NON-PBBM SAFE SPACE APPROACHES

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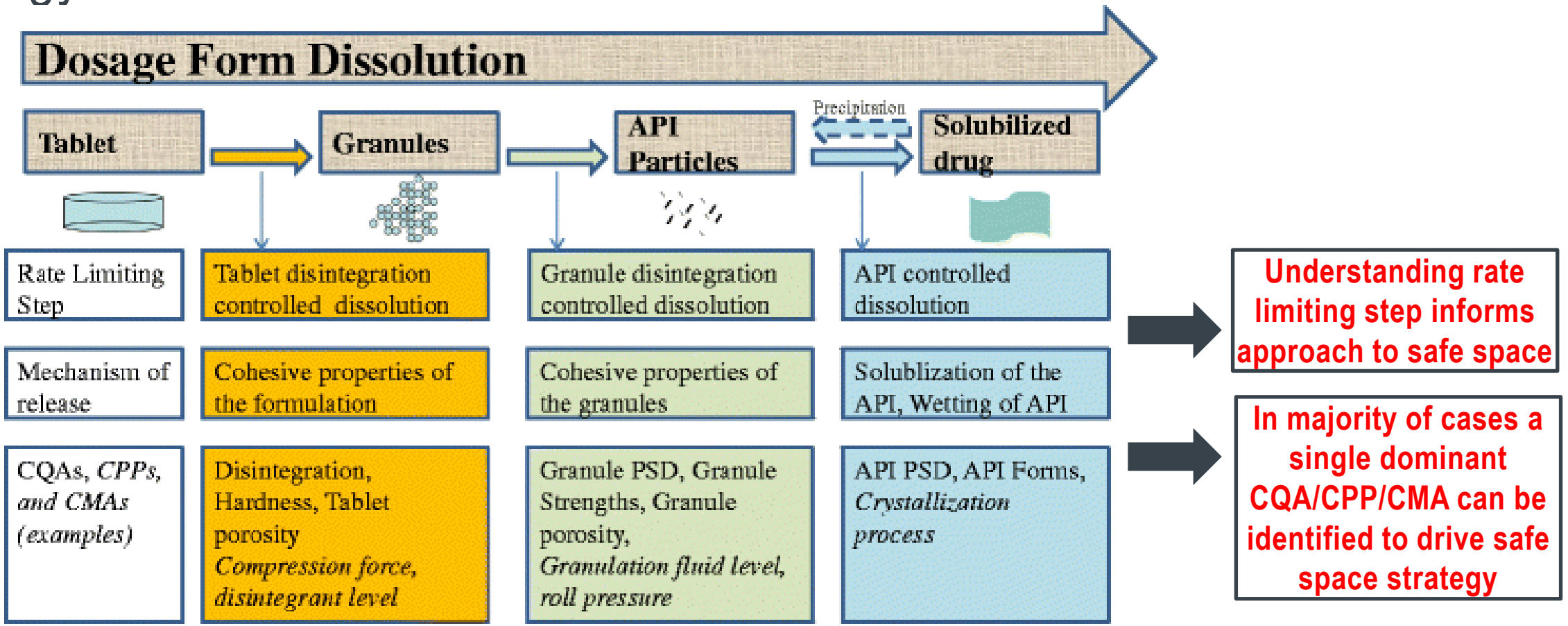
Understanding Rate Limiting Dissolution Step Critical to Safe Space Strategy



Hermans A, Abend AM, Kesisoglou F, Flanagan T, Cohen MJ, Diaz DA, Mao Y, Zhang L, Webster GK, Lin Y, Hahn DA, Coutant CA, Grady H. Approaches for Establishing Clinically Relevant Dissolution Specifications for Immediate Release Solid Oral Dosage Forms. AAPS J. 2017 Nov;19(6):1537-1549.

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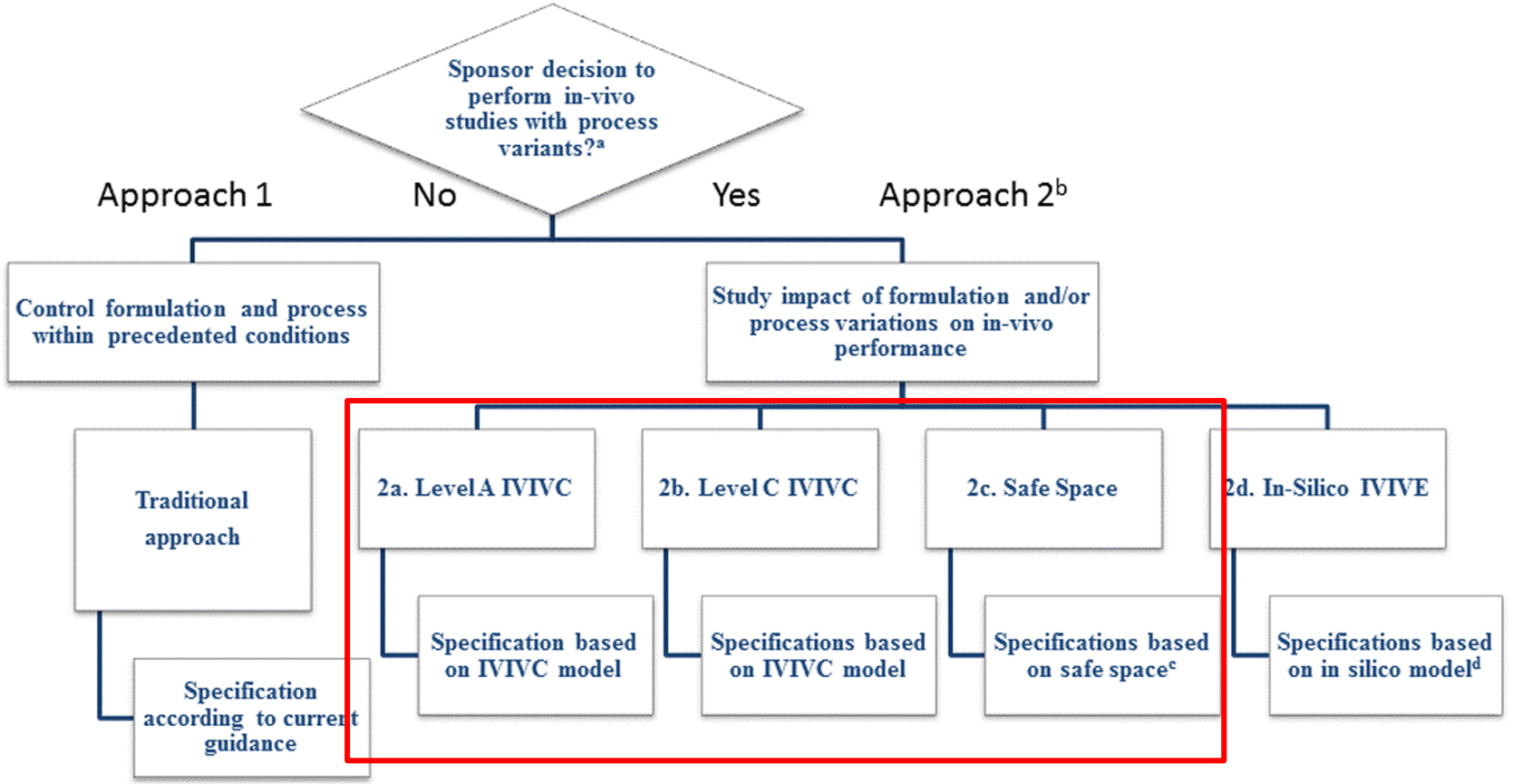
Safe Space Establishing Strategies



