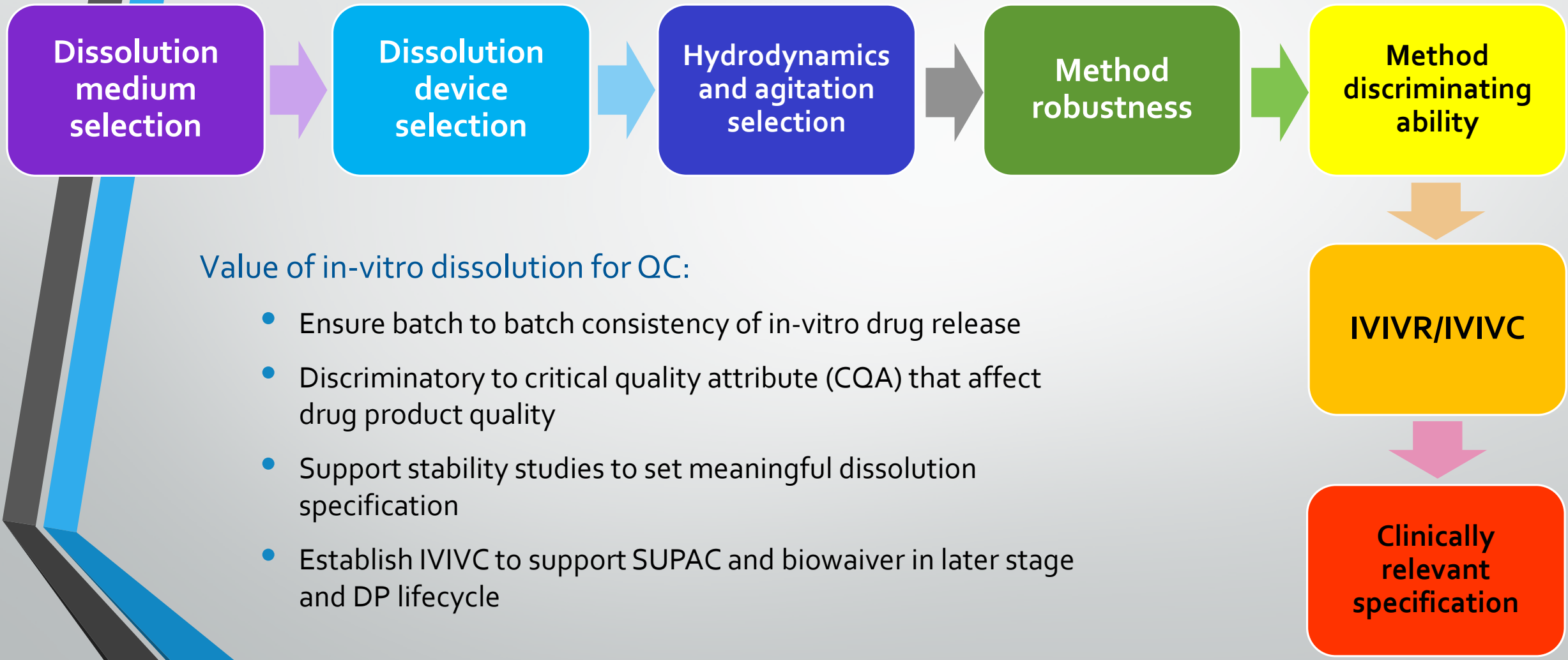
Formulation Development

In vitro dissolution screening → **In vivo animal PK study** → **In silico modeling** → **Guide clinical study design**

Value of biorelevant in-vitro dissolution:

- Biopharmaceutics risk assessment around TPP
- Evaluation of low BA: to explore enabling technology selection (amorphous, lipid, CPT)
- Food effect model (to measure FE ratio)
- pH-transfer model (to measure pH-effect ratio)
- Specialized models: pediatric dissolution, etc.
- Guide product development activities

Dissolution Method Development



Value of in-vitro dissolution for QC:

- Ensure batch to batch consistency of in-vitro drug release
- Discriminatory to critical quality attribute (CQA) that affect drug product quality
- Support stability studies to set meaningful dissolution specification
- Establish IVIVC to support SUPAC and biowaiver in later stage and DP lifecycle

Biorelevant Dissolution vs. Quality Control Dissolution

	Biorelevant Dissolution	Quality Control Dissolution
Purpose	Predicting bio-performance	Ensuring batch to batch consistency
Device	Compendial and non-compendial	Compendial
Medium	Biorelevant media	Conventional buffers w/ or w/o surfactant
Method development	Universal, conditions chosen to mimic in-vivo GI tract	Product specific, conditions chosen to detect process and stability changes
Profile	Non-sink, ranking order	3-5 sink, full release
Early phase	Formulation selection, CQA identification	Clinical batch release
Later phase	IVIVC/IVIVR	Correlating with IVIVC method

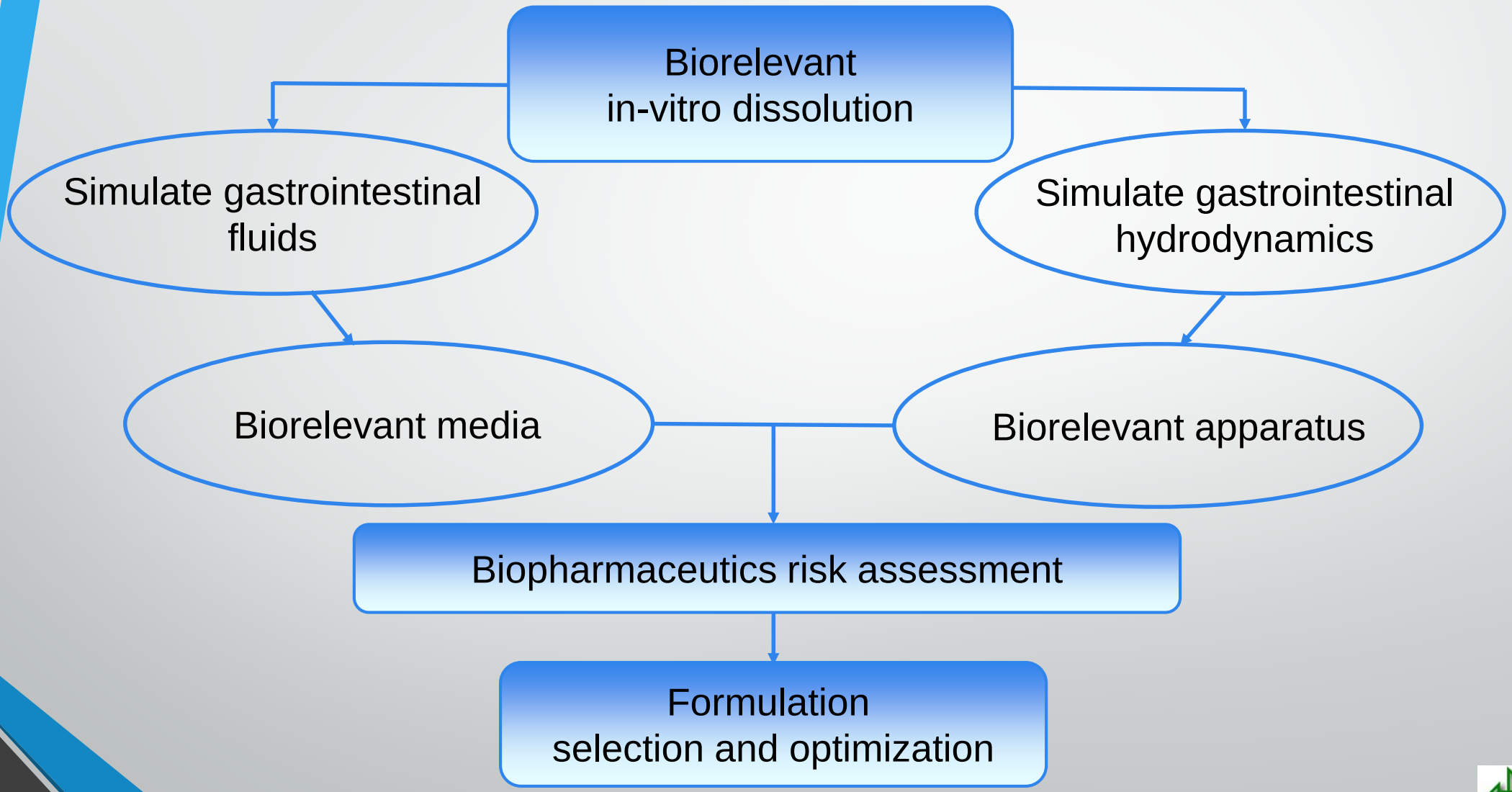
QC Dissolution

- USP dissolution apparatus :
  - USP 1: Basket
  - USP 2: Paddle
  - USP 3: Reciprocating cylinder
  - USP 4: Flow through cell
  - USP 5: Paddle over disk
  - USP 6: Cylinder
  - USP 7: Reciprocating Holder
- Customized methods:
  - Sample and separate method
  - Dialysis sac method

Ref. J-H Han, EAS 2015

- Conventional buffers:
  - 0.1 N HCl
  - Acetate pH 4.5
  - Phosphate pH 6.8
  - Buffers at the other pH
- Method for QC dissolution testing:
  - May not represent all aspects of the physiological conditions of the routes used for drug administration
  - Difficult to correlate with in vivo data

Biorelevant In-vitro Dissolution

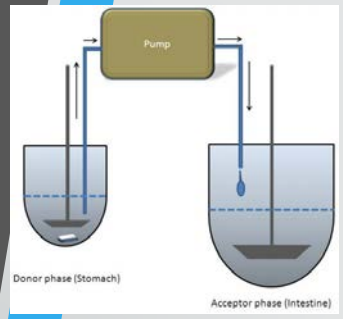


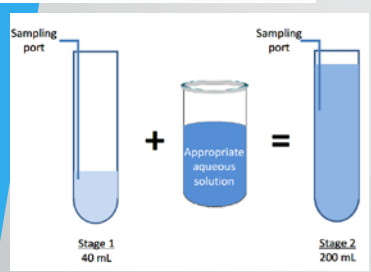
Simulated Biological Fluids

Drug Delivery Route	Simulated biological fluids with potential for use in dissolution testing
Parenteral:	Simulated body fluid
	Simulated synovial fluid
	Simulated plasma
Oral:	Simulated gastric fluid (USP)
	Fasted-state simulated gastric fluid **(FaSSGF)**
	Fed-state simulated gastric fluid
	Simulated intestinal fluid
	Fasted-state simulated intestinal fluid **(FaSSIF)**
	Fed-state simulated intestinal fluid **(FeSSIF)**
	Simulated colonic fluid
	Fasted-state simulated colonic fluid
	Fed-state simulated colonic fluid
Buccal and sublingual:	Simulated saliva
Pulmonary:	Simulated lung fluid
Vaginal:	Simulated vaginal fluid
	Simulated semen
Ophthalmic:	Simulated tears
Skin:	Simulated sweat

Ref. M. Marques, R. Loebenberg, M. Almukainzi, *Diss. Technol.*, 2011(8),15-28.

Biorelevant Dissolution Apparatus

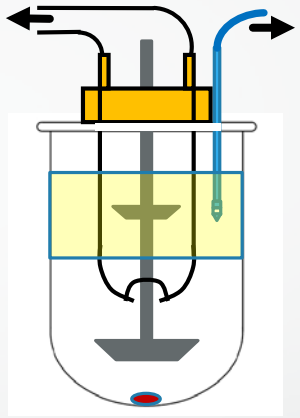




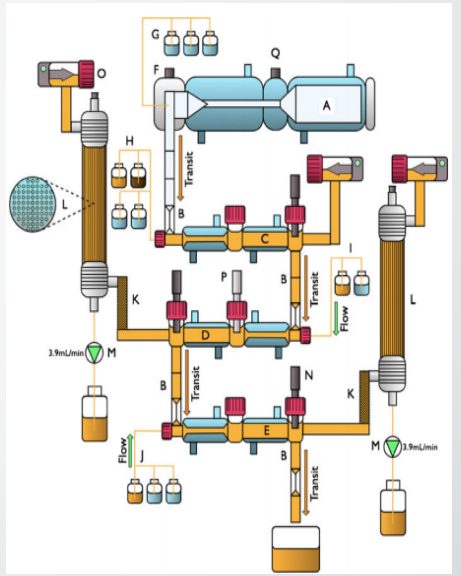
Ref. Kostewicz 2004, Georgaka, 2016

Ref. Agilent and Distek brochures

Ref. pION 2012

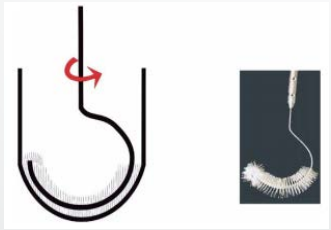


Ref. X. Lu 2016



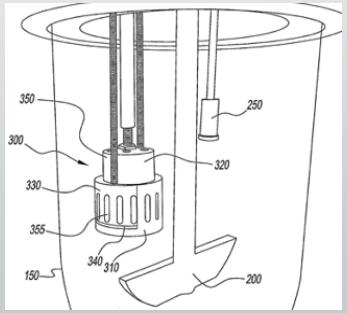
Ref. P.A. Dickinson, 2012

Ref. B.R. Pezzini, 2015

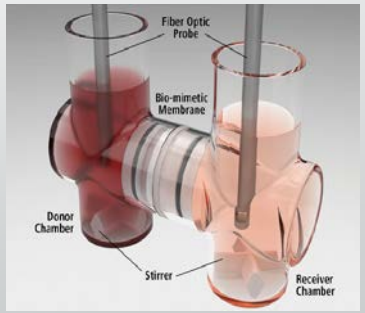


Ref. S.A. Qureshi, 2004.

