"Clinically Relevant Dissolution Specifications: Why, What, How and When?"

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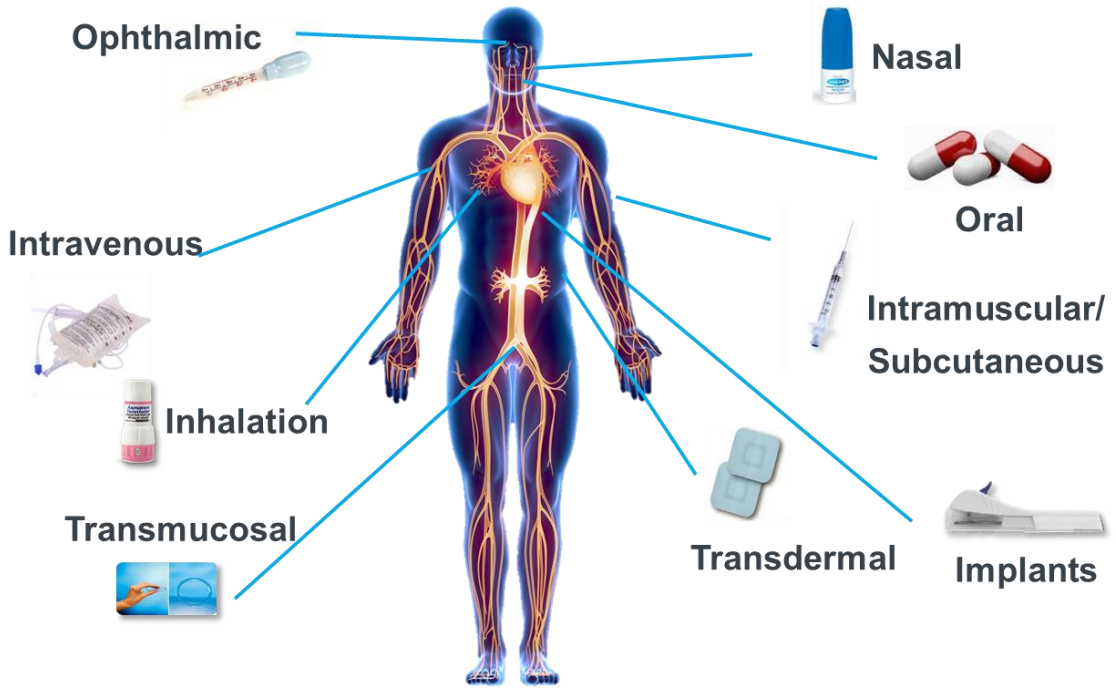
MSD INVENTING FOR LIFE

Outline

- Why is there a need for “meaningful” product specifications?
- What are clinically relevant dissolution specifications?
  - What’s a “safe space” ?
  - Where and when do you apply the safe space concept?
- Principles towards establishing clinically relevant dissolution specifications
- How can clinically relevant specifications be established?
  - CRDS Roadmap
- When should clinically relevant dissolution specifications be established?
- Outlook

Can we expect the same from Drug Products?



All of these products should be supported by ***unambiguous*** tests to ensure ***consistent performance***

Need for Clinically Relevant Specifications: Patient Perspective

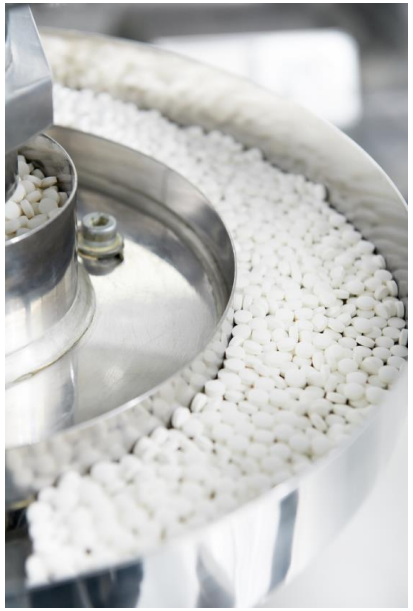
- Patients expect medicines to be Safe and Efficacious
  - Right identity and **<u>performance as described in label</u>**
  - Perform consistently within expiry date
  - Made in a manner that assures quality
  - Are available when needed

Pharmacology and Safety
Pivotal Studies

Pharmaceutical Quality / CMC

Clinically Relevant Specifications
(Implicit but absolute belief)

Need for Clinically Relevant Specifications: Manufacturer Perspective



- Safe and Efficacious Medicine that can be **successfully approved and supplied**
  - Right identity and performance as described in label
  - Perform consistently within expiry date
  - Made in a manner that assures quality (QbD)
  - Are available when needed

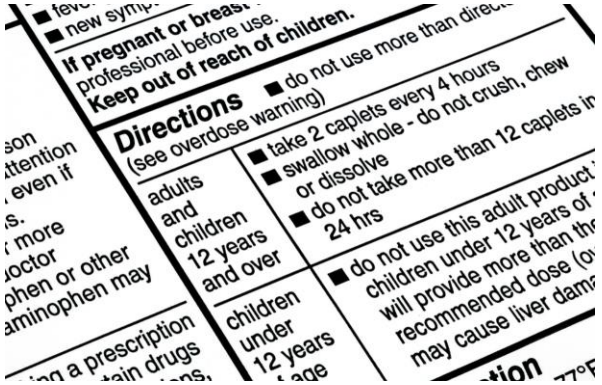
Clinically Relevant Specifications support any changes in DP/process between Pivotal Studies and Commercial supply

CRS show whether any stability changes are relevant for the patient supporting robust shelf-life definition (SLLA vs. “attributes”)

CRS allows a manufacturing process to be developed that produces product of suitable quality to meet patients' expectations wrt safety and efficacy

Allows manufacturing process that is not unnecessarily constrained. Unexpected ‘changes’ or future improvements can be quantified in terms of impact on patients primary concern (safety and efficacy)

Need for Clinically Relevant Specifications:
Paul's View on why important for Regulators



- Safe and Efficacious Medicine that can be **successfully approved and supplied**
  - Right identity and performance as described in label
  - Perform consistently within expiry date
  - Made in a manner that assures quality
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Without CRS can be no significant changes between Pivotal Studies and Commercial supply without other supportive data (patient access issue)

Unknown if changes are relevant: apply arbitrary (narrow) limits

Without CRS set process limits based only on pivotal batches data / arbitrarily or require methods that are very / overly sensitive

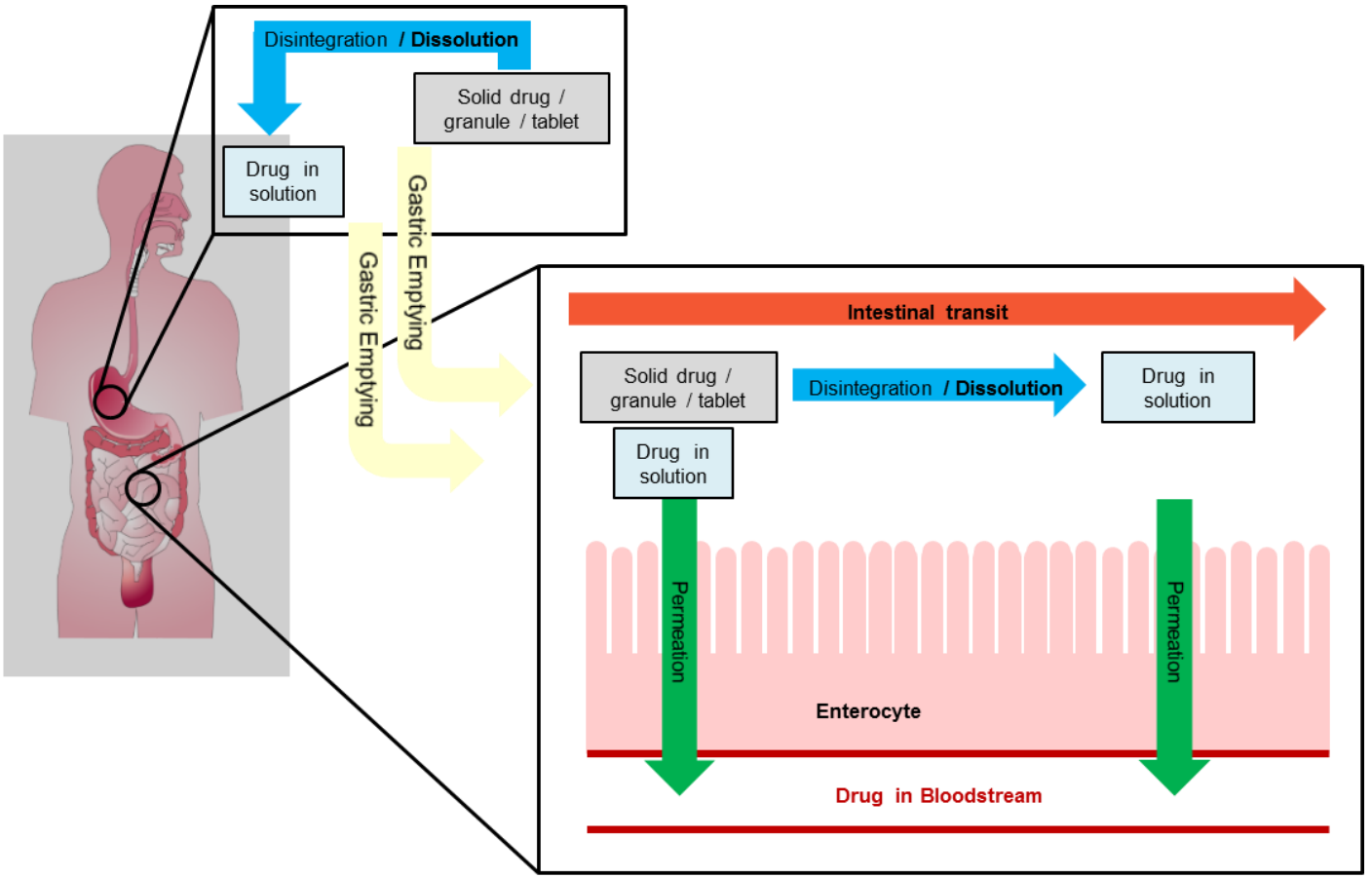
Without CRS might be able to control the quality of product the patient receives but increased risk of constrained process that cannot reliably provide product of necessary quality / or higher costs