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[b] When pursuing Approach 2, aspects such as analytical method variability and manufacturing process history will also be taken into account when selecting the final specification within the established window of acceptable clinical performance.
[c] This refers to other approaches for building safe space. Refer to Table 1 for definition.
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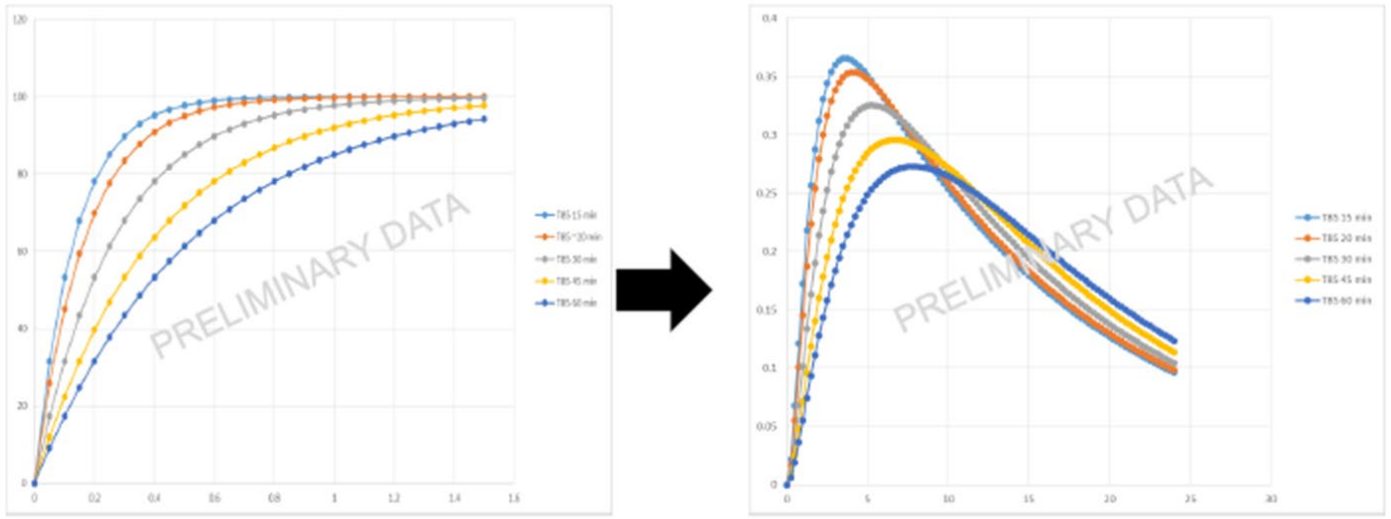
PQRI BTC Project – When is a Model Required to Establish a Safe Space?

Step 1: Generate a Dissolution and PK space using a simplified compartmental model assuming dissolution rate limited absorption

Simplified dissolution + absorption model used



Clinical PK profiles generated via convolution assuming an underlying IVIVC relationship (DISvivo=DISvitro(Timescale*Tvivo)

Model

LUMEN = DISSOLUTION-(2Peff/R)*LUMEN
PLASMA = (2Peff/R)*LUMEN - Elimination

Simulations Space

- Four different underlying correlations explored
- Four different permeability settings (moderate to high permeability)
- Two different half-lives
- With and Without Colonic Absorption

(Total 64 scenarios with 5 profiles each)

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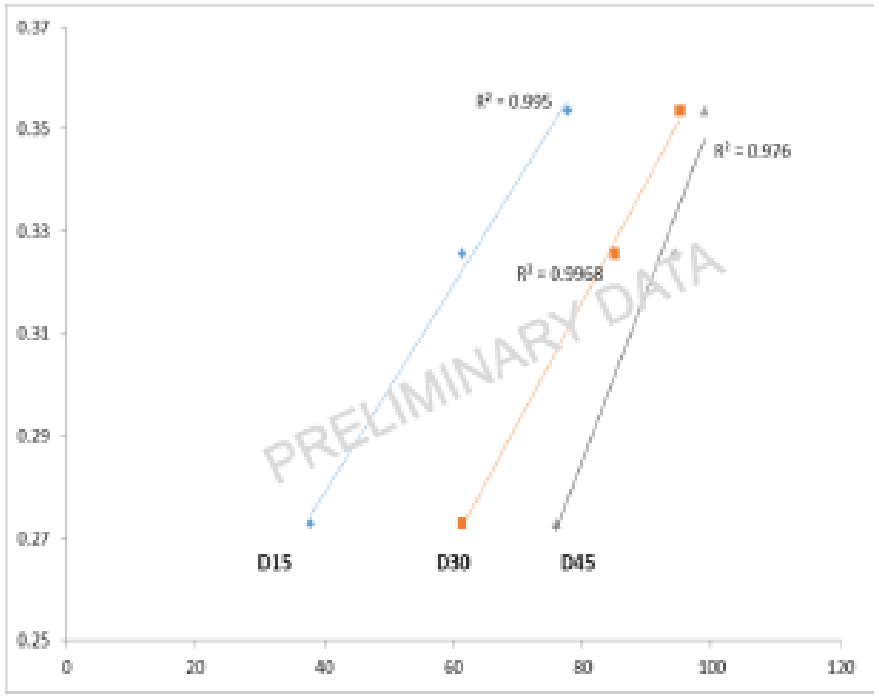
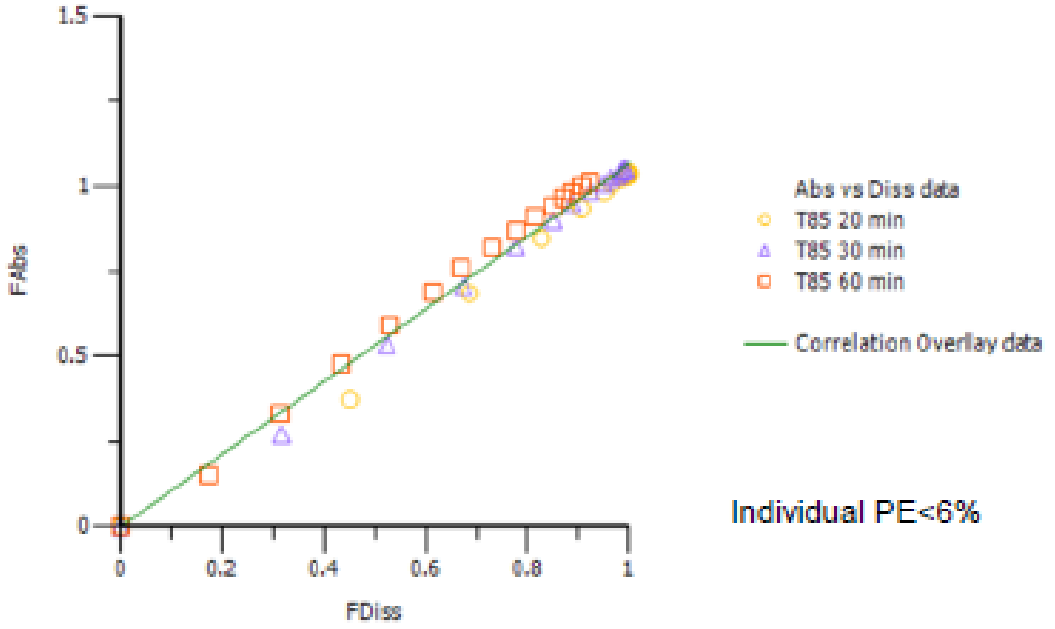
Step 2. “Recover” Multiple Level C vs Level A IVIVC