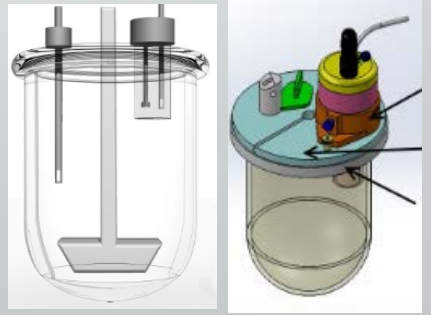
Sotex CE100



Ref. M. Burke, 2013



Ref. pION 2016.

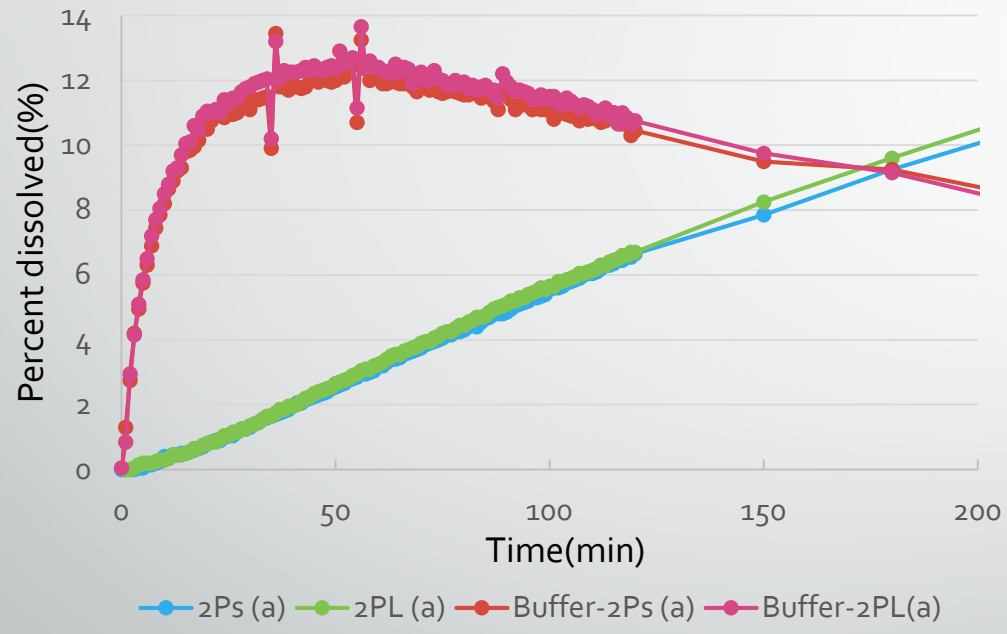


Ref. pION 2017.

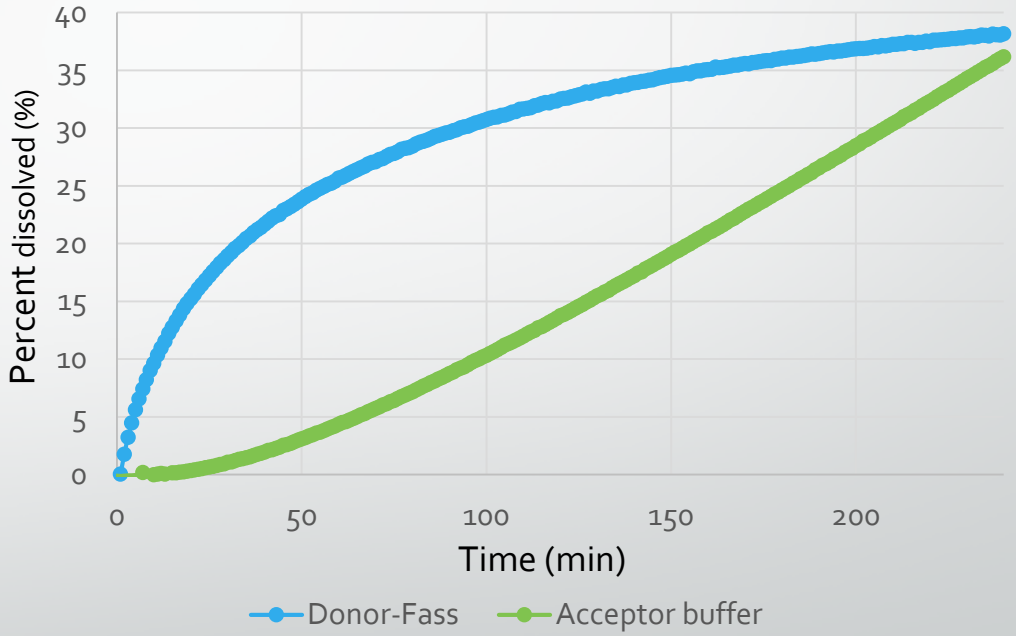
Biorelevant Dissolution - Bioavailability Assessment

BMS-Drug A: 200-mg Tablets

Biphasic dissolution, 50 mM Sodium phosphate buffer/octanol



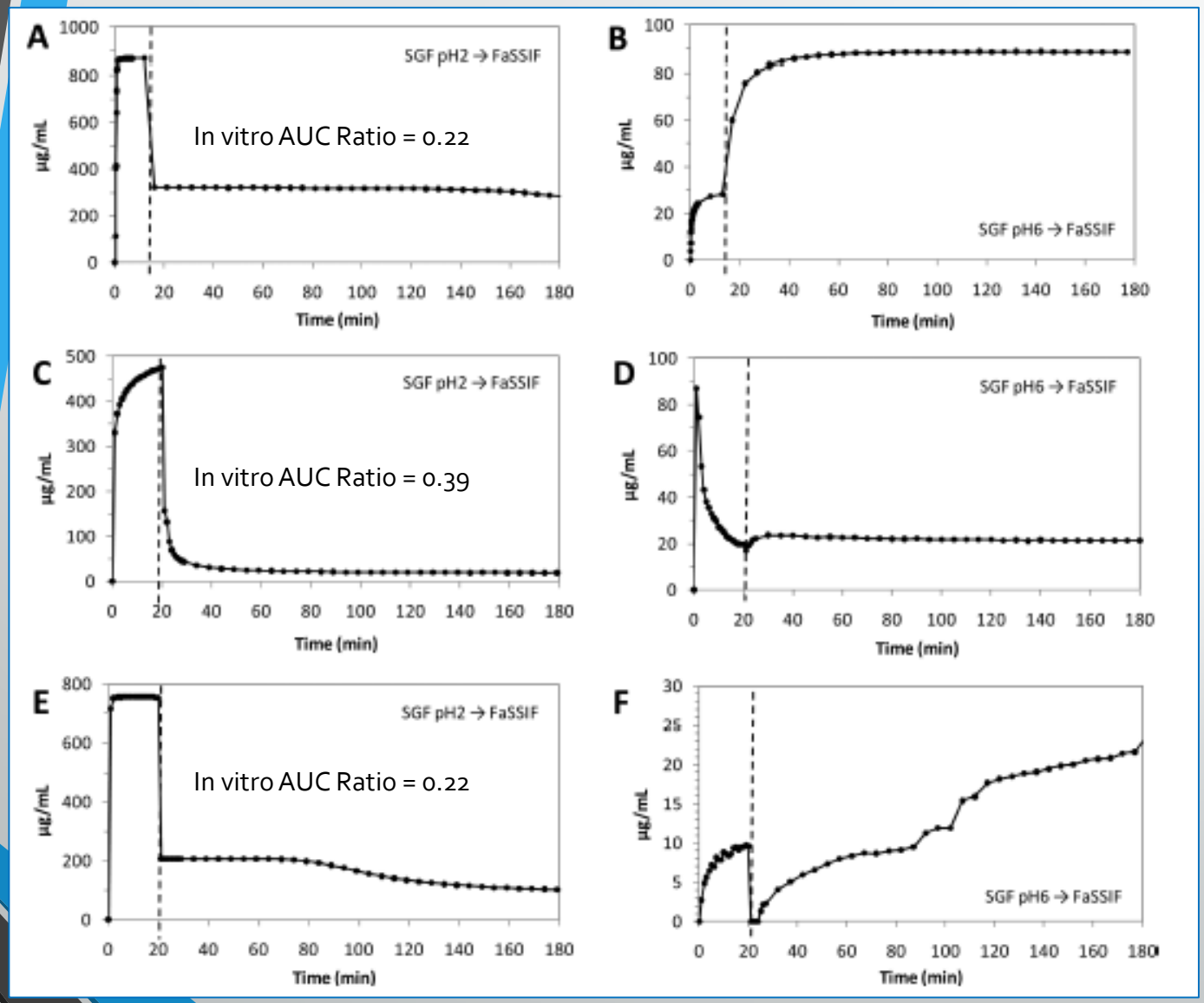
Macro Flux dissolution, FaSSIF/Acceptor buffer solution



- The two biorelevant dissolution methods serve the same function for ranking formulation bioavailability.
- For G+ simulation and modeling usage, the different donor/receptor profiles from the same formulation may give different predictions.

Biorelevant Dissolution – Two-Stage Single-Compartment

for pH Effect Assessment



In Vitro–in Vivo Correlation: pH-Effect Risk Categories

risk category	*in vitro* AUC Ratio	clinical AUC or C_{max} ratio
high	<0.2	<0.5
moderate	0.2–0.5	0.5–0.8
low	>0.5	>0.8

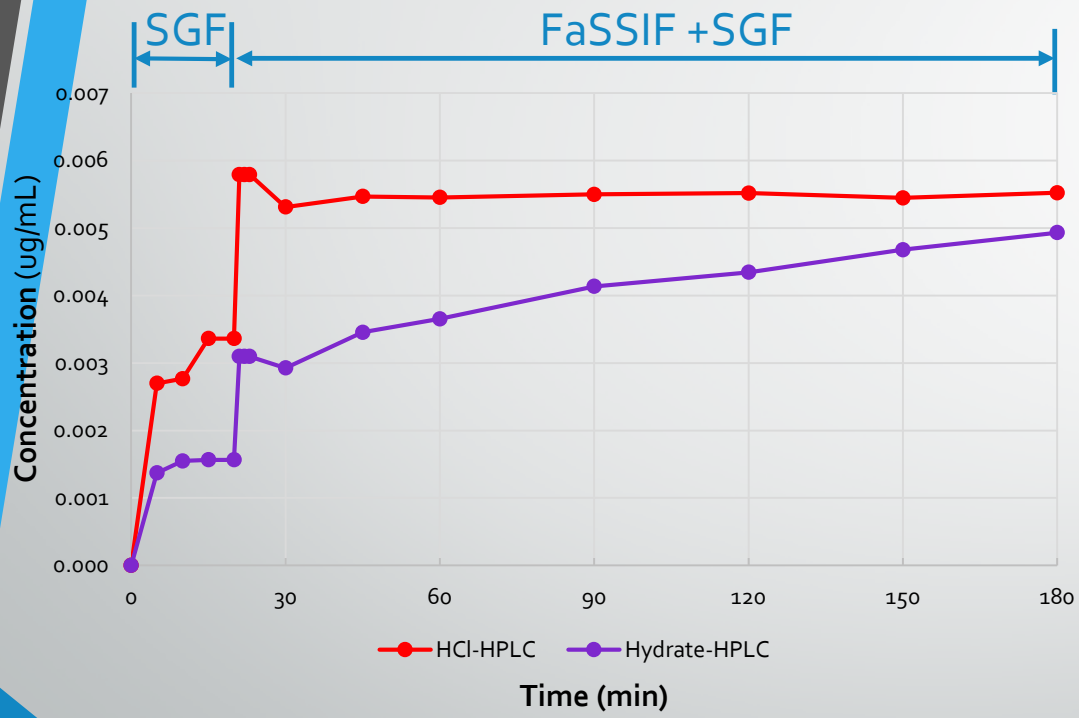
- Kinetic dissolution from in vitro micro dissolution test for model compounds: Gefitinib (A,B), Erlotinib (C,D), Ketoconazole(E,F).