Some Clinically Relevant Specifications are uncontroversial / well accepted

- For instance:
  - Identity (Safety and Efficacy)
  - Assay (Safety and Efficacy)
  - Related Substances/Degradants (Safety)
- Methods can be developed that can accurately measure these attributes and different methods will give the ‘same’ result
  - e.g. related substances meet ICH limits or have been qualified in toxicology / safety studies

Concentration at the target site (activity) is dependent on the rate of input and elimination

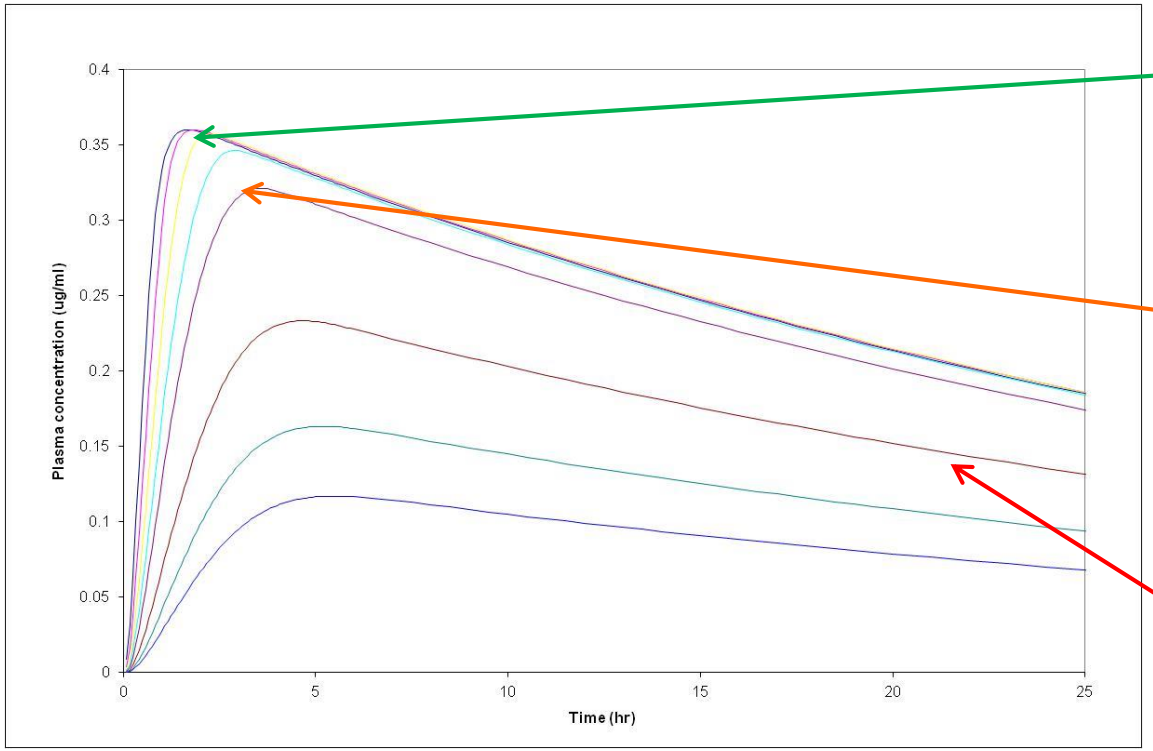
- Usually the product only affects dissolution step
  - excipients
- Drug absorption and product performance in the clinic is a case of understanding the relative balance of three rates
  - Dissolution
  - Permeation
  - GI transit time



Dickinson, Flanagan, Holt and Stott,
http://dx.doi.org/10.4032/9789814745468

Concentration at the target site (activity) is dependent on the rate of input and elimination

- Rate of elimination constant for a particular drug so consistency in the shape of the plasma concentration time profile is dependent on the input rate
  - Dissolution can be the rate limiting step for absorption rate
  - Example of the impact of slowing dissolution on PK profile



Fast dissolution: complete absorption (high AUC and rapid absorption (early T_{max}, high C_{max})

Slowing dissolution initially as little impact as physiological processes are still slower than dissolution but as dissolution slows more:

- T_{max} becomes later
- and C_{max} lower

Eventually dissolution becomes so slow (or incomplete) that there is not enough time for the drug to permeate after dissolution

- AUC is affected

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  - Dissolution can be the rate limiting step for absorption rate
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Why dissolution testing?

Drug absorption from a solid dosage form after oral administration depends on the release of the drug substance from the drug product, the dissolution or solubilization of the drug under physiological conditions, and the permeability across the gastrointestinal tract. Because of the critical nature of the first two of these steps, in vitro dissolution may be relevant to the prediction of in vivo performance. *Based on this general consideration, in vitro dissolution tests for immediate release solid oral dosage forms, such as tablets and capsules, are used* ***to (1) assess the lot-to-lot quality of a drug product; (2) guide development of new formulations; and (3) ensure continuing product quality and performance after certain changes,*** *such as changes in the formulation, the manufacturing process, the site of manufacture, and the scale-up of the manufacturing process**

*A dissolution procedure intended to be **used as a routine control test for immediate release drug products** should be robust, reproducible and discriminatory in order to assure a consistent product quality and **to detect product quality attributes, which, if altered, may affect the in vivo performance*****.

- *Guidance for Industry Dissolution Testing of Immediate Release Solid Oral Dosage Forms, 1997; U.S. Department of Health and Human Services Food and Drug Administration (CDER)

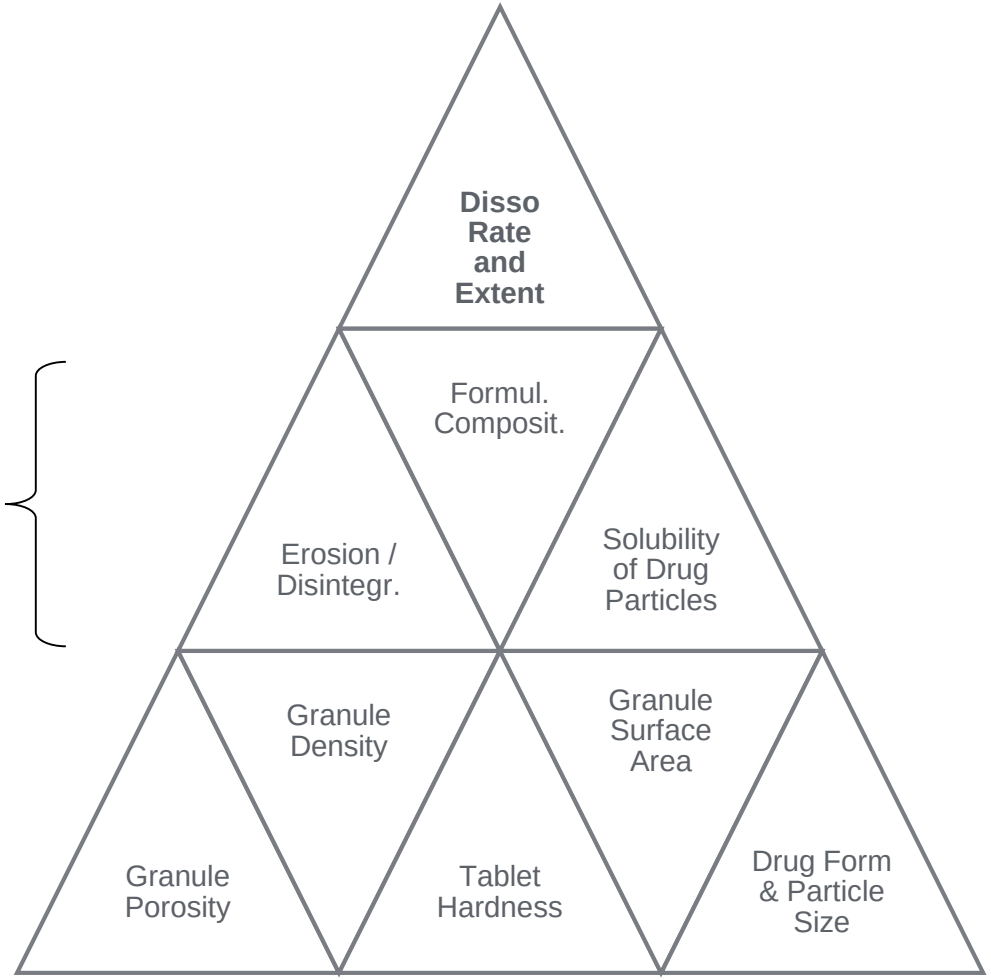
** Reflection paper on the dissolution specification for generic solid oral immediate release products with systemic action, EMA/CHMP/CVMP/QWP/336031/2017

So this all seems straight forward, why do we need a seminar series?

- Quality Aspects: Mechanistic understanding and dissolution
- Manufacturing consistency and Safety and Efficacy: not always the same thing?

Dickinson, 2015

More specific testing & control



Product attributes

Process linked product attributes

Test to ensure Manufacturing Consistency / QC method

Test to ensure Clinical Performance:

Dissolution is the first step in drug absorption and therefore may affect Patients Pharmacokinetics

More general testing & control

Seems straight forward: Why do we need a seminar series?