Step 2: Try to “recover” the Multiple Level C and Level A IVIVC using standard methodologies





Individual PE<6%

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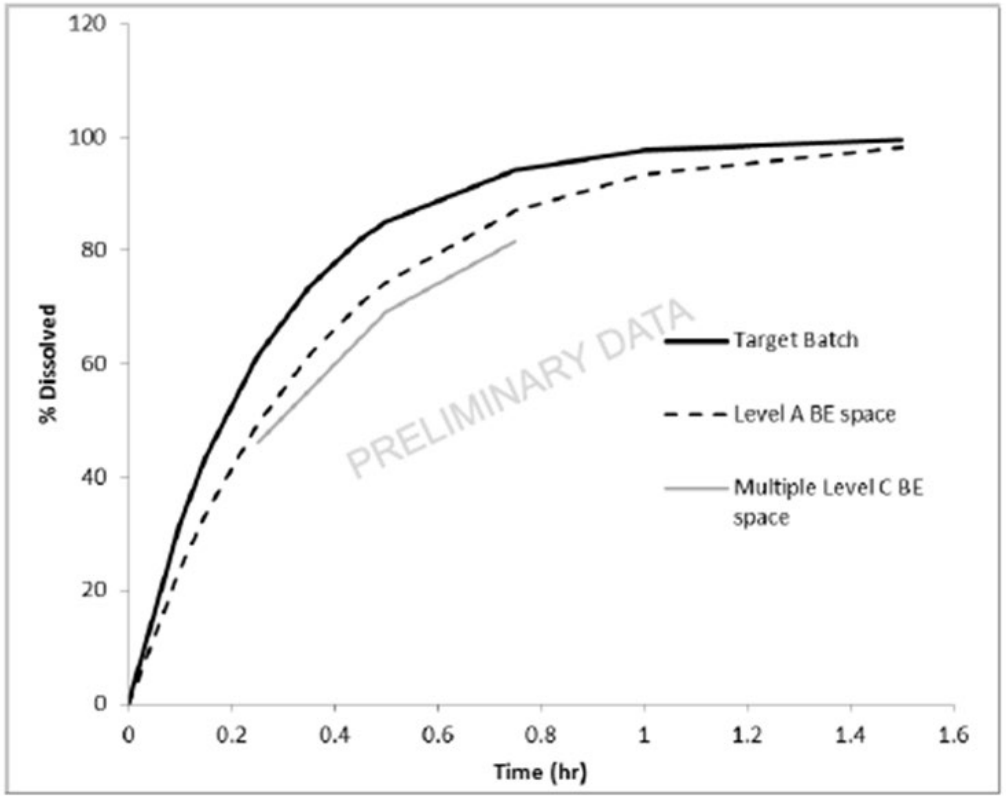
Step 3. Use derived model to project BE space

Step 3: Project the BE space



Small differences in prediction of BE space between Multiple Level C and Level A

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A case where both Level A and Level C IVIVC was seen

Sim 63-64: Very high permeability (10x10-4 cm/sec), time-scaling of 0.25 or 0.125, Tcutoff of 4 hrs (i.e. slow dissolving BCS II compound with limited colonic absorption)

Level A IVIVC:

			Level A IVIVC	
	Observed AUC	Observed Cmax	AUC %PE	Cmax %PE
T85 15 min	2.08	0.33	-0.8%	2.8%
T85 30 min	2.04	0.28	-1.4%	-3.9%
T85 45 min	1.91	0.25	-2.6%	-2.5%

Level C IVIVC:

	% PE for Cmax at each of the timepoints				
	10 min	15 min	20 min	30 min	45 min
T85 15 min	0.2%	0%	0.2%	0.7%	1.5%
T85 30 min	1.4%	0.3%	0.6%	2.5%	-5.2%
T85 45 min	-0.5%	-0.1%	0.3%	0.9%	0.9%

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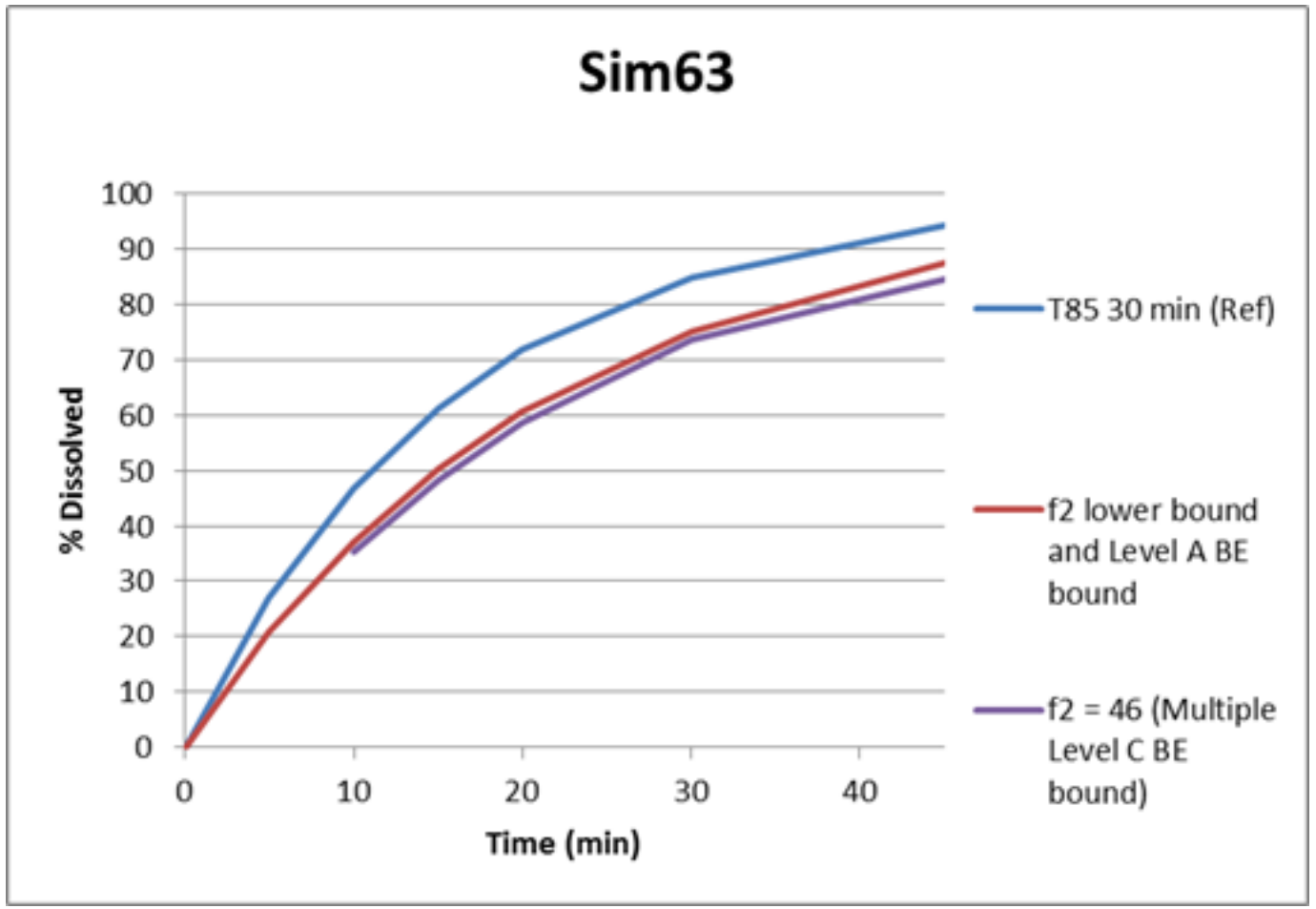
Differences between Level A and Level C model are small