Ref. N. Mathias et al. Mol. Pharm. 2013

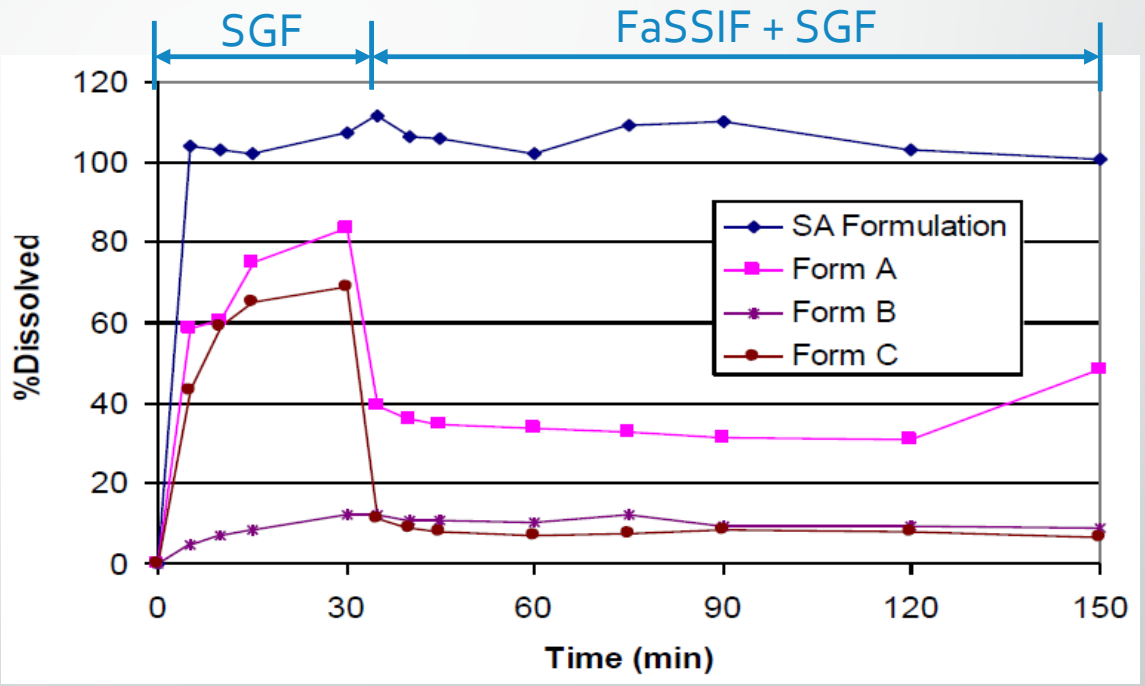
Biorelevant Dissolution – Two-Stage Single-Compartment

for pH Effect Screening

Weak Basic Drug Substance B Evaluation



Weak Acid Drug C Formulation Evaluation

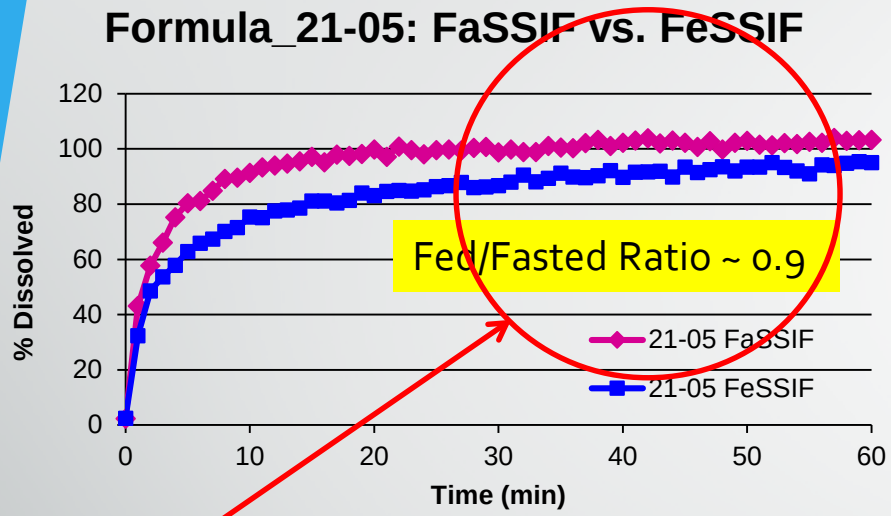


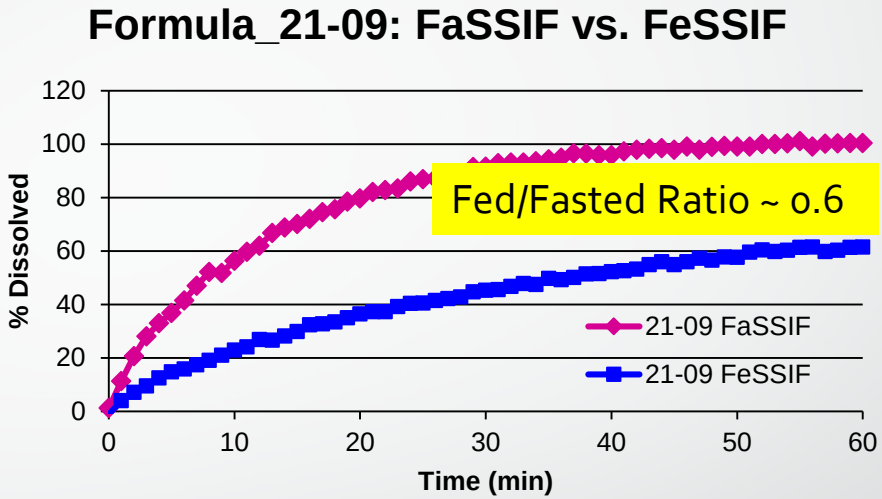
Ref. Y. Mao, AAPS 2009

- The pH transfer model operates under non-sink condition to evaluate supersaturation or precipitation.
- Non-sink condition is not acceptable in QC dissolution methods.

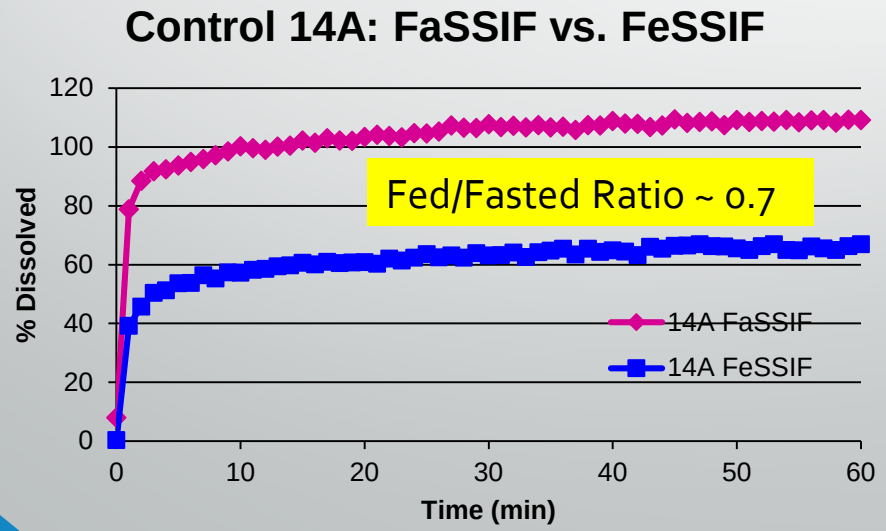
Biorelevant Dissolution – Micro Dissolution

for Food Effect of BMS-Drug B: Lipid Tablet Using Co-Processed API





Food effect is less significant.



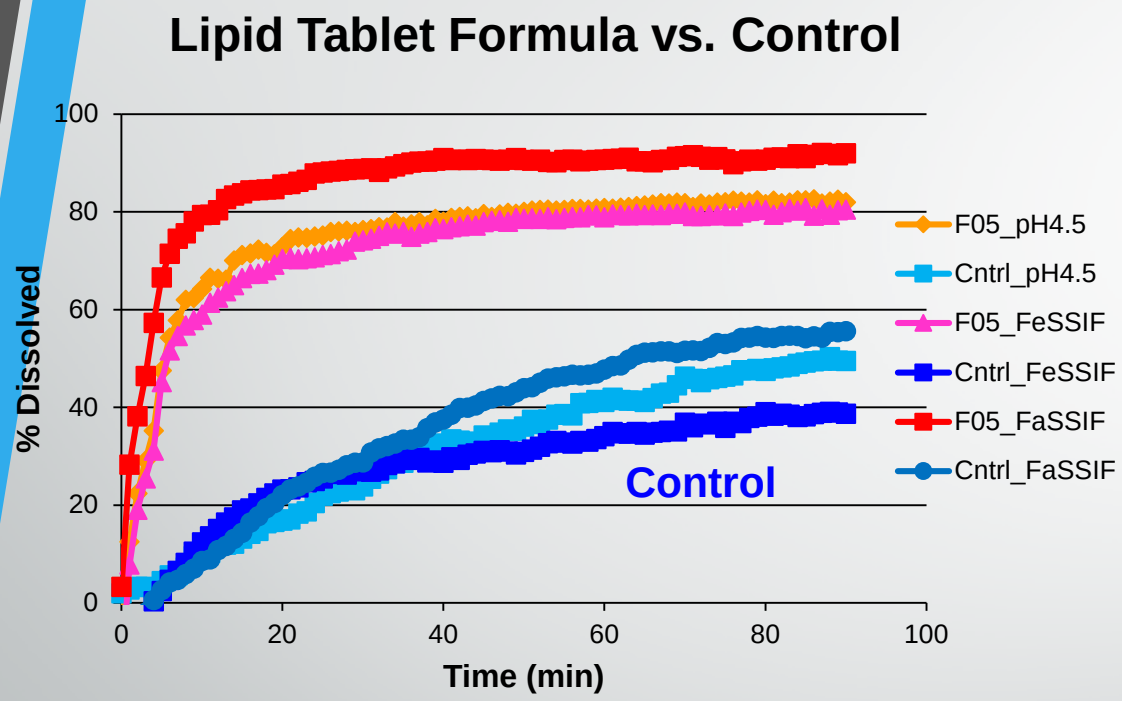
In Vitro, In Vivo, and Human Correlations for FE risk

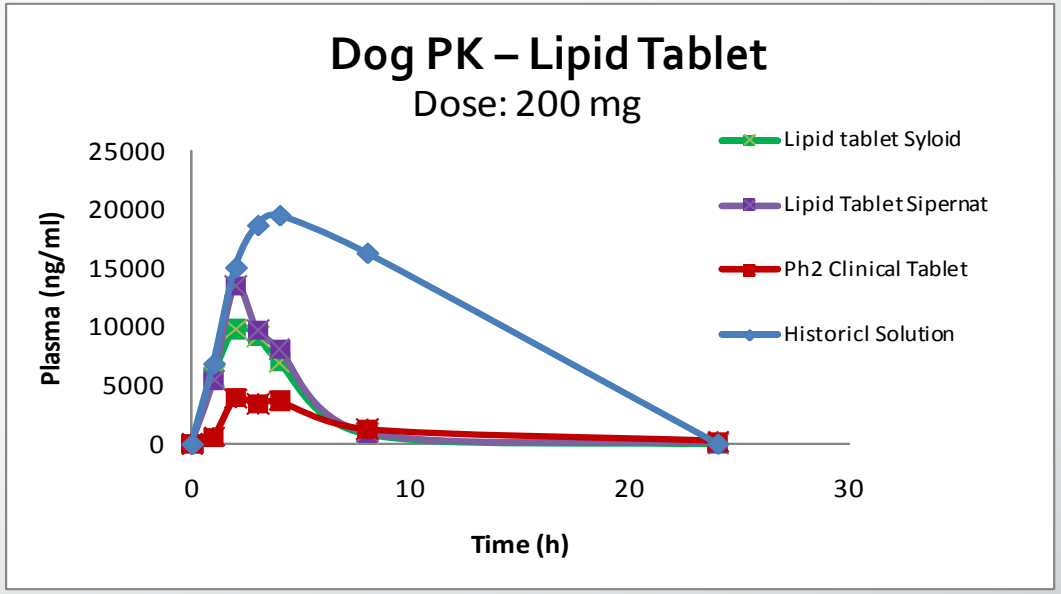
	In Vitro dissolution FE ratio	Dog PK FE ratio	Human PK FE ratio
Positive FE risk	>1.5 (9)	>1.5 (8)	>1.2 (11)
No FE risk	0.8–1.5 (9)	0.8–1.5 (5)	0.8–1.2 (8)
Negative FE risk	<0.8 (2)	<0.8 (2)	<0.8 (3)

Ref. N. Mathias et al. AAPS J. 2015

Biorelevant Dissolution – Micro Dissolution

for Food Effect of BMS-Drug B: Lipid Tablet Using Co-Processed API

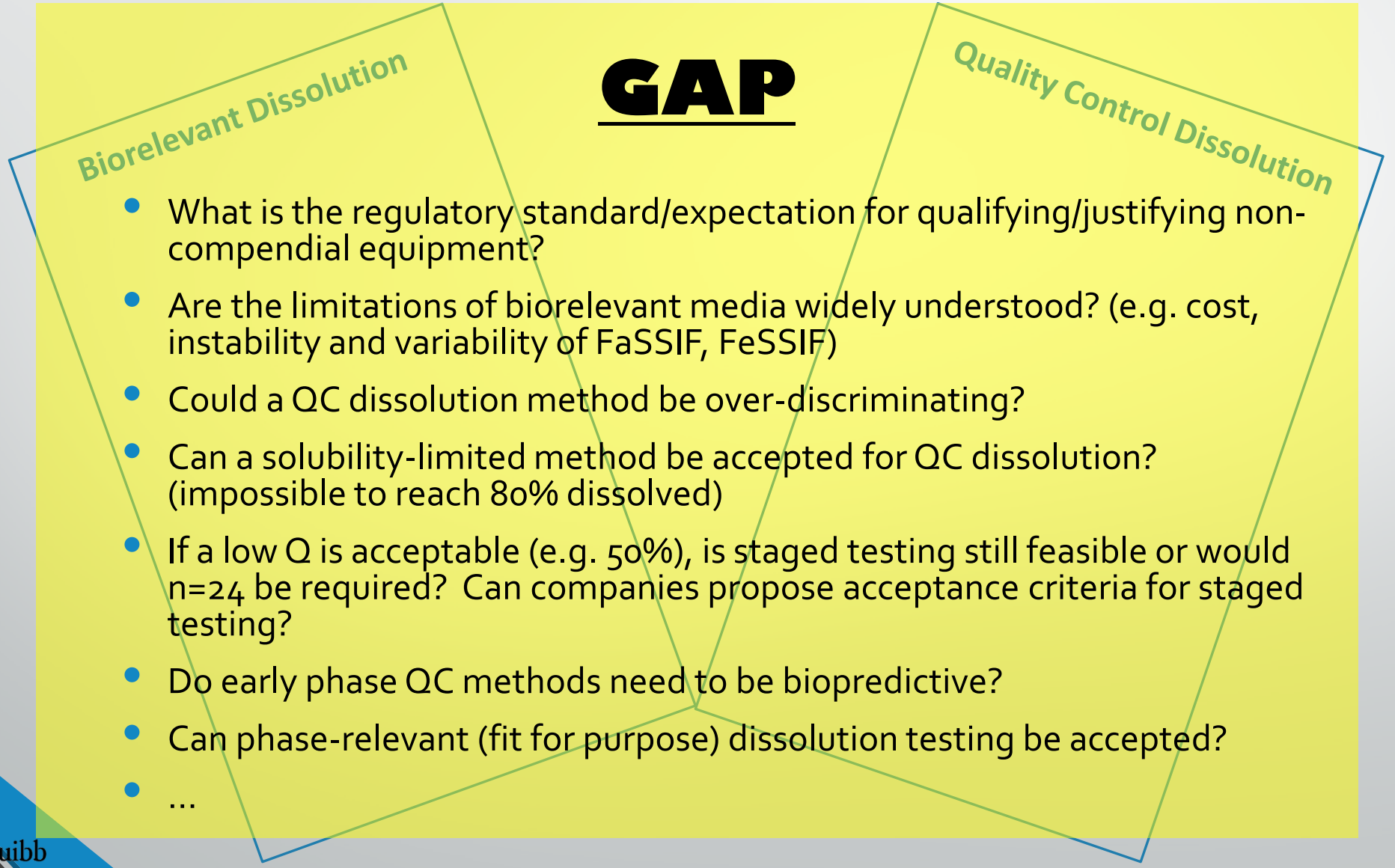




Dog study report by Y. Xu/N. Mathias

- The food-effect model operates through two dissolution runs (One in FaSSIF, another one in FeSSIF).
- The purpose is to compare different prototype formulations.