- Unlike other tests different dissolution methods can produce very different results

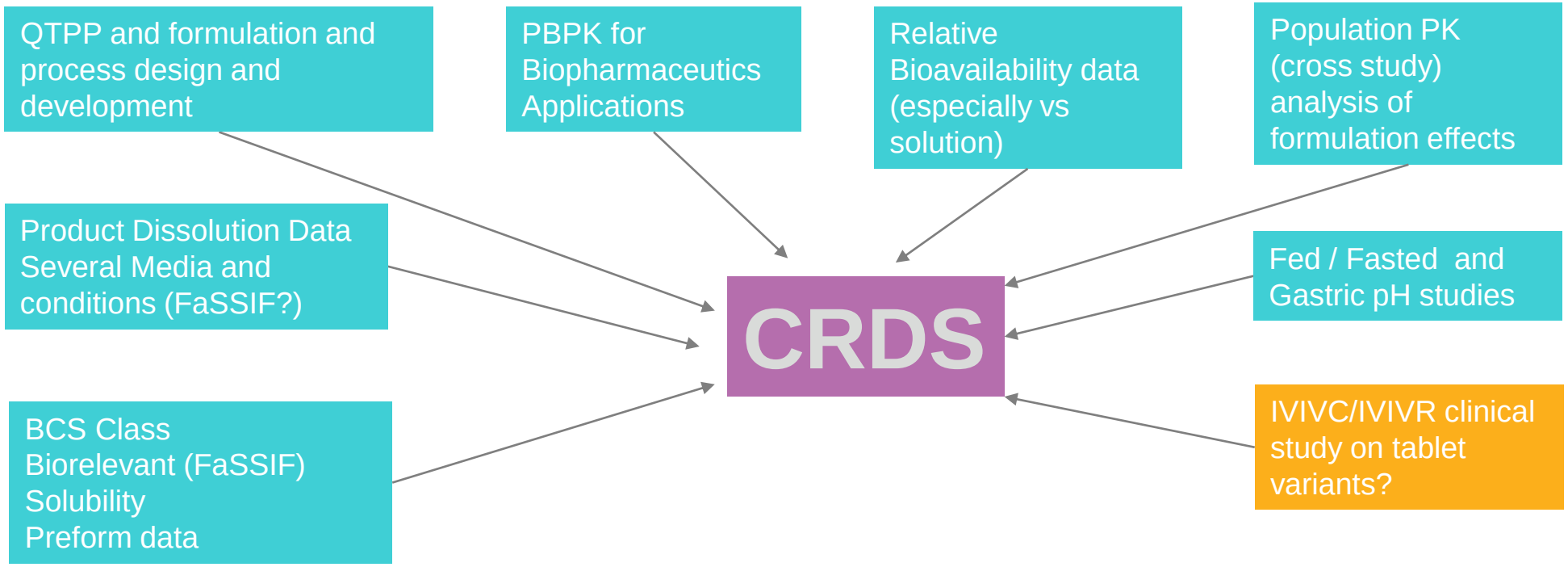
Performance of the different dissolution methods against desired method capabilities				
Desired method capability	**pH 1.2 aqueous buffer**	**pH 4.5 aqueous buffer**	**pH 6.8 aqueous buffer**	**Surfactant**
Discriminatory	Low	Low	High	High
Stability Indicating	Low	Low	Low	High
Complete Release	Yes	Yes	No	Yes
Routine Use	Yes	No	No	Yes
Controls Clinical Performance	Unclear	Low	Seminar series. Quite complicated Low	High / Moderate
Biorelevant / Physiological	Yes	No	High / Moderate	Unclear

Dissolution and Product Performance

Drug Product type	Performance test(s)	Can clinical relevance be established?
	Dissolution	
	Emitted dose + APSD/ + Dissolution ?	
	Dissolution	
	Dissolution	
	Dissolution	

Disciplines/data /techniques required for CRDS and covered in this seminar series:

- Clinically relevant dissolution specification can seem to be all about clinical studies and dissolution test (see following slides) but they are really about building knowledge base to show we **understand clinical performance** and can describe the **level of risk** associated with the test and control of clinical quality



Systems approach to building the knowledge required for CRS

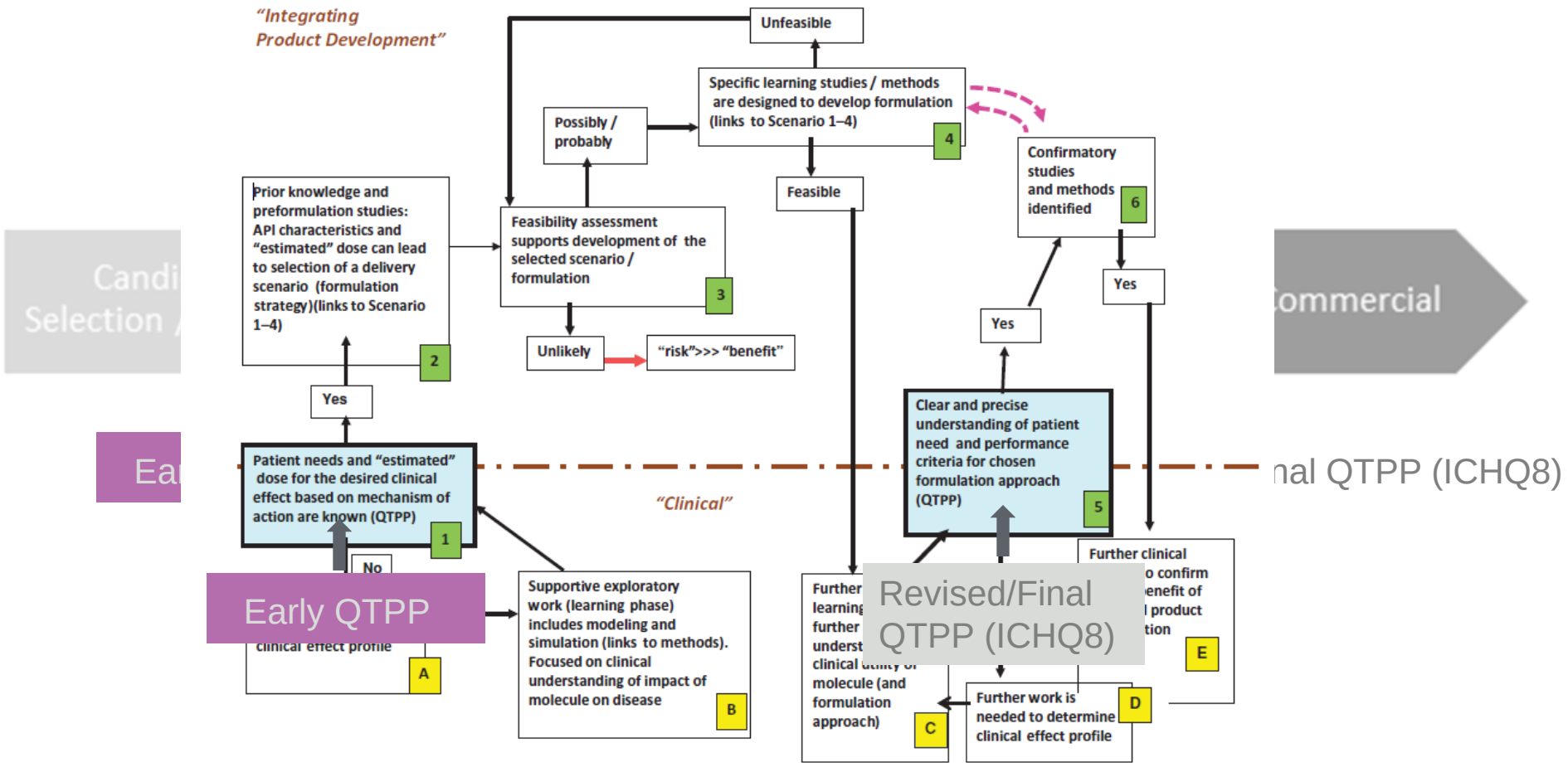
- If good biopharmaceutics risk understanding / ability to describe clinical performance is required. This likely requires this to be thought about right from the start of clinical development
  - See later slides: CRS usually seen as a later phase activity
- BioRAM is a useful framework to implement systems thinking throughout development and highlights the concept of an early QTPP
  - Focussed on answering critical questions and moving quickly to decision point to ensures that patient centric drug products are developed and the necessary knowledge and data exists to ensure appropriate drug product quality can be maintained in pivotal studies and on and after launch
- The focus of BioRAM is patient centric drug design and the roadmap including early QTPP plus scoring grid facilitate this process and will likely result in CRS

A. Selen, P.A. Dickinson, A. Müllertz, J.R. Crison, H.B. Mistry, M.T. Cruañes, M.N. Martinez, H. Lennernäs, T.L. Wigal, D.C. Swinney, J.E. Polli, A.T.M. Serajuddin, J.A. Cook, J.B. Dressman (2014) The Biopharmaceutics Risk Assessment Roadmap for Optimizing Clinical Drug Product Performance. J. Pharm Sci. 103: 3377–3397. http://dx.doi.org/10.1002/jps.24162

P.A. Dickinson, F. Kesisoglou, T. Flanagan, M.N. Martinez, H.B. Mistry, J.R. Crison, J.E. Polli, M.T. Cruañes, A.T.M. Serajuddin, A. Müllertz, J.A. Cook and A. Selen (2016) Optimizing Clinical Drug Product Performance: Applying Biopharmaceutics Risk Assessment Roadmap (BioRAM) and the BioRAM Scoring Grid. *J. Pharm. Sci.* 105: 3243-3255. http://dx.doi.org/10.1016/j.xphs.2016.07.024