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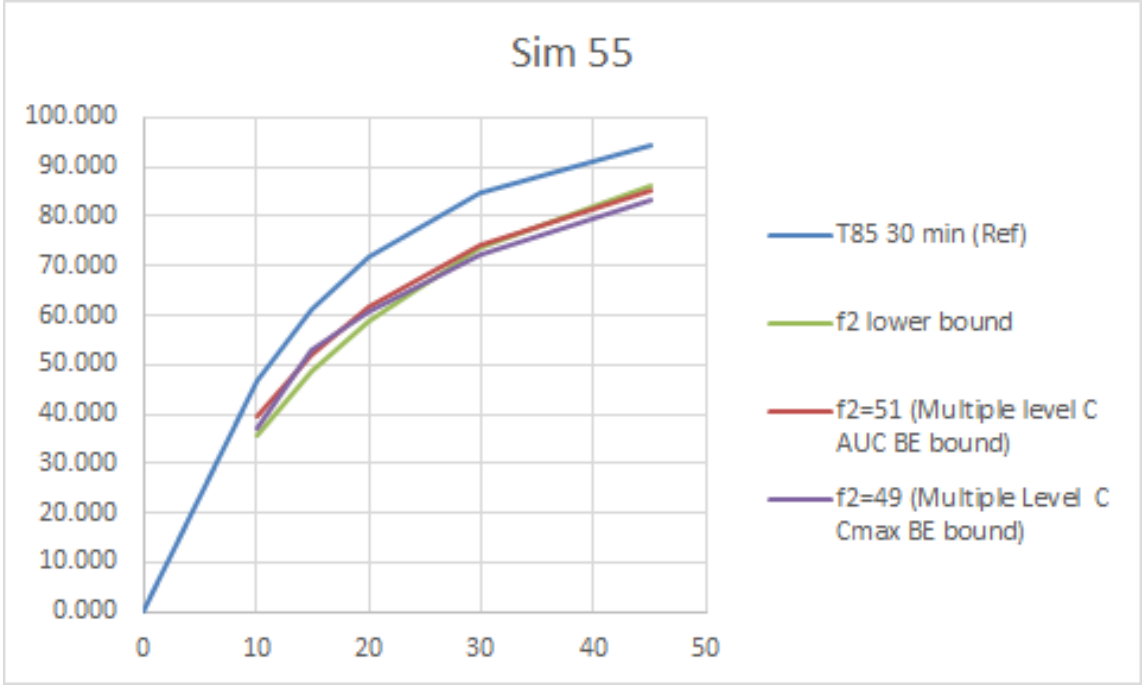
A case where Level A failed but Level C "passed"

Sim 55: *Moderate permeability (1x10-4 cm/sec), time-scaling of 0.25, Tcutoff of 4 hrs (i.e. slow dissolving BCS IV compound with limited colonic absorption)* The T85 15, 30 and 60 min formulations were used. While a successful Level A IVIVC was established for AUC (average error ~3%), it was not established for Cmax. Cmax prediction errors were just beyond those allowed in the IVIVC guidance (average error was 11%, individual errors 9%, 6% and 17%).



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Overall Observations – “Safe space” a frequent outcome

- The majority of simulations conducted resulted in a “safe space”
  - i.e. difference between the fastest and slowest profile being less than 20%
- ALL scenarios simulated assuming a 1:1 correlation between in vitro and in vivo release rate resulted in safe space
- Although not the focus of the project
  - this indirectly indicates that direct incorporation of dissolution data via empirical models in PBBM is either not a good idea or there is no value in running the model to begin with.
  - The suggestion to validate PBBM against non-BE variants may not be practical/make the model obsolete in many cases. Value of modeling should be on extrapolating, with confidence, to untested scenarios.
- Majority of scenarios for which meaningful PK differences (and thus potentially an IVIVC) were observed, were the ones with significant time scaling. These can be considered to represent relatively slow dissolving BCS II/IV compounds, including compounds with wetting issues.

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Overall Observations – IVIVC successes

- Identification of the Level A IVIVC for at least Cmax was increasingly difficult with increasing permeability limitations.
- For low permeability (BCS IV) the Cmax model was not successfully established. The Multiple Level C was still successful.
- In general, there were no significant differences observed between the Level A and the Multiple Level C estimations of BE; there was no clear bias that one provides more or less conservative/permissive bounds.
- It would appear that a Multiple Level C IVIVC is a reasonable (alternative to Level A) approach for application in estimating clinically relevant dissolution bounds for formulations where dissolution is the rate controlling factor to absorption.

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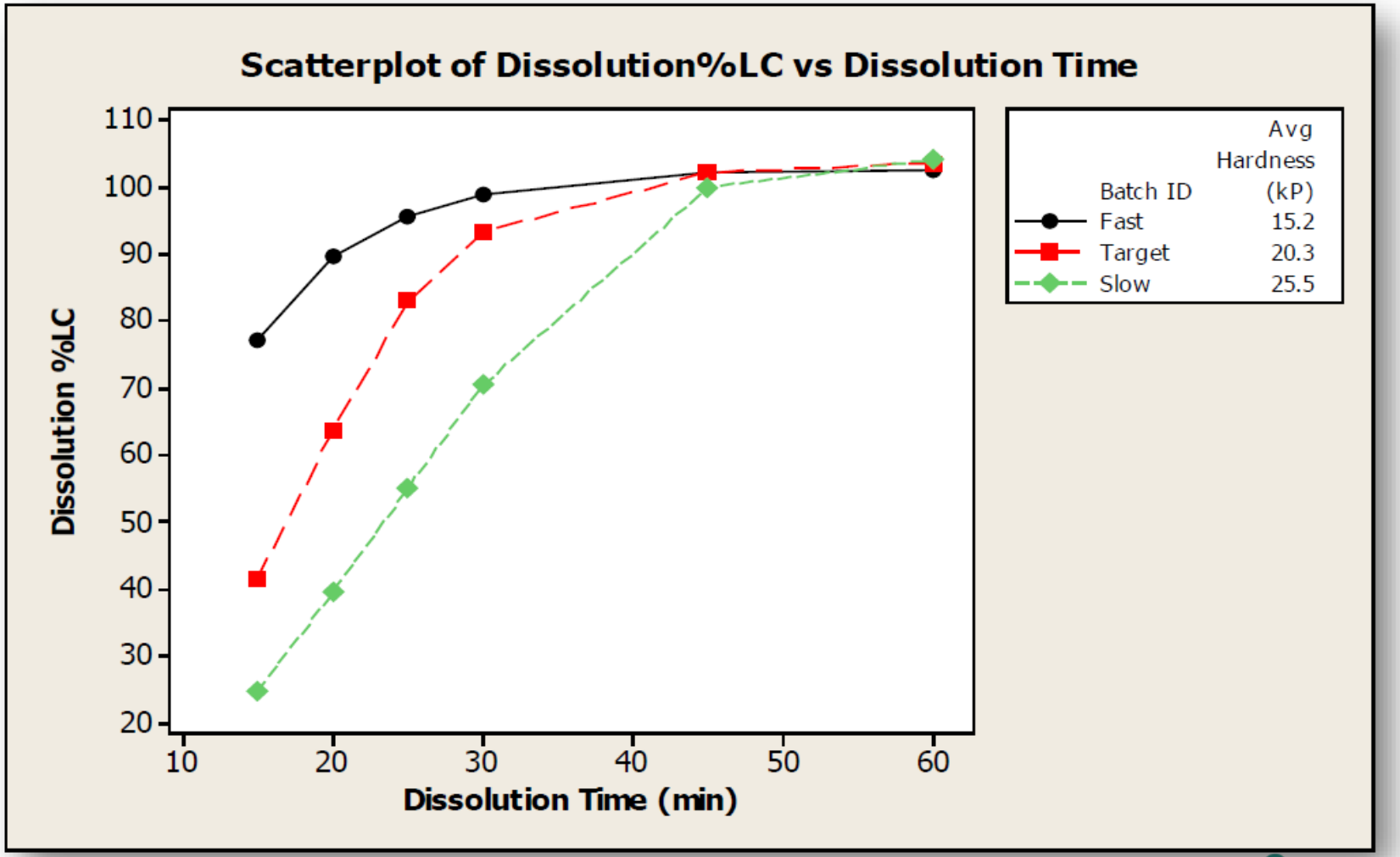
Case Study – Direct Demonstration of Safe Space Clinically