Biorelevant Dissolution vs. Quality Control Dissolution



- What is the regulatory standard/expectation for qualifying/justifying non-compendial equipment?
- Are the limitations of biorelevant media widely understood? (e.g. cost, instability and variability of FaSSIF, FeSSIF)
- Could a QC dissolution method be over-discriminating?
- Can a solubility-limited method be accepted for QC dissolution? (impossible to reach 80% dissolved)
- If a low Q is acceptable (e.g. 50%), is staged testing still feasible or would n=24 be required? Can companies propose acceptance criteria for staged testing?
- Do early phase QC methods need to be biopredictive?
- Can phase-relevant (fit for purpose) dissolution testing be accepted?
- …

From Biorelevant to QC – when it works?

- **From biorelevant to QC - It may work:**
  - When drug is in BCS 1 or 3
    - When bioavailability is not dissolution limited
    - When conventional buffer solutions are used as the medium
    - When no surfactant is needed in dissolution
  - When FDA new guidance (August 2015) is followed
    - Dissolution Testing and Specification Criteria for Immediate-Release Solid Oral Dosage Forms Containing Biopharmaceutics Classification System Class 1 and 3 Drugs
    - Biorelevant specifications: For BCS 1, Q=80% in 30 min; For BCS class 3, Q=80% in 15 min.
  - When EMA reflection paper (May 2016) is followed
    - Dissolution specification (75% release in 45 min) for generic oral immediate release products
    - Provided details for development of dissolution method and test conditions and discriminatory power.

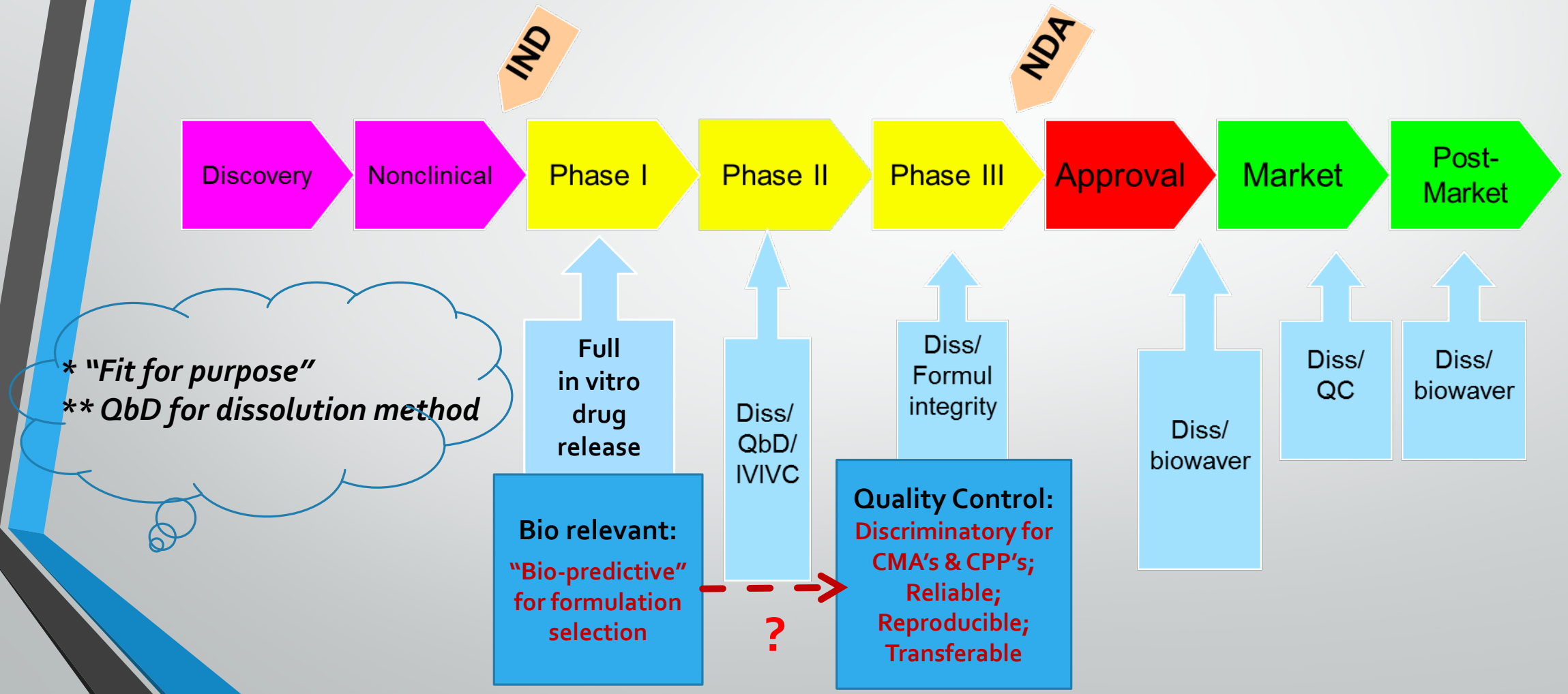
From Biorelevant to QC – challenges

- **From biorelevant to QC – when is it challenging?**
  - BCS II and IV
  - When bioavailability is dissolution rate limited
  - When drug release is pH dependent or affected by food
  - When surfactant is needed in the medium of the QC method
  - When IVIVC can not be established
  - Biorelevant dissolution for formulation development not suitable for QC
  - Over emphasizes discriminating ability for processing variables without biorelevance or clinical relevance

How to overcome the challenges and bridge the gaps between biorelevant dissolution to a method for Quality Control?

Phase Relevant Dissolution Consideration

The product development of different projects have different needs at different phases.



Source: Dr. Patrick Marroum with some additions.

Phase Relevant Dissolution Considerations

	FIH (Pilot stage)		Phase 1b-2b (Development)		Phase 2b-3 (Late Stage)	
	Goal	**Methodology**	**Goal**	**Methodology**	**Goal**	**Methodology**
Focus	Physical/Chemical properties of API, FIH formulation		Formulation screening and variability and process sensitivity assessment		Process control, formulation design space and control strategy	
Biorelevant Dissolution	Bioavailability assessment for crystal form, salt form, particle size, amorphous dispersion, in-vivo stability	Micro dissolution or 250 mL in FaSSIF, comparison ranking	Evaluation of risks in low bioavailability, pH effect, food effect, and drug delivery	FaSSIF and FeSSIF, pH transfer model, USP 3 or 4	IVIVC development, in-vitro data for modeling and in-vivo correlation	Deconvolute clinical data, pivotal batch dissolution, model development
QC Dissolution	Full drug release of formulation	Standard apparatus and conditions for BCS 1 and 3, minimal modifications for BCS 2 and 4. Disintegration?	Reliable and reproducible method, differentiability, method lock for LTSS.	Method justification according to formulation/process understanding and clinical results. QbD for method.	Method sensitive to CMAs and CPPs capable to reject non-bioequivalent batches, set clinical relevant spec.	Correlating with IVIVC method

Bridging Biorelevent Dissolution with QC Dissolution

- Method Attributes - the dissolution method space
  - Understanding the purpose and implementation
    - Method Design / Apparatus Selection
    - Media Selection (pH's, salt effect, surfactant effect, etc.)
    - Agitation – RPM, DPM, Flow Rate
  - Other considerations
- Biorelevant ➔ QC ➔ Clinical relevant – Case studies
  - **Case A, No Discrimination – BCS 1/3**
    - QbD – Design Space; Control Strategy (CMA's & CPP's) => Safe Space
  - **Case B, Overly Discriminating Dissolution Method**
    - Method limitation due to certain factors. Design Biostudies to support Dissolution
  - **Case C, IVIVR/IVIVC Approach**
    - Dissolution Method Space
    - Formulation Design
    - Biostudy to support Dissolution
  - **Case D, BCS 2/4; IR: Development Process**

Case A – BCS 1/3 Rapid Dissolving Product

Dissolution Conditions*

- App 2
- 50 RPM
- Medium Volume: 500 mL

Very mild condition ➔ Similar Profiles

*Follow FDA 2015 Draft Guidance

Study Design

- Bioavailability
- Stability
- Manufacturability

Confirmed BE for major Process change (i.e. WG vs. DC & no difference in dissolution)

DOE to secure the "Safe Space"

Case A – DOE for Extend the Design Space

(At least 10~15% of the target!)

Dissolution Conditions

- App 2
- 50 RPM
- 500 mL
  - 0.1N HCl
  - pH 4.5
  - pH 6.8

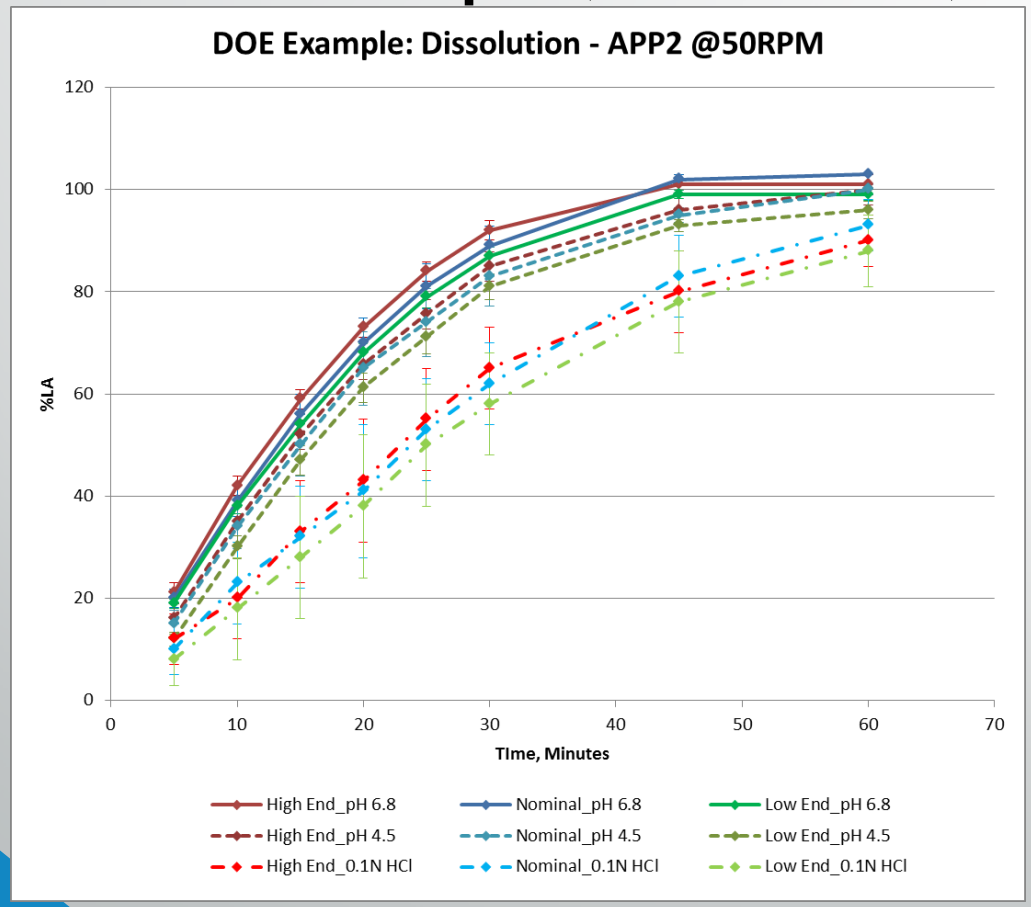
CMA's CPP's & Stability

- API Particle Size
- API Bulk Density
- Functional (Critical) Excipient Amount
- Filler Amount
- Granule PSD / Ribbon Solid Fraction
- Tablet Hardness
- Lubricant
  - Level/Amount
  - Blending Time
- **Stability**