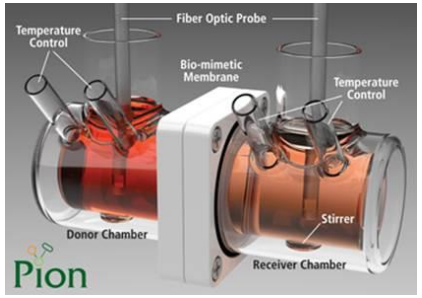
A. Selen, A. Müllertz, F. Kesisoglou, R.J.Y. Ho, J.A. Cook, P.A. Dickinson and T. Flanagan (2020) Integrated Multi-stakeholder Systems Thinking Strategy: Decision-making with Biopharmaceutics Risk Assessment Roadmap (BioRAM) to Optimize Clinical Performance of Drug Products. AAPS J 22: 97- 117. https://doi.org/10.1208/s12248-020-00470-z

Systems Approach: the BioRAM roadmap



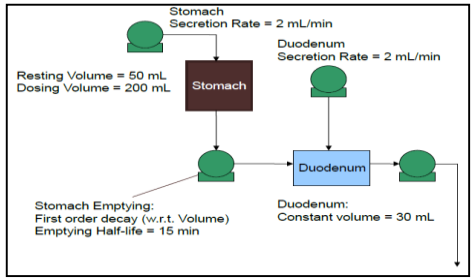
The Challenge: Linking *in vitro* dissolution to *in vivo* dissolution

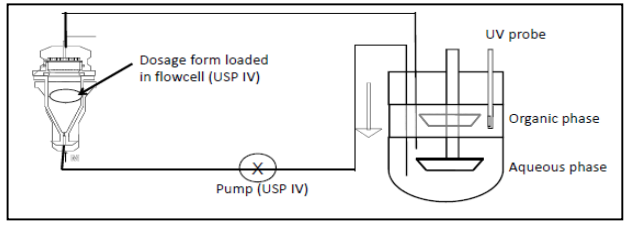
By measuring the rate and extent of drug release in vitro……



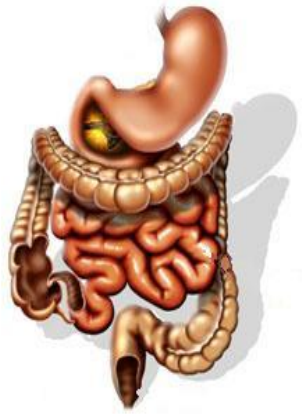
“Non-traditional”

“Traditional” (USP 1-7)





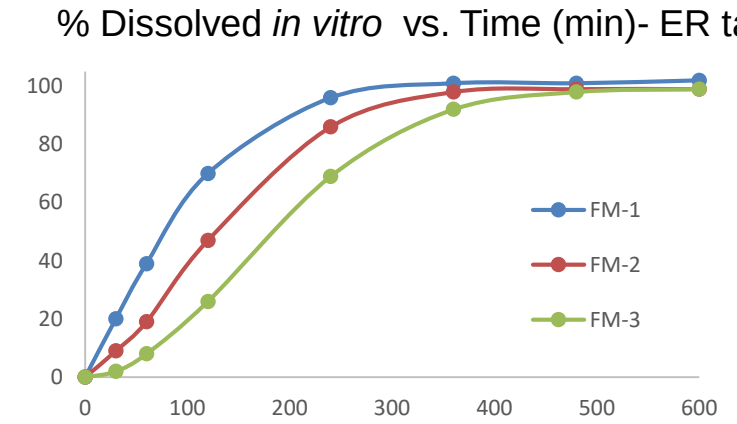
…..we (try to) predict or confirm the rate and extent of drug release in vivo



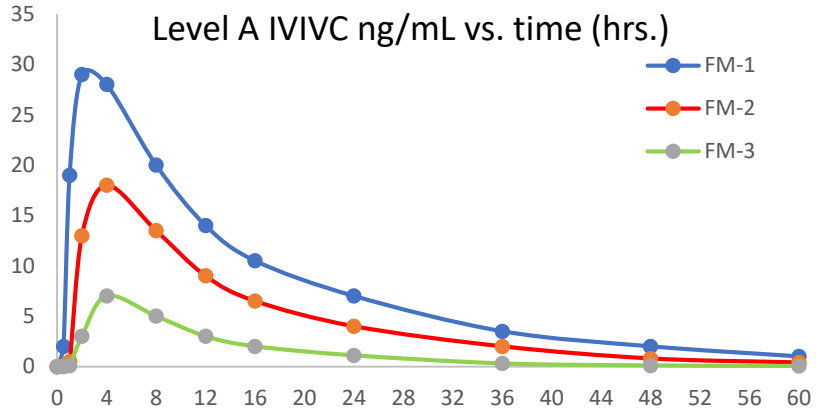
Ideally…..

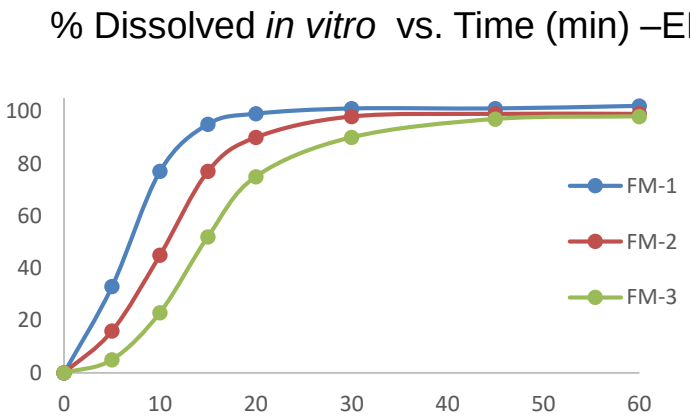
- *In vitro* methods available to assess *in vivo* impact = *In Vitro-in Vivo Correlation (IVIVC)*:
- Streamlined patient centric product development
  - ✓Justifies discriminating power of the *in vitro* dissolution method
  - ✓Enables efficient and unambiguous drug product development (QbD)
- Efficient Post-Approval Change management

In practice we achieve:



Correlation





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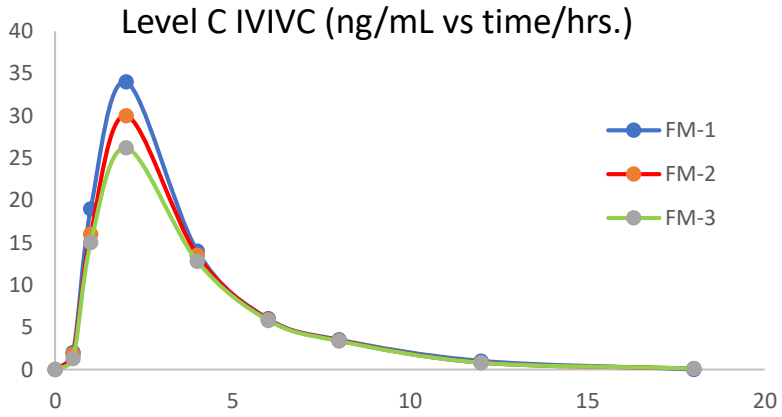
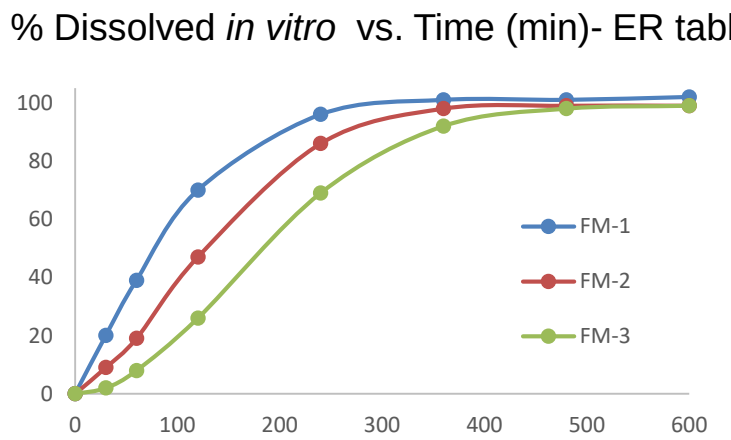


Or we may observe:



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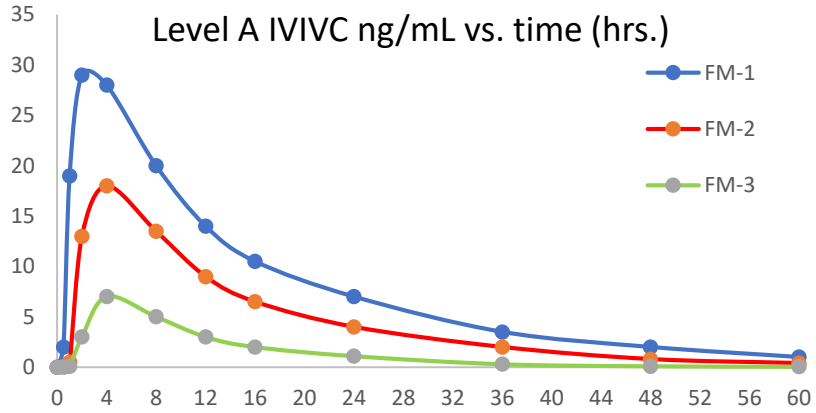
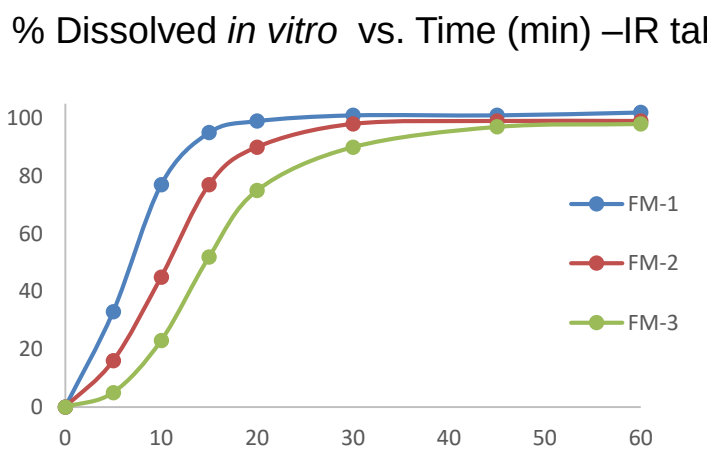
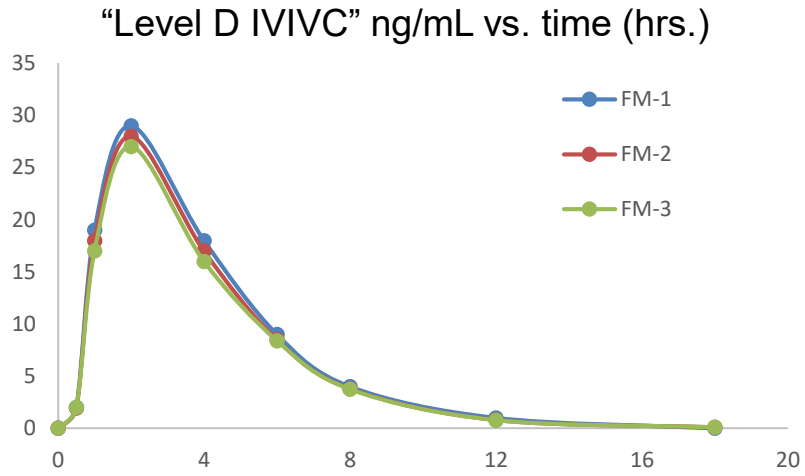