Grazoprevir ASD tablets

Grazoprevir Safe Space Clinical Study Design

Parameter	Study conduct
Design	Single-dose, randomized, open-label, 3-treatment, 3-period, 6-sequence, 7-day washout
N	24 healthy normal subjects
Dose	50 mg tablet
Treatments	Fast, Target, Slow Tablets
PK metrics	AUC_{0-t}, $AUC\infty$, C_{max}, T_{max}, $t_{1/2}$
Statistics	Ln-transformed PK parameters analyzed by linear mixed-effect model with fixed-effects terms for treatment and period
BA comparisons	Geometric mean ratios (GMRs) and 2-sided 90% Confidence Intervals (CIs) calculated for test = fast or slow versus reference = target

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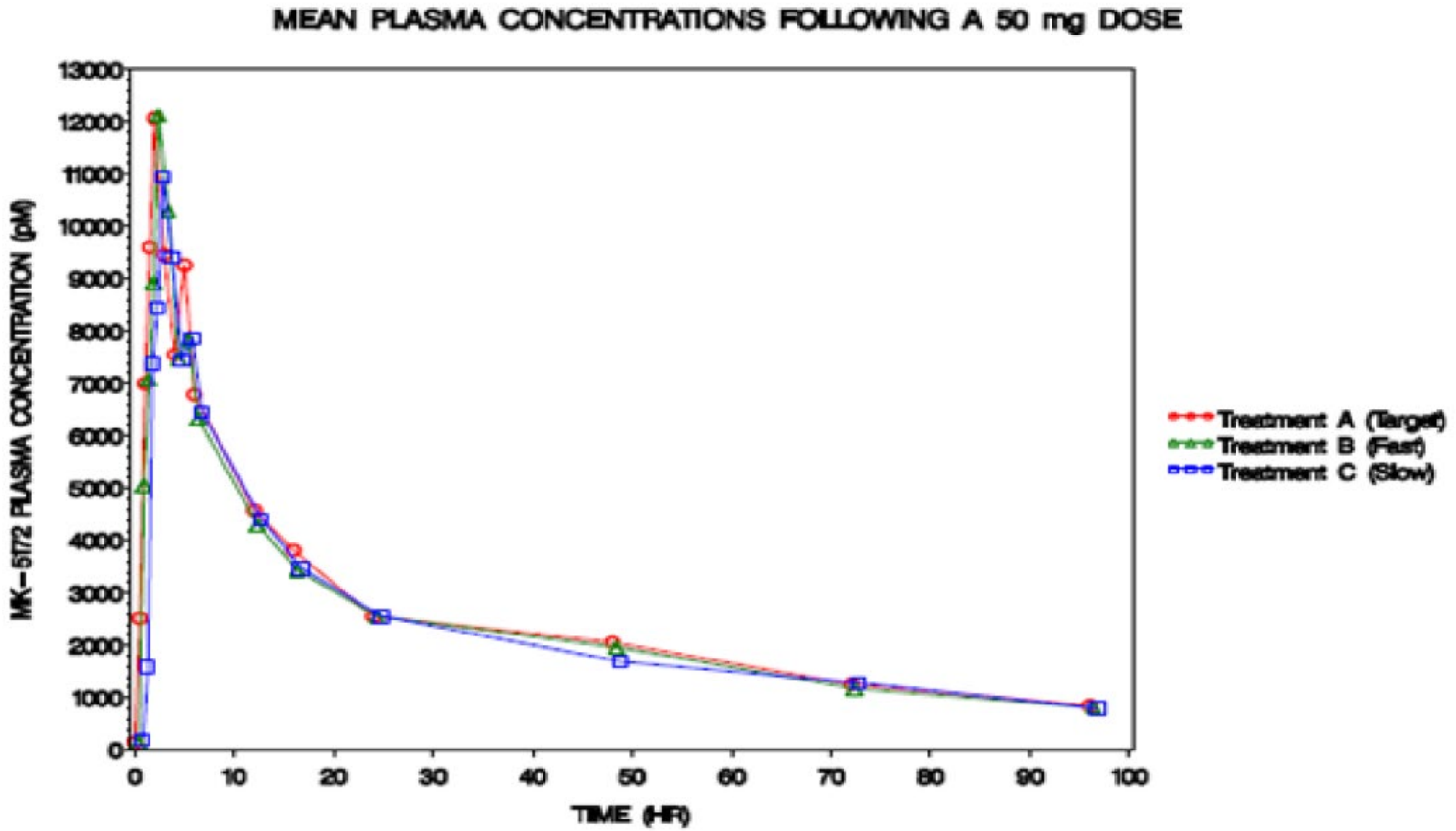
Study Results – Plasma Concentration Profiles