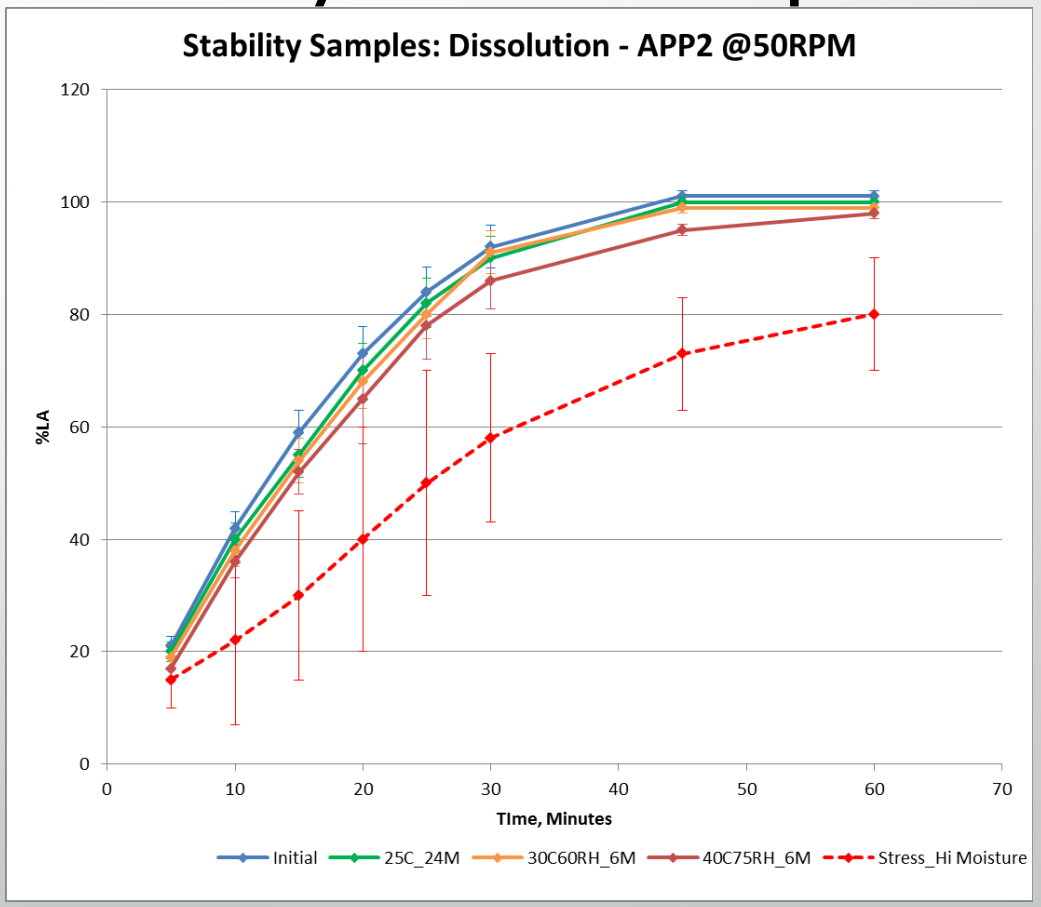
Case A – DOE / Dissolution Results

(Method Shows Discrimination against Stability Samples)

Disso – Example (All Similar!)

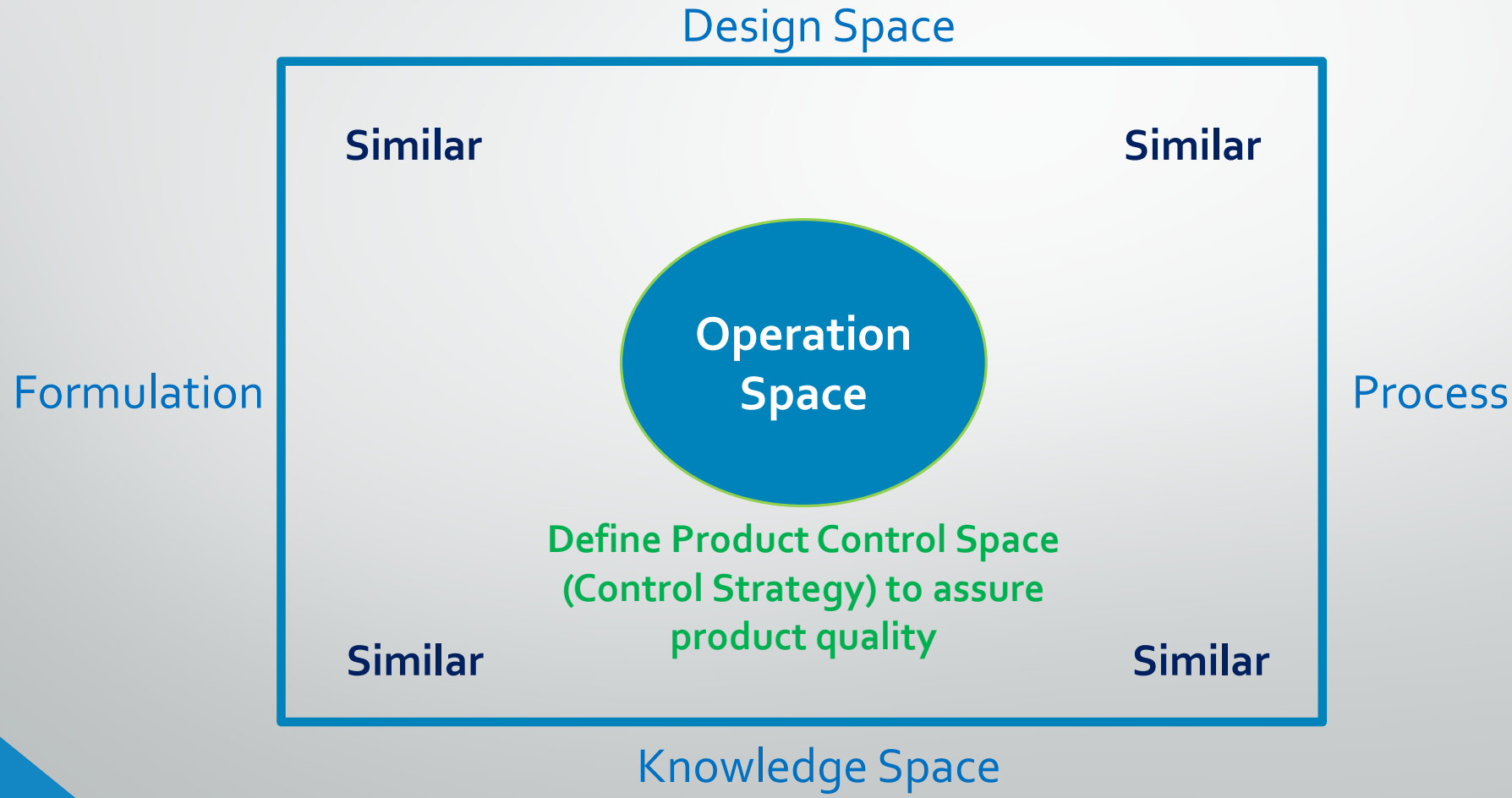


Stability & Stress Samples



Case A: Robust Product ➔ Safe Space

No difference in dissolution and assume similar in vivo performance



Case B – Overly Discriminatory Dissolution

Dissolution Conditions Explored

- BCS 1/3
- App 1, App 2, App 3
- RPM's & DMP
- Medium pH's (i.e. 0.1N HCl, pH 4.5, pH 6.8)
- Medium Volume: 500 mL

Semi-Solid Dosage Form ➔ Final Method Selected for Discrimination against CMA's / CPP's and Better method reproducibility (sample handling)

Study Design

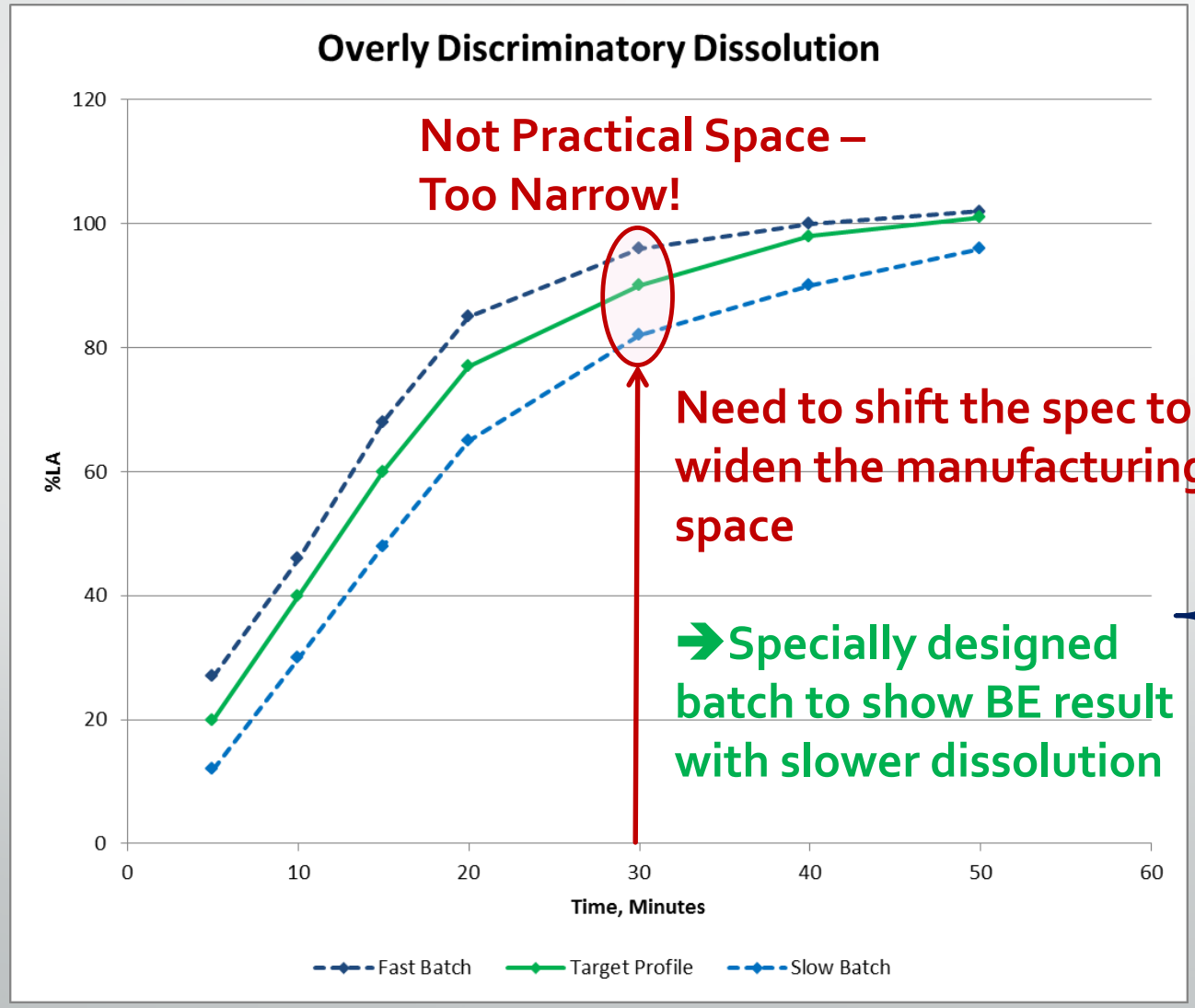
- Bioavailability
- Stability
- Manufacturability

Confirmed BE for Original Formulation and Improved Formulation

➔ Design Biostudy to support Manufacturability (Design Space/Control Strategy)

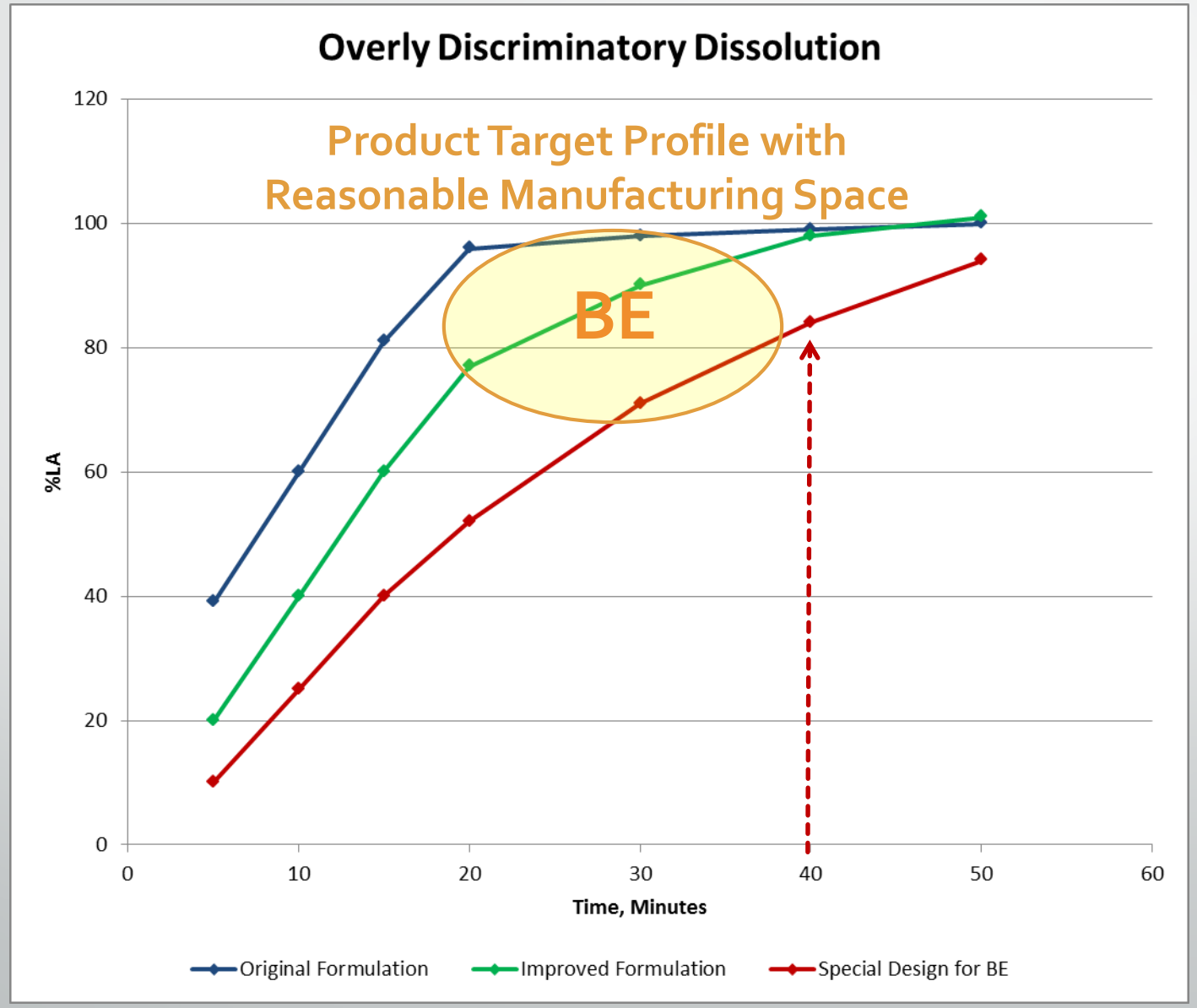
Case B – Too Narrow Manufacture Space

Material property impact dissolution, but all batches are "BE"