Relationship



Terminology

Clinically relevant	**The term "clinically relevant" implies the establishment of a link between drug product quality attributes (e.g., in vitro dissolution, purity, etc.), CMAs/CPPs, and in vivo performance (e.g., systemic exposure).**
Safe space– or bioequivalent space	Boundaries defined by in vitro specifications (i.e., dissolution or other relevant drug product quality attributes), within which drug product batches are anticipated to be bioequivalent to one another, or less optimally, but still possible, bioequivalent to the pivotal clinical batch(es). Drug product specifications are expected to be set within these boundaries.
Biorelevant dissolution method	A set of testing conditions for monitoring in vitro dissolution designed to closely mimic a relevant biological fluid and a physiological environment.
Clinically relevant dissolution specifications	A set of in vitro dissolution testing conditions and acceptance criterion (ia), that can identify and reject drug product batches that are not expected to be bioequivalent to clinical pivotal product batches.
Discriminating dissolution specifications	A set of in vitro dissolution testing conditions that, along with the acceptance criterion (ia), are able to differentiate drug products manufactured under target conditions vs. drug products that are intentionally manufactured with meaningful variations (i.e., formulation and manufacturing variants) for the relevant manufacturing variables (e.g., drug substance particle size, compression force, tablet hardness, etc.).

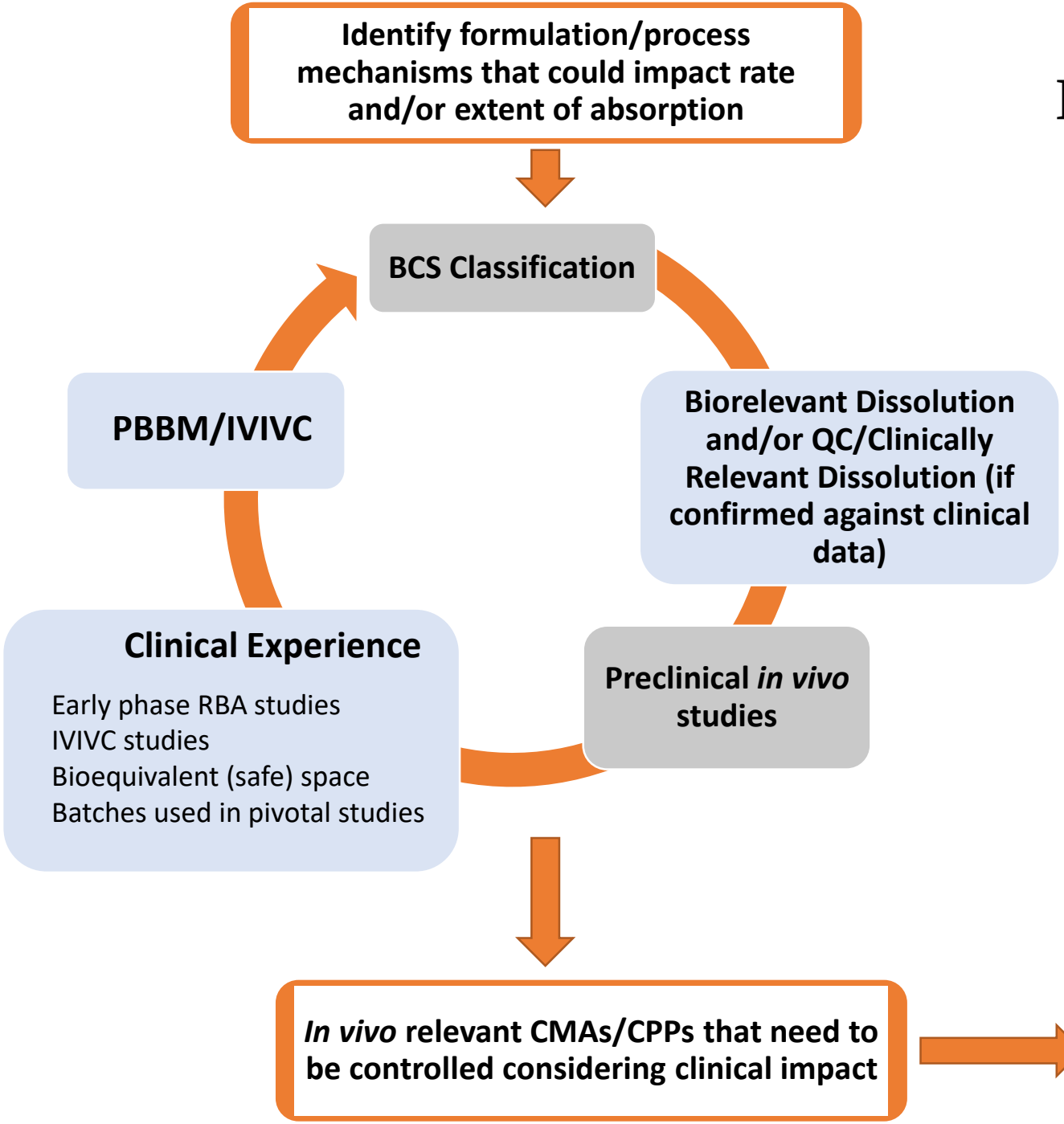
Abend, A.; Heimbach, T.; Cohen, M.; Kesisoglou, F.; Pepin, X.; Suarez, S., Dissolution and Translational Modeling Strategies Enabling Patient-Centric Drug Product Development:

M-CERSI Workshop Summary Report. *AAPS J.* **2018.**

EMA reflection 2017 reflection paper uses similar concepts (not using the same terminology)

- Are Biopharm Risks understood- and how can they be controlled?
- Can a dissolution method detect biopharmaceutics risk attributes?
- What process and materials factors impact rate and extent of dissolution in vitro?
- Are these factors critical from a biopharmaceutics perspective?

Biopharmaceutics Risk Assessment

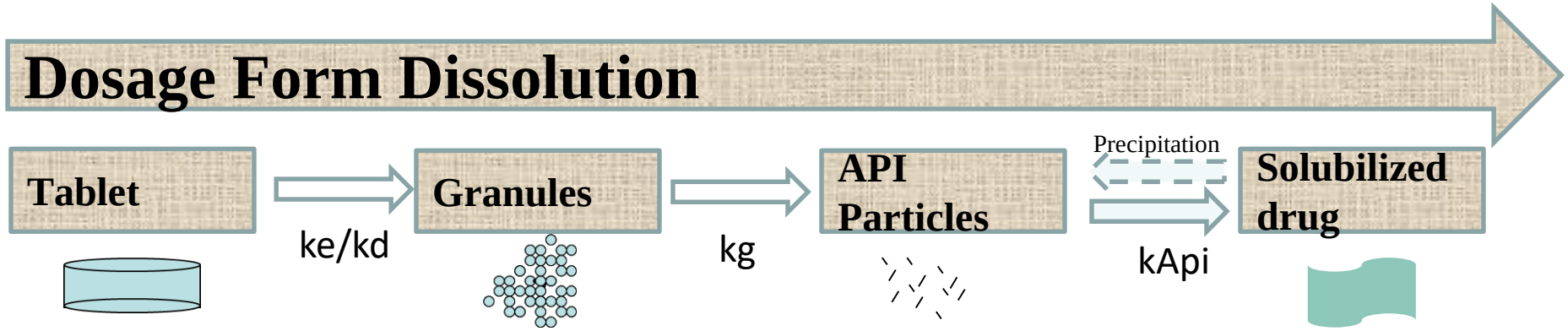


Mechanistic understanding of *in vitro* dissolution

Control space for clinically relevant formulation/process parameters

Dissolution (QC) specifications with clinical relevance ensured either by sensitivity to clinically relevant formulation/process parameters and/or clinical experience (observed or projected safe space)