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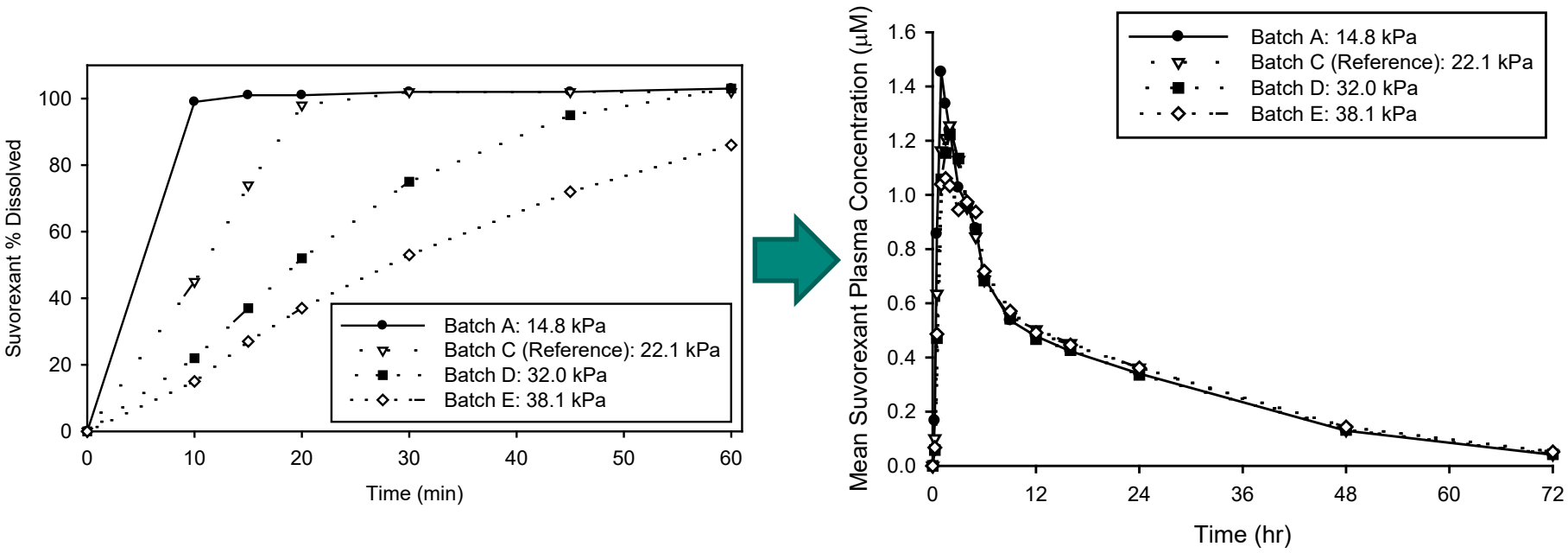
Study Results: GMRs

Test	Parameter	GMR, test/ref	90% CI, test/ref
Fast Tablet	AUC	0.99	0.92, 1.06
	C_{max}	0.91	0.77, 1.08
Slow Tablet	AUC	0.98	0.91, 1.05
	C_{max}	0.95	0.79, 1.15

Case Study: Safe Space Application to Dissolution Specifications

- The dissolution safe space identified in the PK study informed a Q value and sampling time
- These specification were proposed at the time of filing application for marketing in Japan
- The Japanese MHLW accepted the proposal
- The clinically relevant specification proposed as defined by the in vivo safe space were incorporated into the grazoprevir 50 mg tablets stability and quality control programs

Case Study - Multiple Level C Example



Formulations (manufactured by varying compression force) selected to cover a wide dissolution range

All dissolution curves outside F2 bounds

No meaningful differences in AUC observed – Modest Cmax differences seen

Kesisoglou F, Hermans A, Neu C, Yee KL, Palcza J, Miller J. Development of In Vitro-In Vivo Correlation for Amorphous Solid Dispersion Immediate-Release Suvorexant Tablets and Application to Clinically Relevant Dissolution Specifications and In-Process Controls. J Pharm Sci. 2015 Sep;104(9):2913-22.

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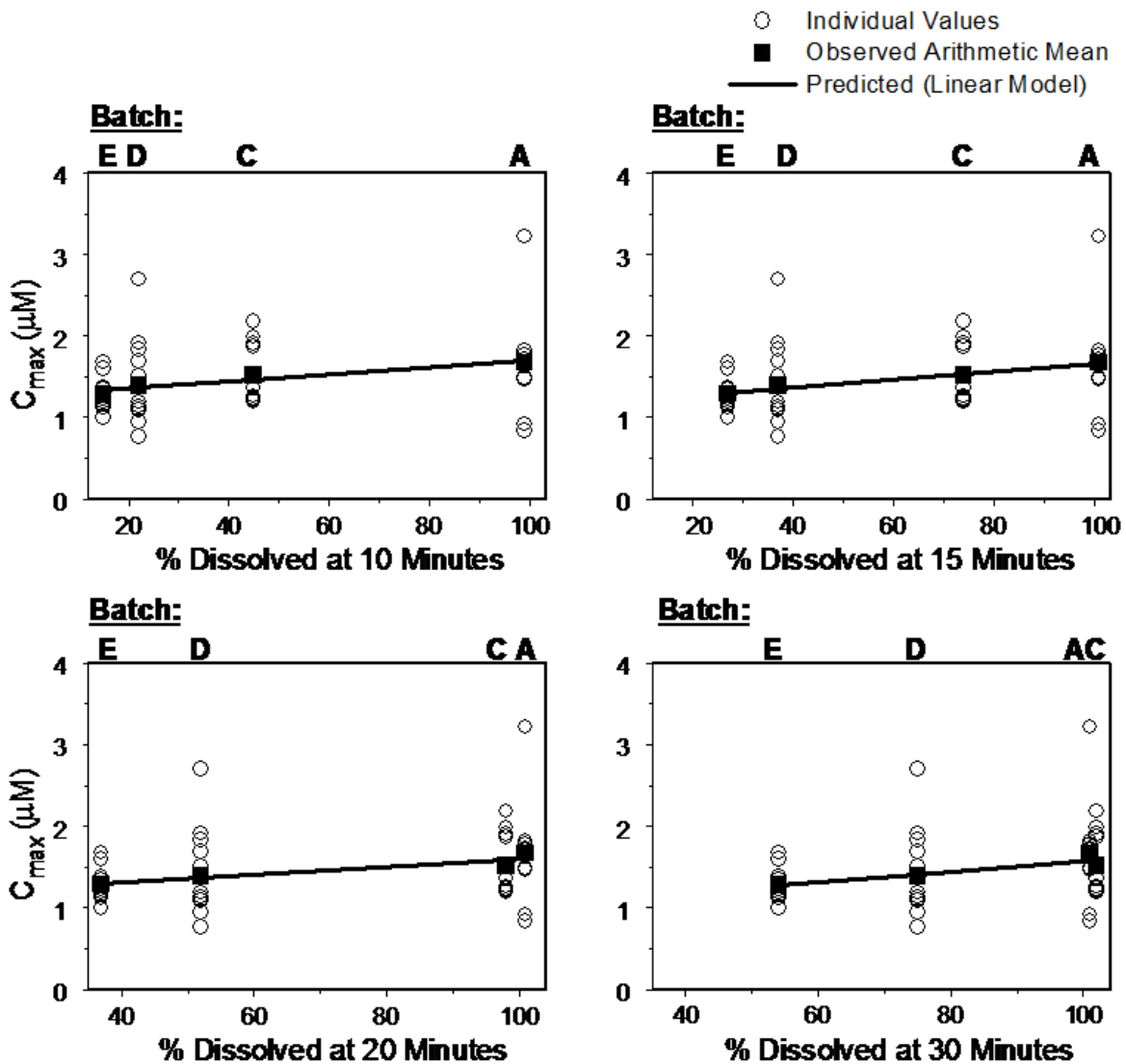
Multiple Level C IVIVC for Dissolution