Formulation, PK

Case B – Clinically Justified Specification



Case C – Dissolution for IVIVR/IVIVC

Dissolution Conditions Explored

- App 1, App 2
- RPM's
- Medium pH's (i.e. 0.1N HCl, pH 4.5, pH 6.8)
- Dual pH method
- Medium Volume: 900 mL

Final Method Selected for Better reproducibility (suite for QC)

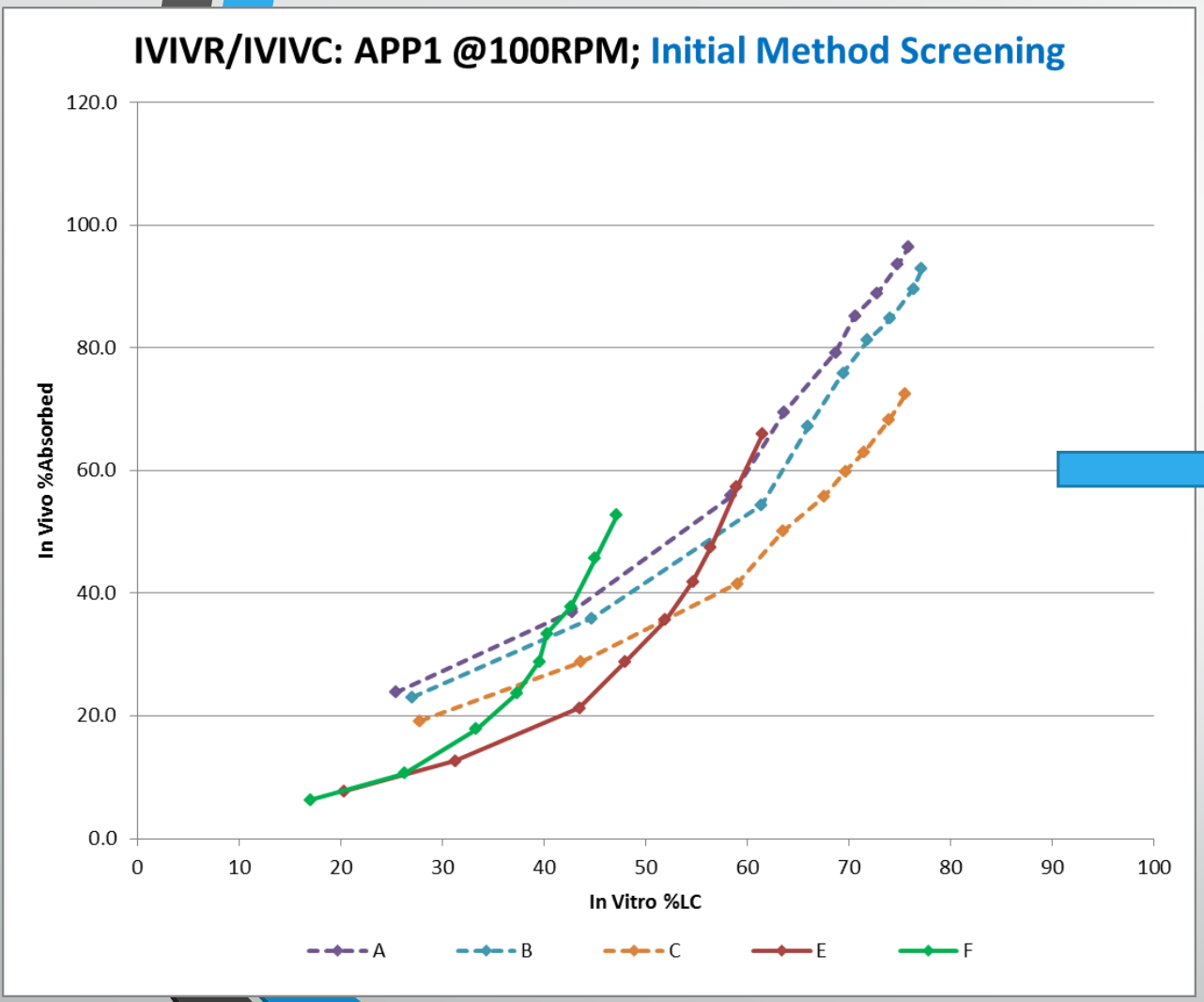
Study Design

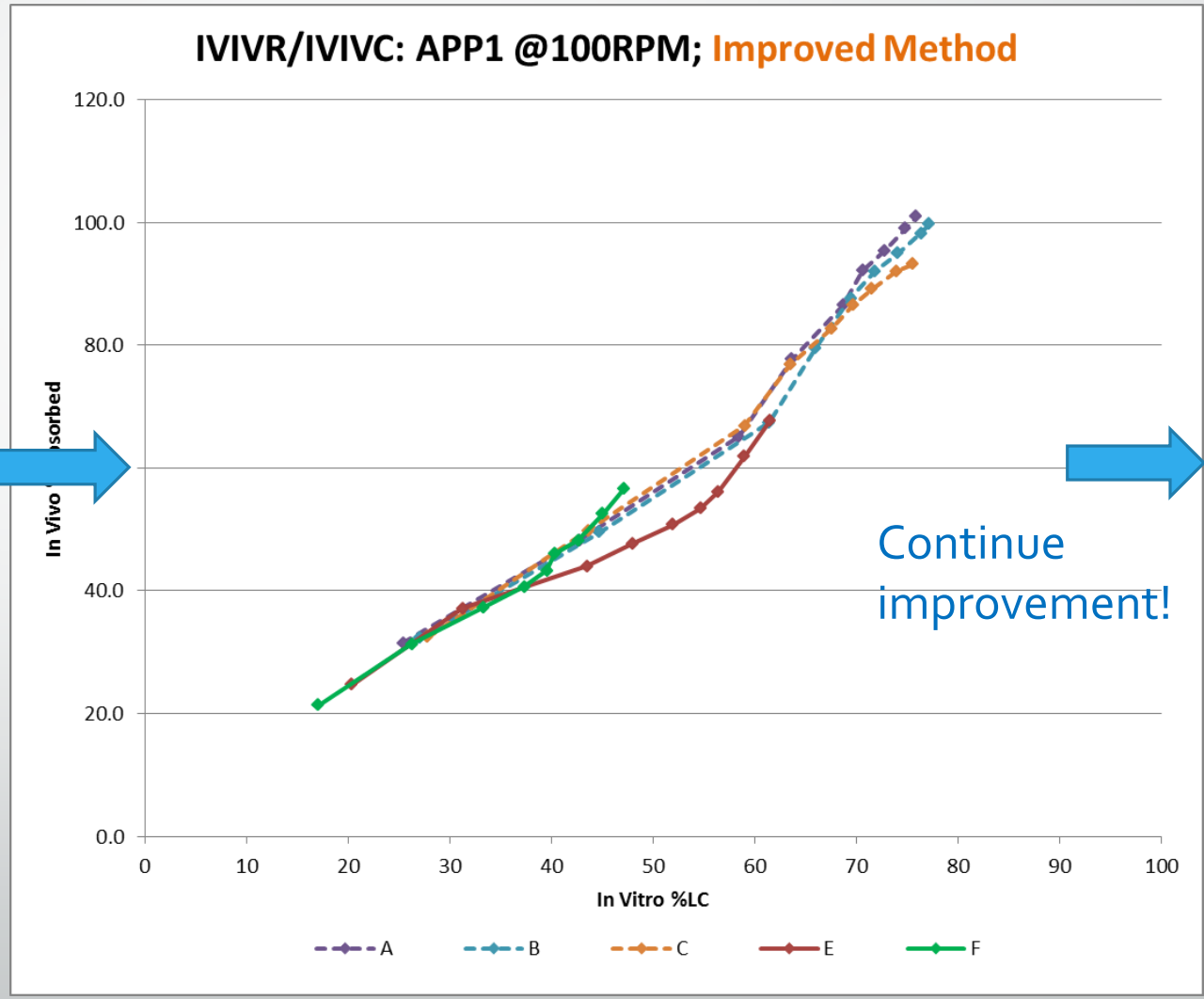
- Bioavailability
- Stability
- Manufacturability