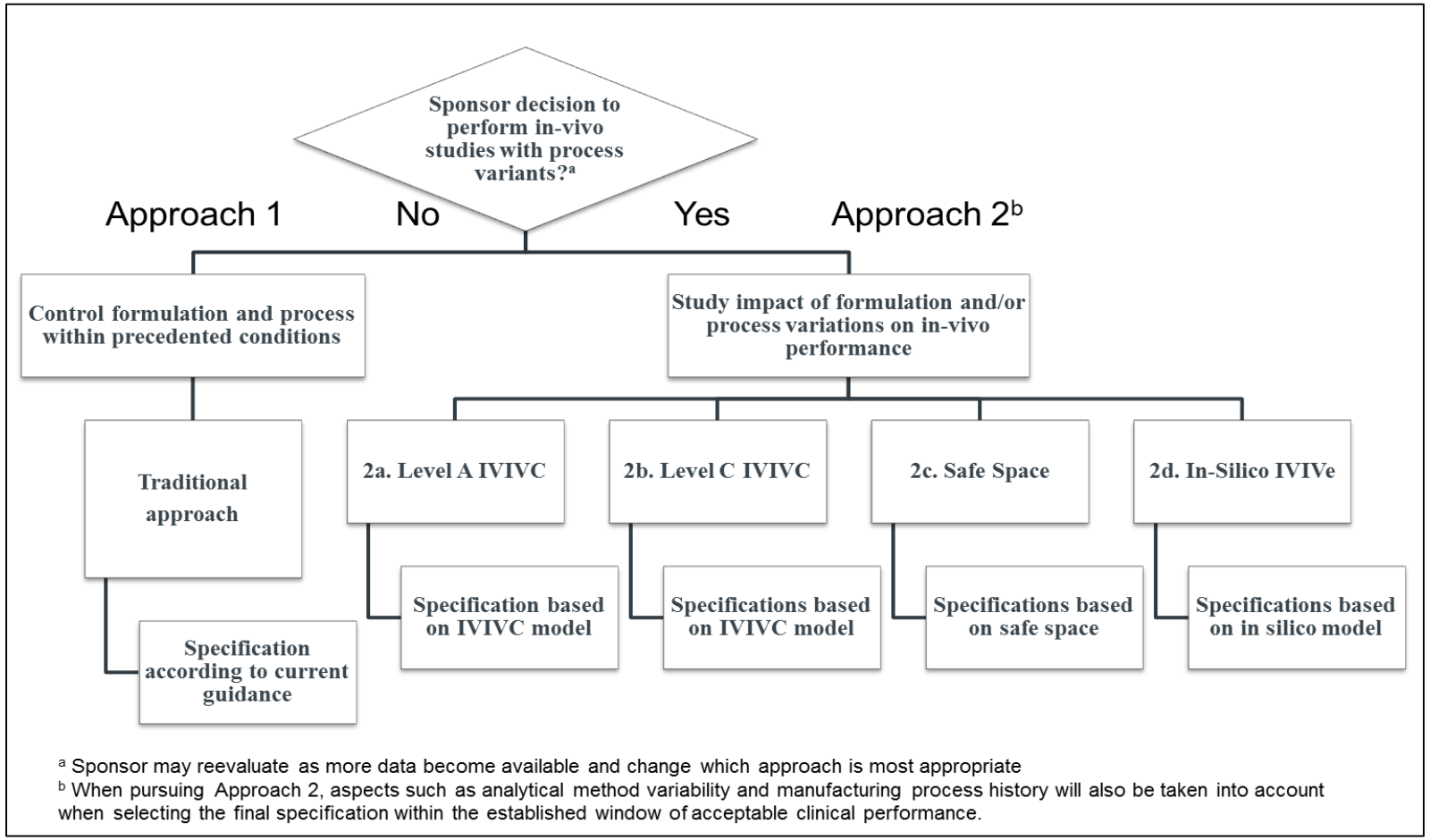
Mechanistic understanding of the dissolution process



$$k_{dissolution} = f(k_{erosion\ /disintegration}; k_{granule\ diss} ; k_{APIdiss})$$

- Interrogate the contribution of each step to the overall dissolution rate
- Each rate constant is often impacted by different formulation and process parameters
- Focus on the formulation and process parameters that have the most significant impact on *in-vitro* dissolution rate
- Identify Critical Materials Attributes and (Critical) Process Parameters and develop a sensitive dissolution method (based on prior knowledge, deliberate changes/variations)

CRDS Road-Map IQ/2017



Hermans, A., A. Abend, et al. (2017). " Approaches For Establishing Clinically Relevant Dissolution Specifications During Drug Development." AAPS J.; DOI: 10.1208/s12248-017-0117-1

Approach 1 – general assumptions:

- Acceptable if the *biopharmaceutical risks* are understood and a robust manufacturing control strategy is in place:
  - An *appropriately sensitive* QC method indicative of unacceptable process and formulation variability has been developed
    - This may be supported by either
      - Pre-clinical data
      - Applying biorelevant dissolution under various conditions
      - PBBM

Advantages and Disadvantages of Approach 1

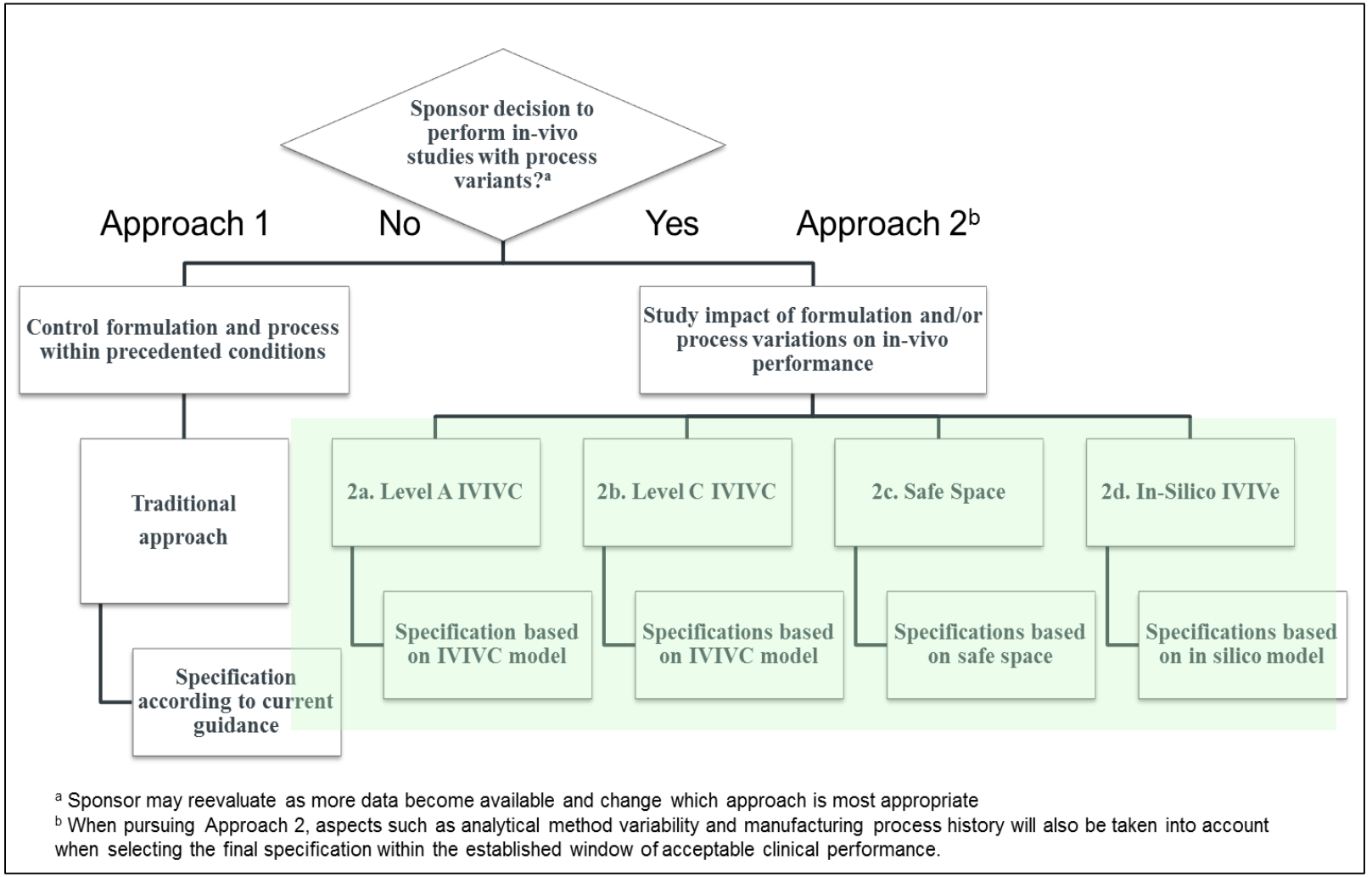
Advantage

- Speed of development
- Avoidance of unnecessary PK studies (i.e., BCS1 and BCS3)
  - In some cases, exposing healthy volunteers to potent compounds can be unethical

Disadvantage

- Discriminating power of the method (BCS 2&4)?
- Risk of tight specification
  - → Tight process controls
  - → Product discards
- Risk of “loose” spec
  - Release of product that is not equivalent to pivotal batches