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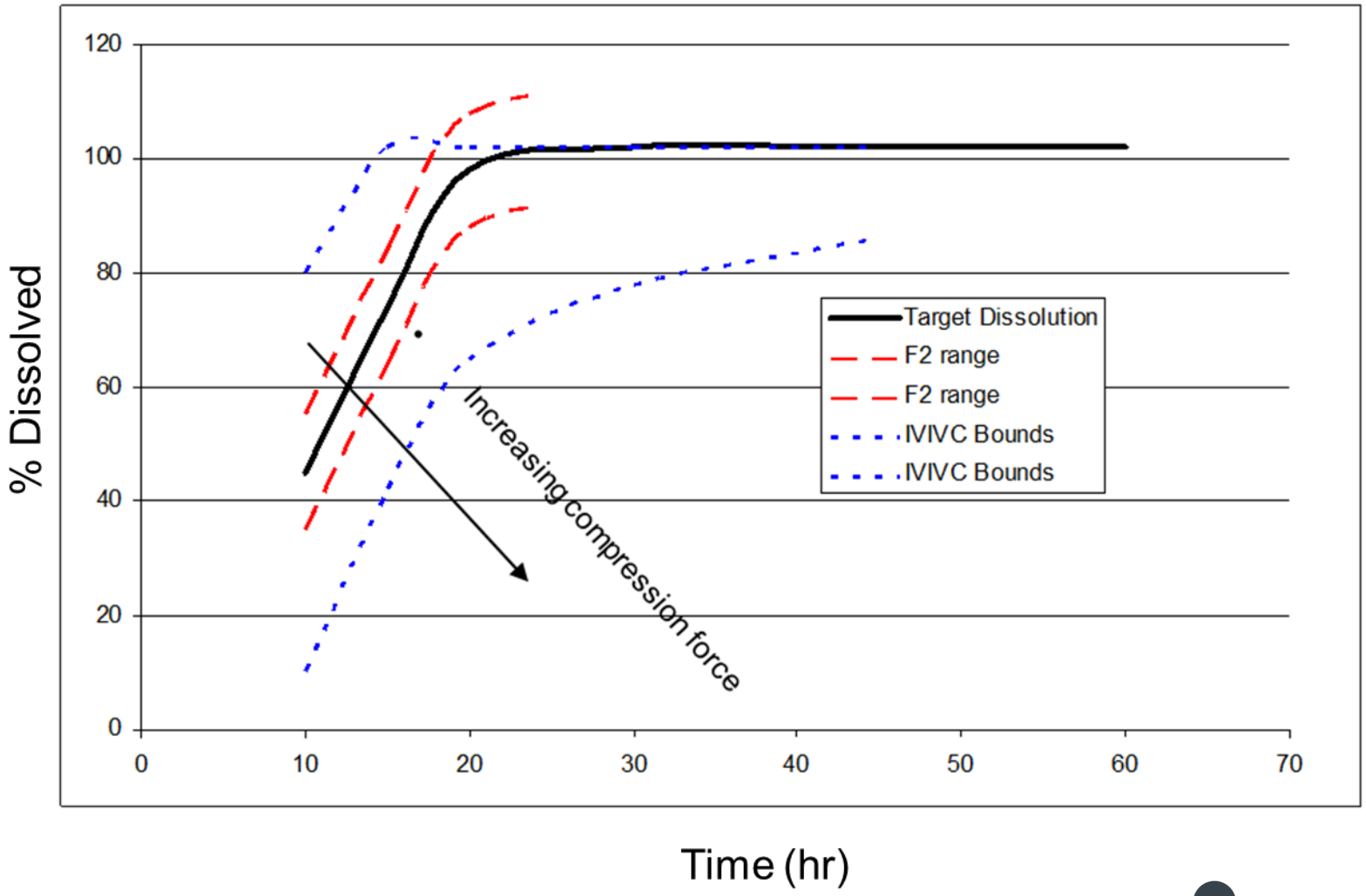
Use of IVIVC to Establish Clinically Relevant Dissolution Bounds



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Can Multiple Level C be used to predict BE?

Bioequivalence study between strengths to support interchangeability (much faster dissolution for 15 vs 30 mg and 20 vs 40 mg tablets)

IVIVC used to inform POS and power study (maximum 9.5% difference predicted based on 20 min dissolution)

	AUC0-t	AUC0-inf	Cmax	Cmax IVIVC prediction
2x20 (n=59) vs 1x40 mg (n=60)	102.52% (99.09-106.07%)	102.33% (98.80-105.99%)	96.58% (90.96%-102.55%)	105.3%
2x15 (n=60) vs 1x30 mg (n=59)	99.71% (96.66%-102.85%)	99.66% (96.52%-102.91%)	108.74% (101.10%-116.95%)	109.5%

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Beyond PK – Can PK/PD Establish the Safe Space?

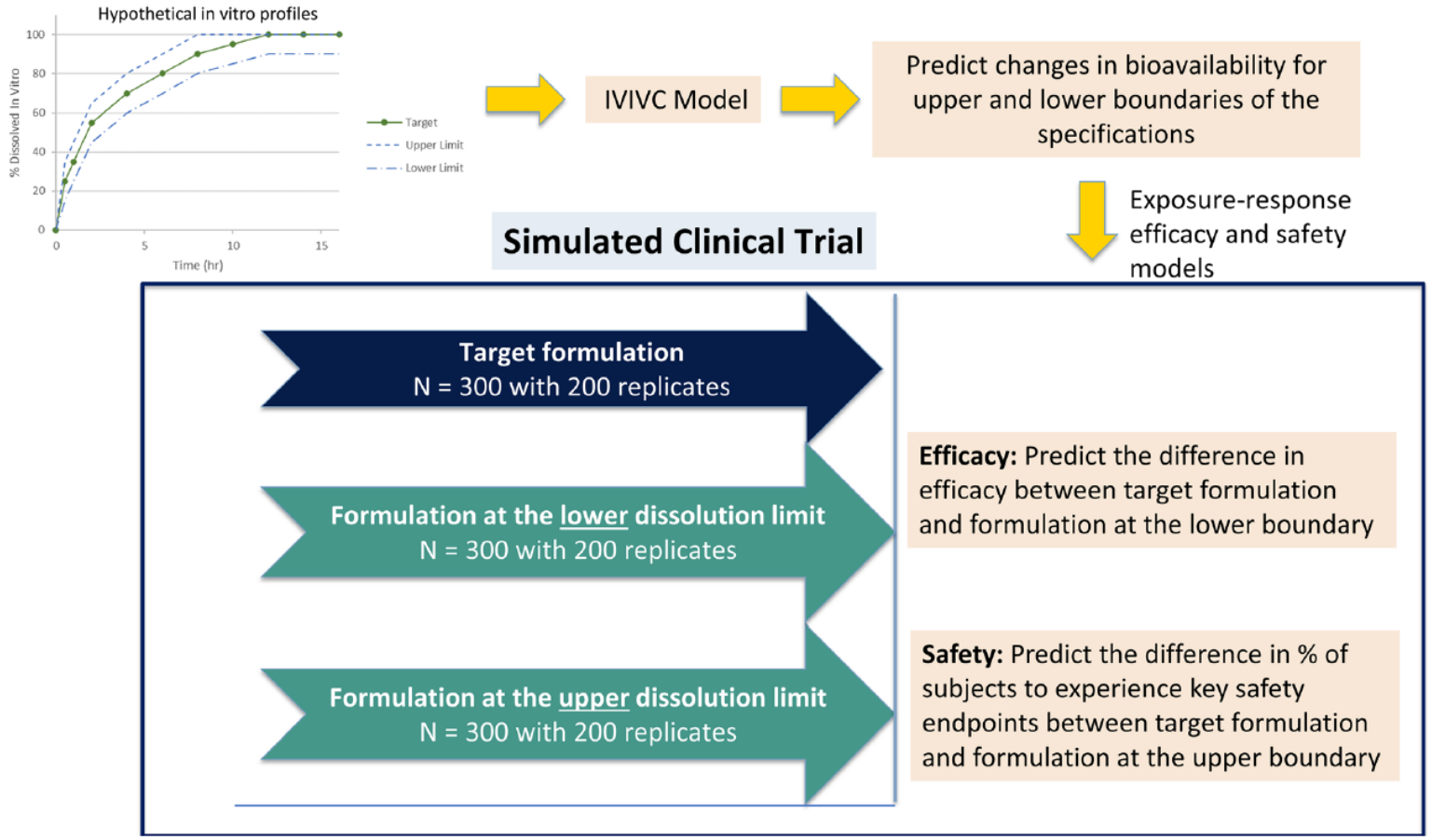

Figure 1 Process for assessment of upper and lower dissolution specification for clinical relevance

Mohamed MF, Winzenborg I, Othman AA, Marroum P. Utility of Modeling and Simulation Approach to Support the Clinical Relevance of Dissolution Specifications: a Case Study from Upadacitinib Development. AAPS J. 2022 Mar 1;24(2):39. doi: 10.1208/s12248-022-00681-6. PMID: 35230556.