Designed Formulations to have different in vitro drug release profiles

➔ Design Biostudy to evaluate the in vivo performance of these formulations

Case C –Dissolution for IVIVR/IVIVC

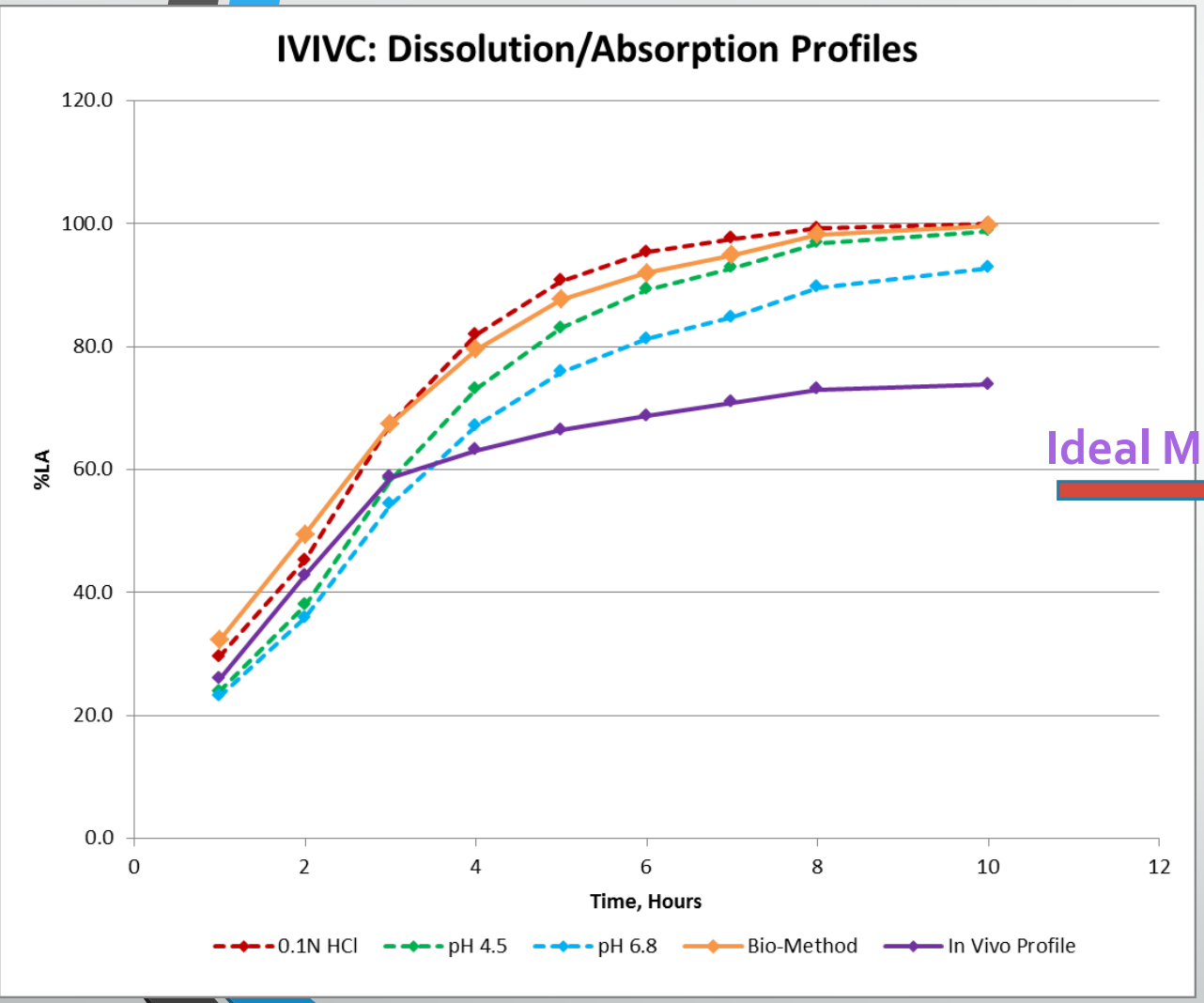




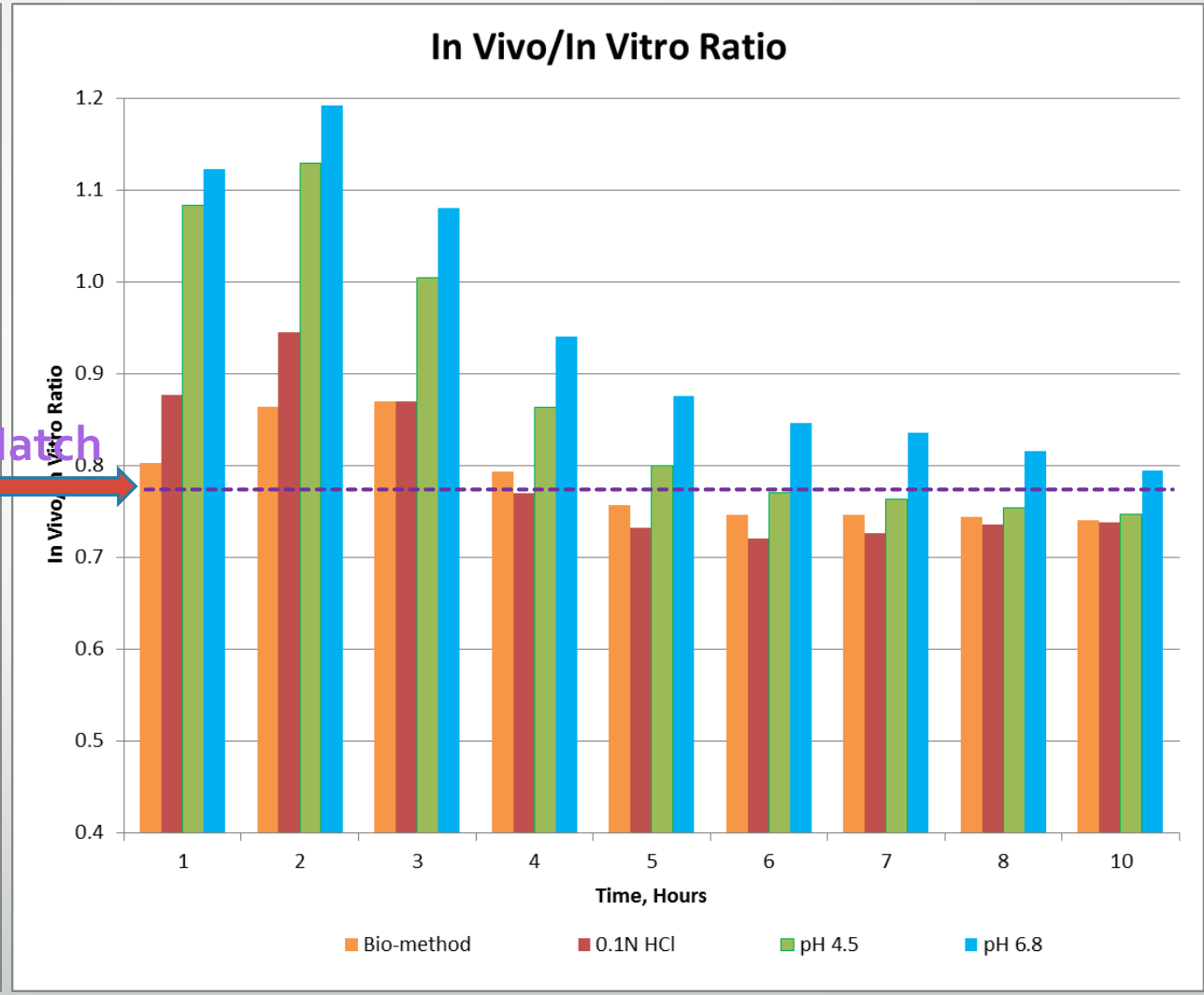
Continue improvement!

Life goes on…..

Case C – IVIVR/IVIVC Analysis



Ideal Match



Q: Can Reverse-Engineering work?

Case D – BCS 2/4; IR: Development Process

Dissolution

- Original QC method (Not Clinically Relevant)
- New Method Consideration based on Bio-relevant information
- Method Screening
  - Apparatus
  - Medium pH's
  - Surfactant – Type & Conc.
- Performance Confirmation

Final Method Selected for Clinical relevancy and Suitable for QC implementation (reliable, reproducible, and transferrable)

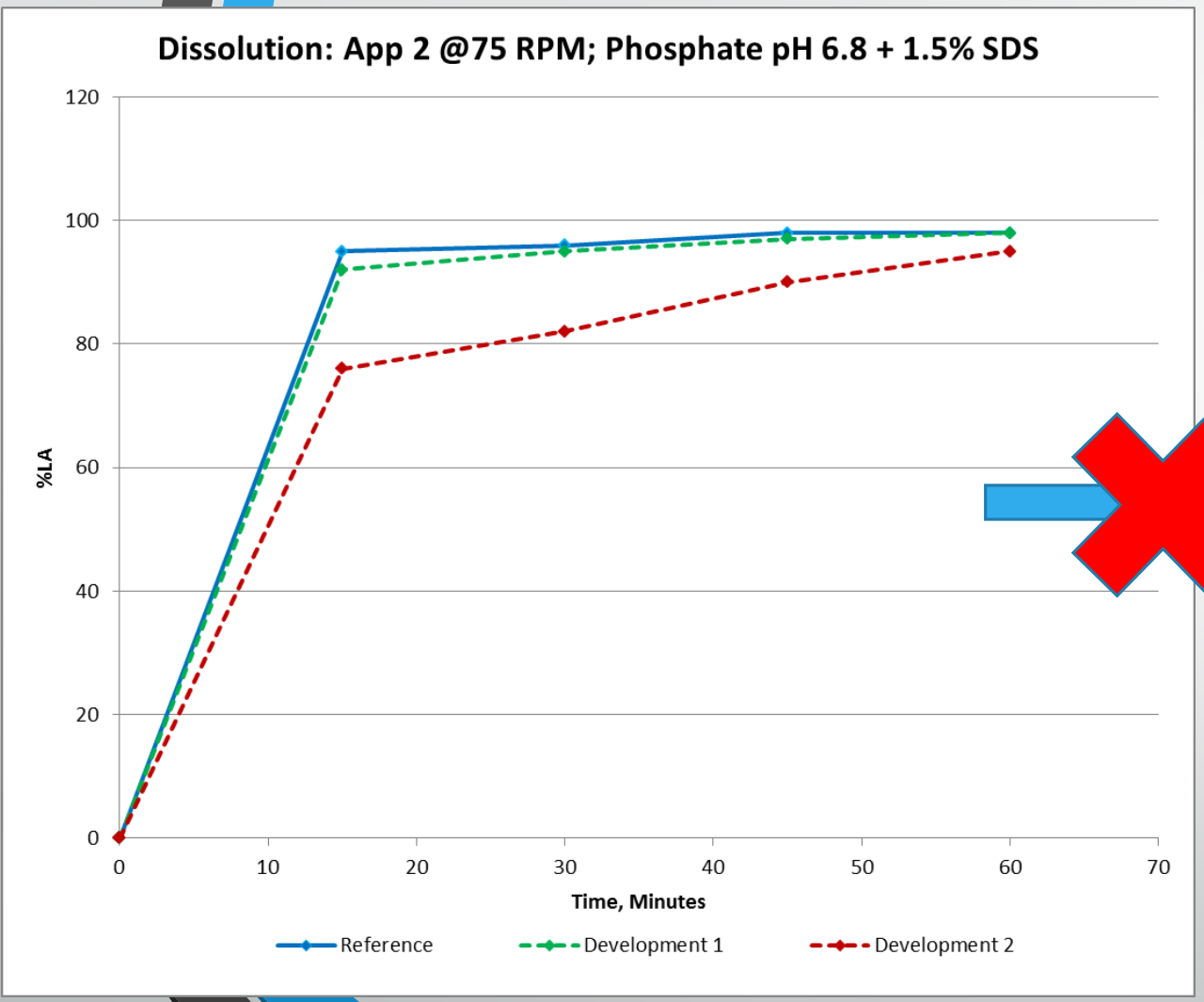
Study Design

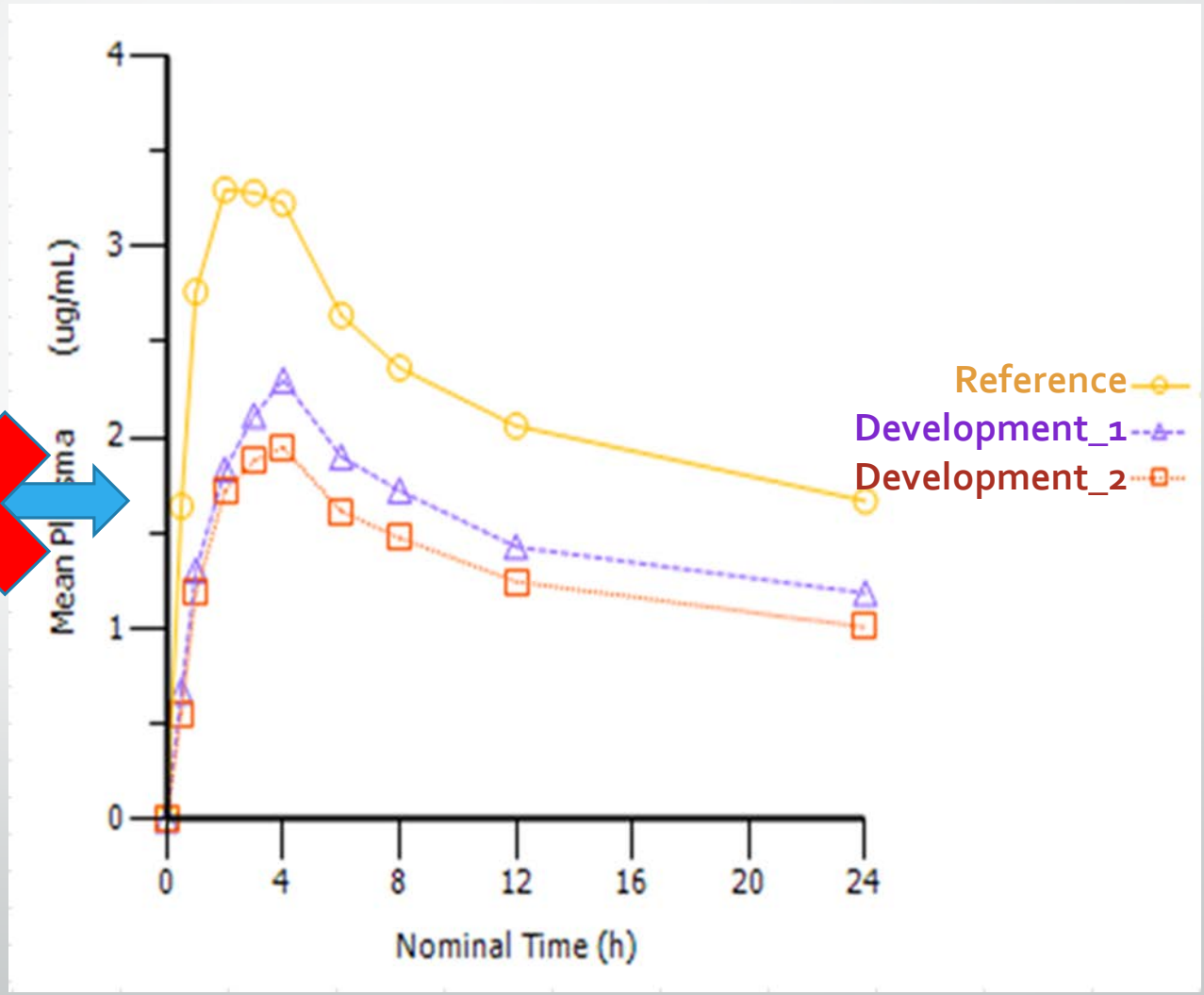
- Dissolution
- Formulation (API Particle Size)
- Bioavailability
- Modeling
- New Track ➔ Confirmation

Designed Formulations to have different in vitro drug release profiles

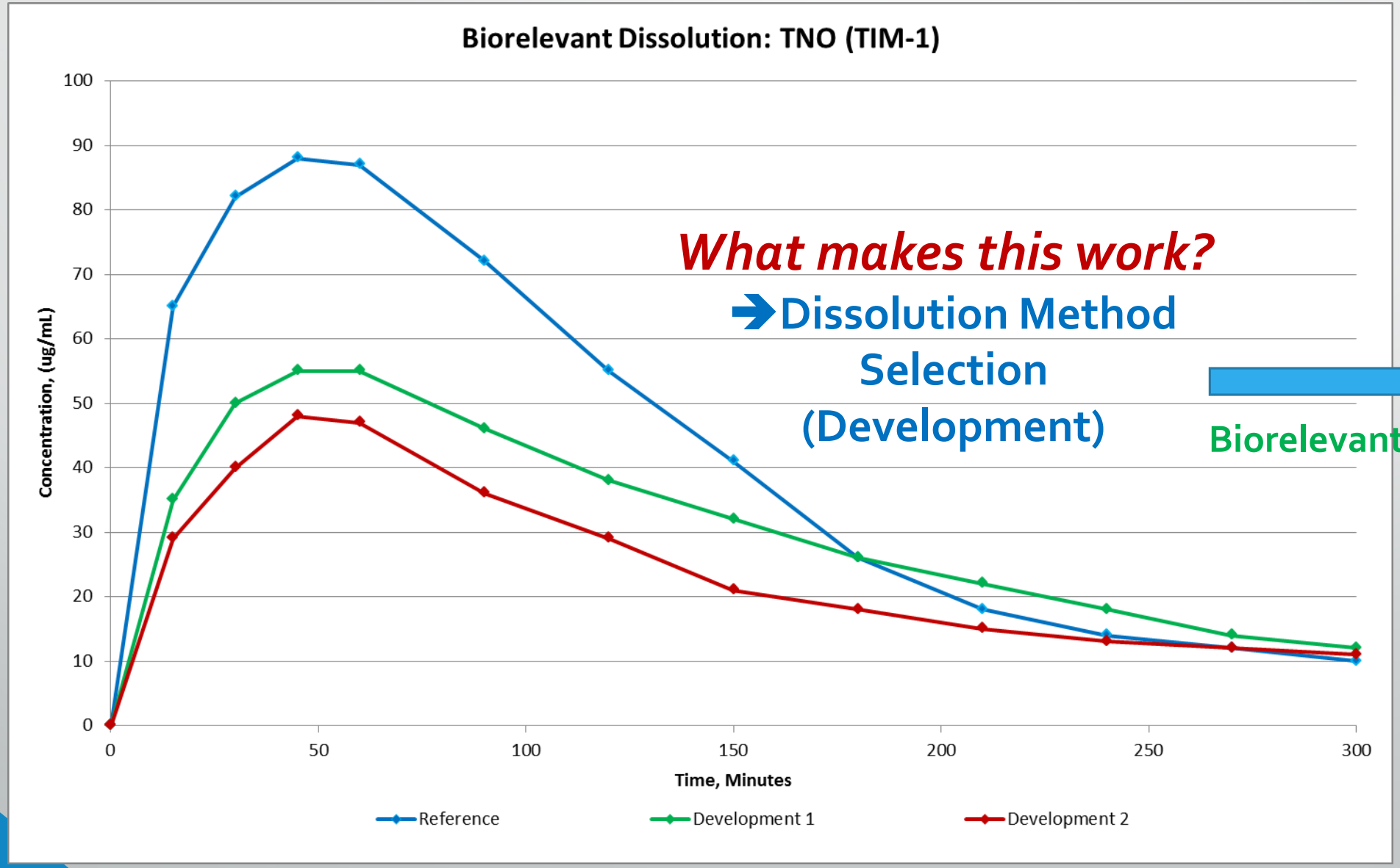
➔ Design Biostudy to evaluate the in vivo performance of these formulations
➔ Verify the dissolution method performance