Approach 2

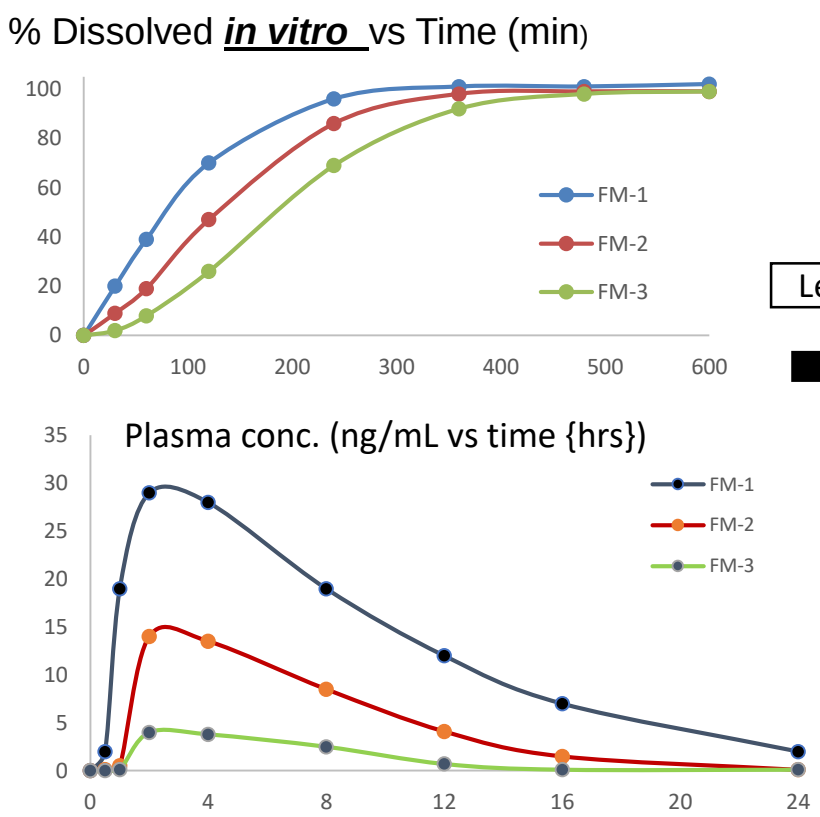


[a] Sponsor may reevaluate as more data become available and change which approach is most appropriate

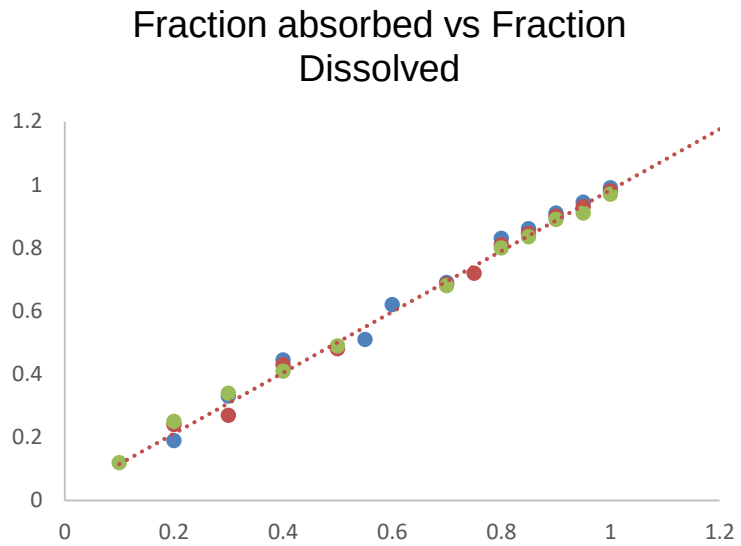
[b] When pursuing Approach 2, aspects such as analytical method variability and manufacturing process history will also be taken into account when selecting the final specification within the established window of acceptable clinical performance.

2a: Level A IVIVC*

- Definition of IVIVC (FDA): "A **Predictive** Mathematical **Model** Describing the Relationship Between an ***In Vitro*** **Property** of an Extended Release Dosage Form (Usually the Rate or Extent of Drug Dissolution or Release) and a Relevant ***In Vivo*** **Response**, e.g., Plasma Drug Concentration or Amount of Drug Absorbed"