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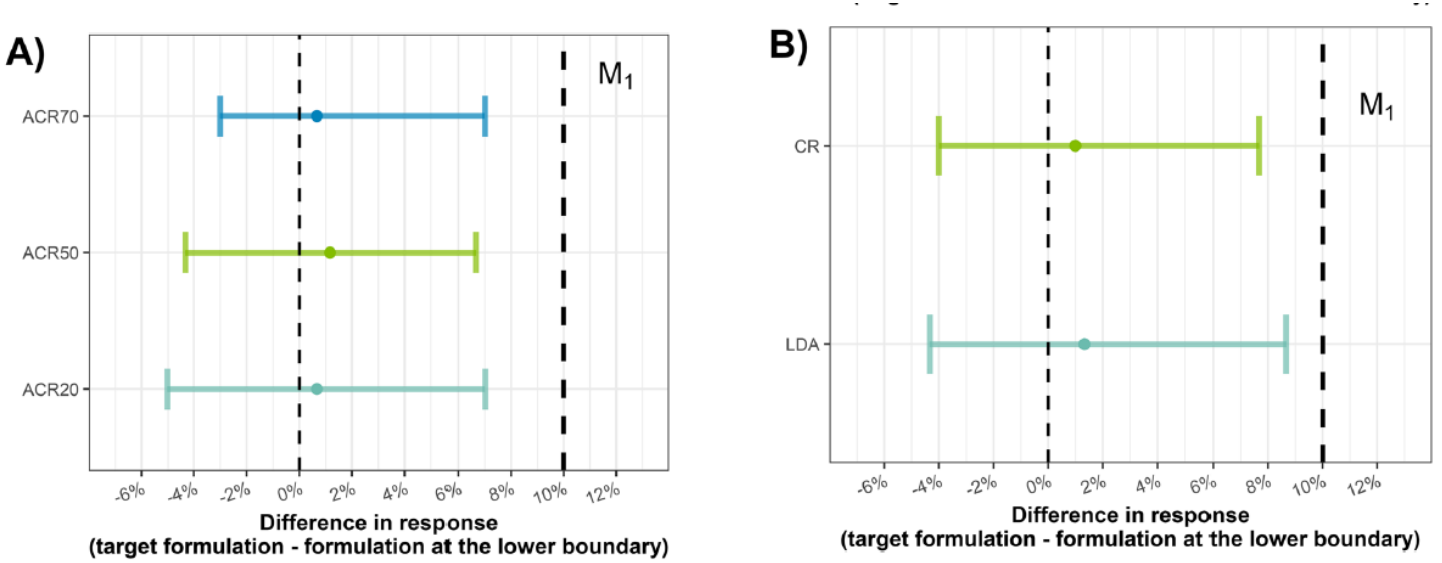

Figure 2 Non-inferiority efficacy simulation results at week 12 (upadacitinib 15 mg QD tablet at lower dissolution boundary vs. target 15 mg formulation). **A** ACR response and **B** LDA/CR response. Dot: median difference in response; error bars: 95% confidence intervals of difference in response; dashed line: 0% difference in response; bold dashed line: non-inferiority margin (M1) representing 10% difference in response

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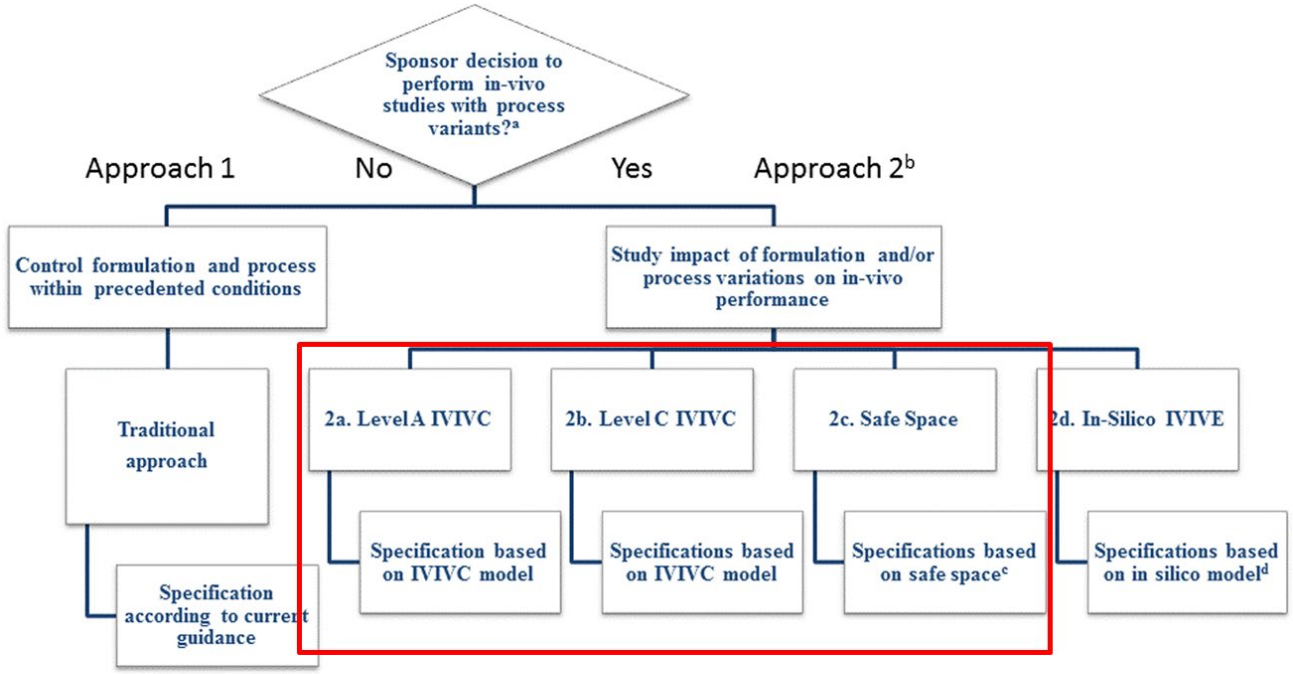
Conclusions

- Multiple paths to establishing a dissolution safe space
- Understanding rate limiting step to dissolution and identifying key CQAs/CPPs/CMAs critical to deciding on strategy
- For IR products, in majority of cases safe space can be demonstrated directly in the clinic via a relative BA study without additional modeling
- Level C IVIVC models are likely more than adequate for estimation of dissolution safe space



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Acknowledgements

- PQRI BTC IVIVC WG: X. Zhang, D. Sperry, D. Good, A. Narang
- PQRI BTC members
- IQ Dissolution WG
- Merck colleagues: A. Hermans, C. Neu, KL Yee, J Palcza, J Miller, A. Abend, B. Davit, M. Marota

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