Case D – Method has No Proper Discrimination





Case D – Biorelevant Method (TNO/ TIM1)

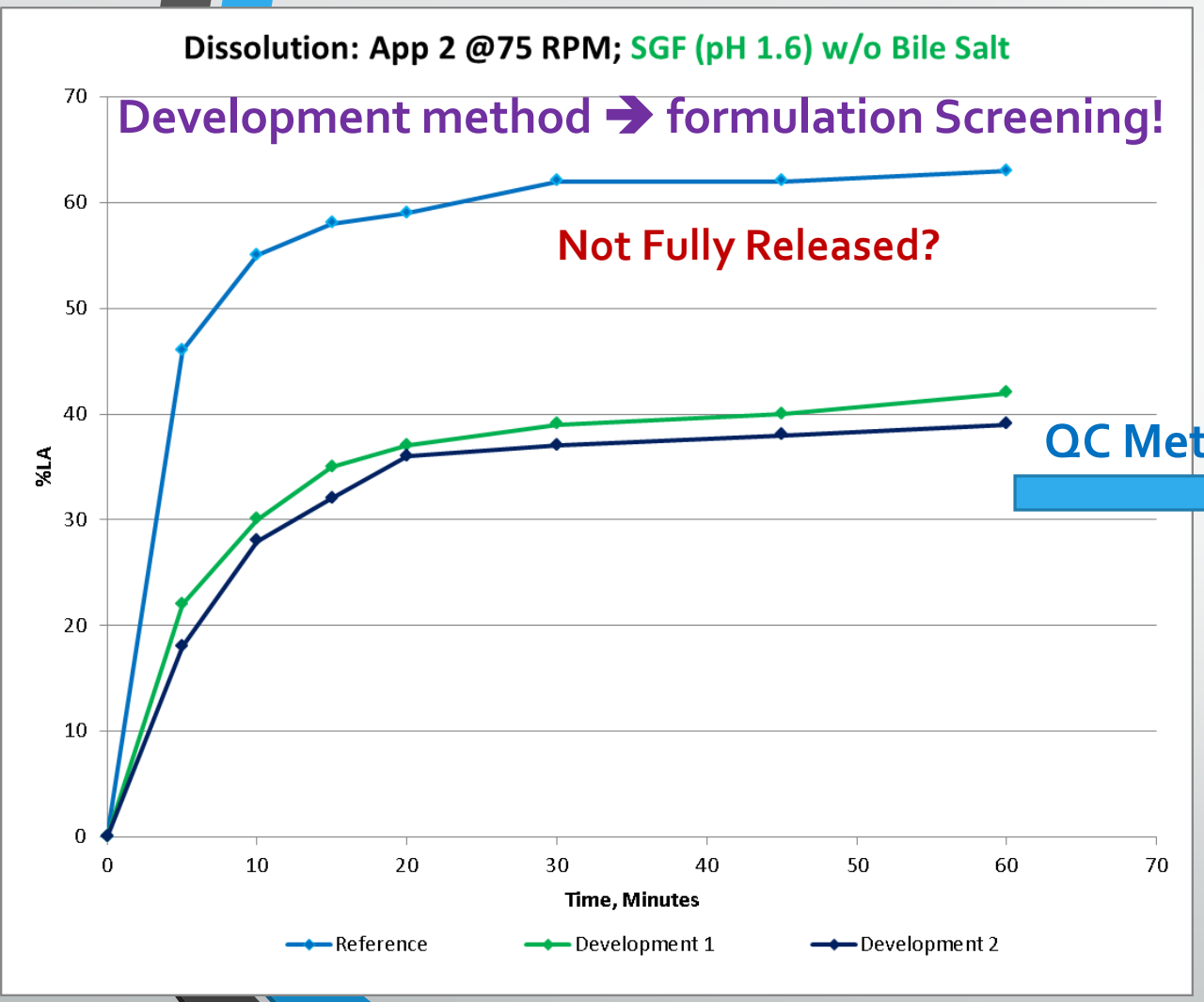


What makes this work?

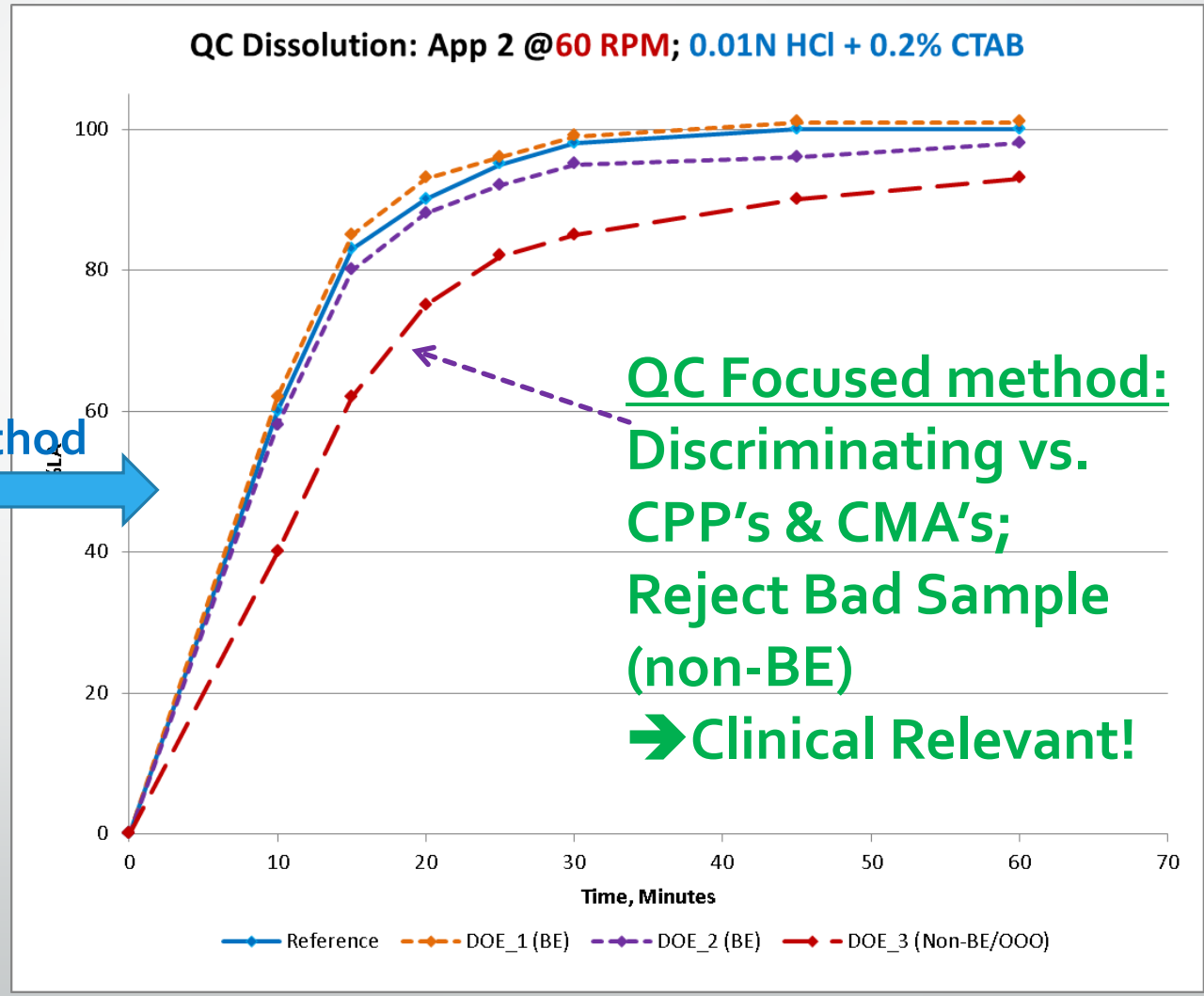
➔**Dissolution Method Selection (Development)**

Biorelevant Method?

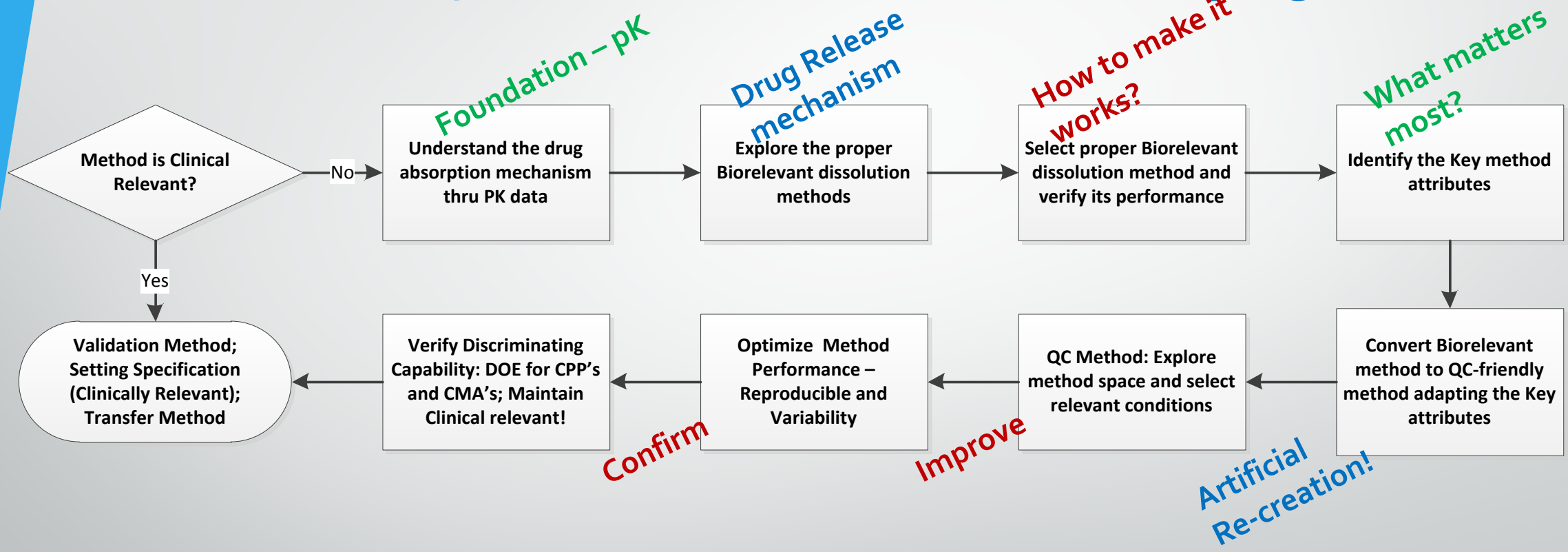
Case D – New Method with Proper Discrimination



QC Method



Road Map for Biorelevant to QC Bridging



From Biorelevant to QC – Gaps & Challenges

- **Collaboration**
  - **Analytical ⟷ Formulation ⟷ Clinical PK**
  - **Key to success**
- **Technical**
  - Biorelevant dissolution maybe too complicated/variable for QC use
  - How to make surfactant work for biorelevant methods?
  - Sink or non-sink?
  - Not fully released profile
- **Regulatory Acceptance and Guidance**

Summary

- Biorelevent dissolution and QC dissolution have different focuses and serve different purposes in pharmaceutical development. Their methodologies and criteria are also different.
- Bridging the two types of dissolution methods is current regulatory expectation, but faces significant gaps and challenges in practice for industry, especially in early phase development before an IVIVC is established.
- Efforts have been made to bridge these two types of methods, including phase relevant dissolution considerations, use of FDA guidance, and application of QbD and IVIVC, which work primarily for BCS 1 and 3 and some BCS 2 and 4 cases.
- Significant changes may have to be made to adopt/convert biorelevant dissolution methods for quality control applications, including use of non-compendial dissolution devices, biorelevant dissolution media, non-sink dissolution conditions, truly clinically relevant specifications, and balance between bio-predictive and process-discrimination, which will need clear regulatory guidance for acceptance.
- **Using a single method throughout all phases of development may not be practical.**

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AAPS-IVRDT Focus Group

"Biorelevant or Clinical Relevant Dissolution Methods and Specs" Sub Team

- Jian-Hwa Han (AbbVie)
- Xujin Lu (BMS)
- Nikoletta Fotaki (Univ. of Bath, UK)
- David Curran (GSK)
- Limin Zhang (BMS)
- Sanjaykumar Patel (Merck)