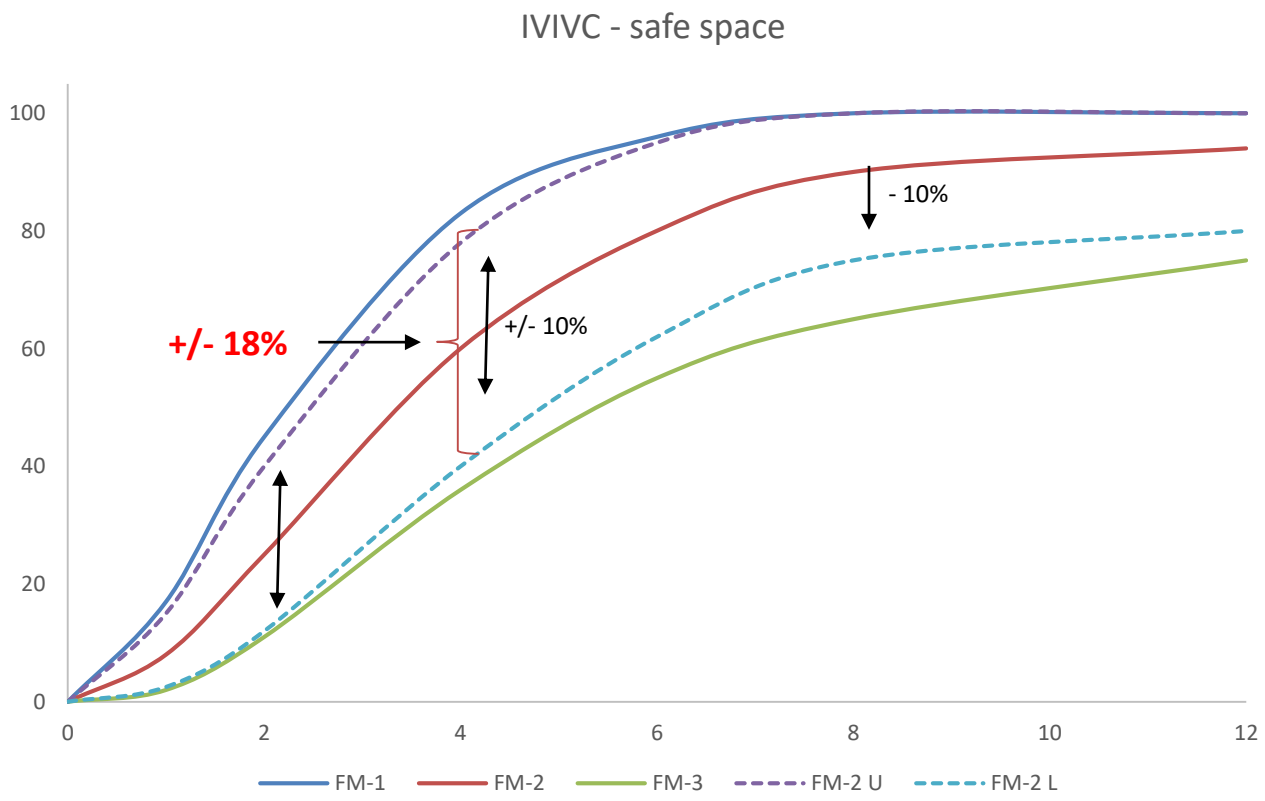


Level A Model



* High POS for most ER, but low POS for most IR products

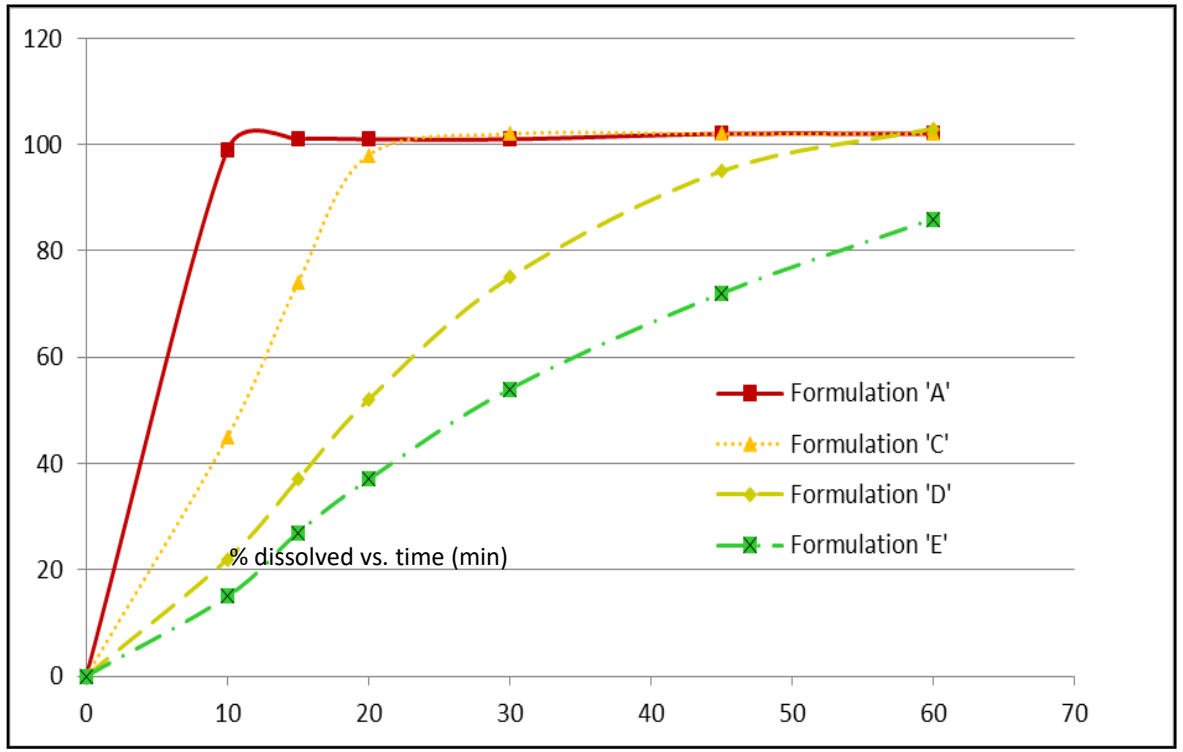
IVIVC Level A continued

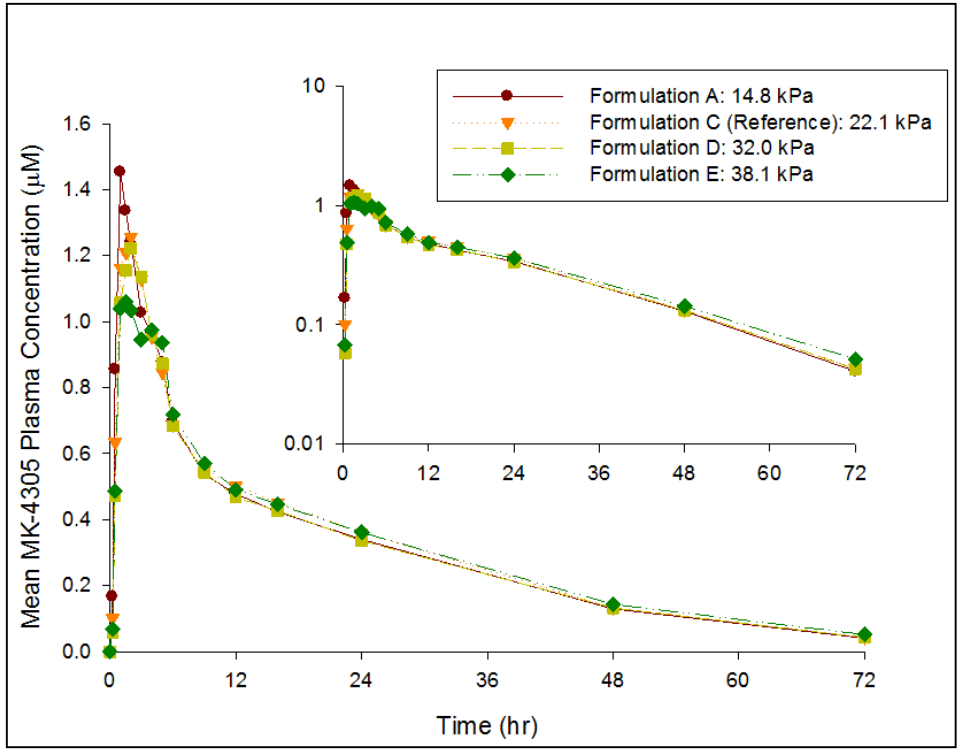


Similar to Sandra Suarez, FDA's Experience on IVIVC-New Products, PQRI Workshop on Application of IVIVC in drug product development, Bethesda, MD, Sept. 2012

2b: Level C IVIVC

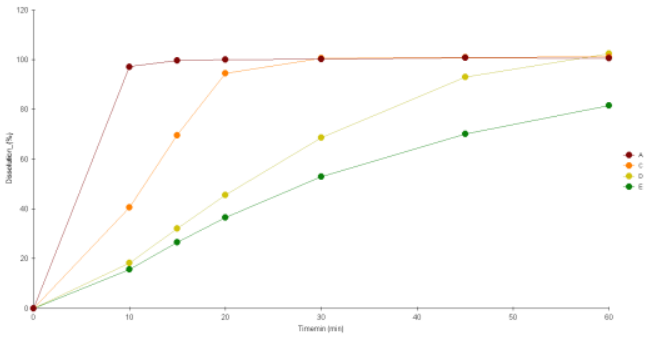
- IVIVC attempted – Got lucky….!

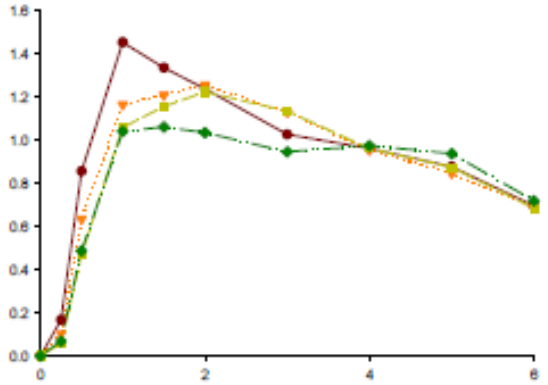




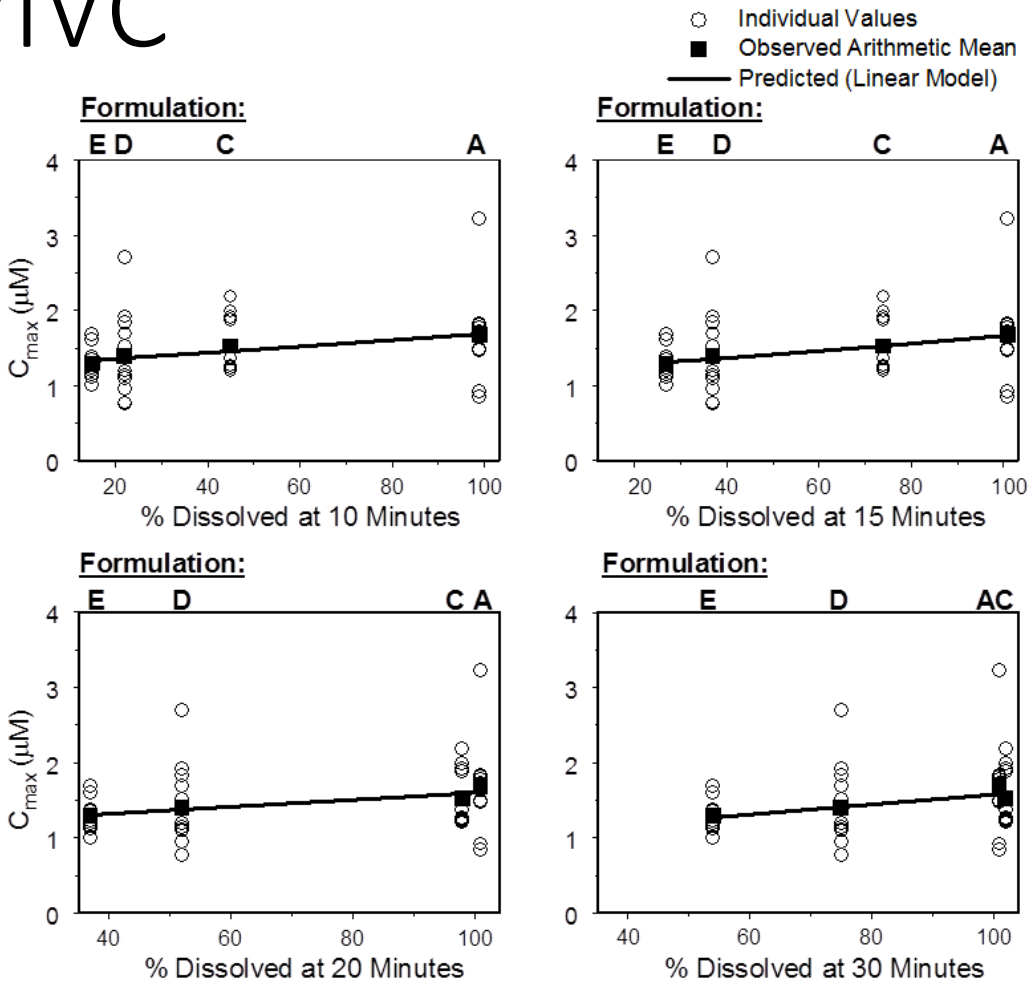
Relative Bioavailability Study on formulations with f_2<50 that include desired compression range

IR Tablet Level C IVIVC



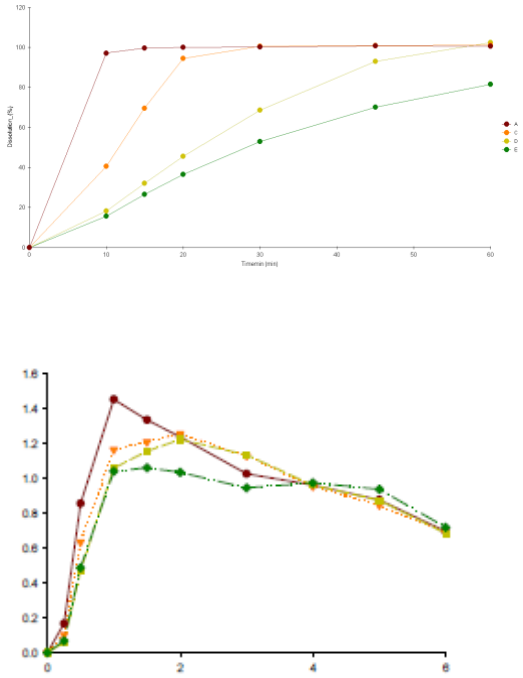


Relative Bioavailability Study on formulations with f_2<50 that spans the desired compression range

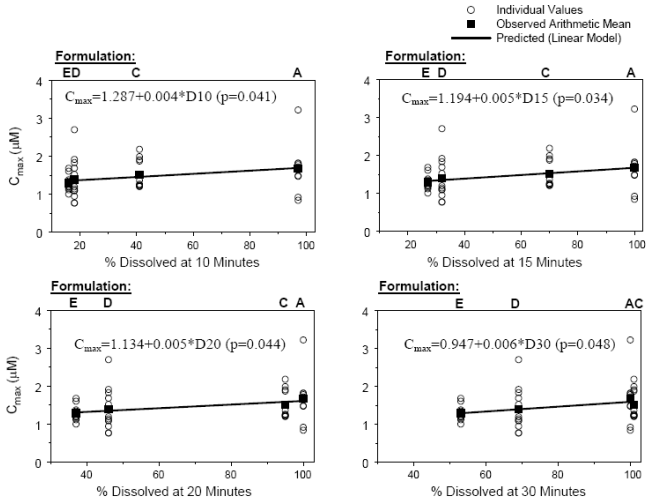


Multiple Level C IVIVC on Dissolution vs. Cmax (AUC not sensitive)

IR Tablet Level C IVIVC



Relative Bioavailability Study on formulations with f_2<50 that include desired compression range

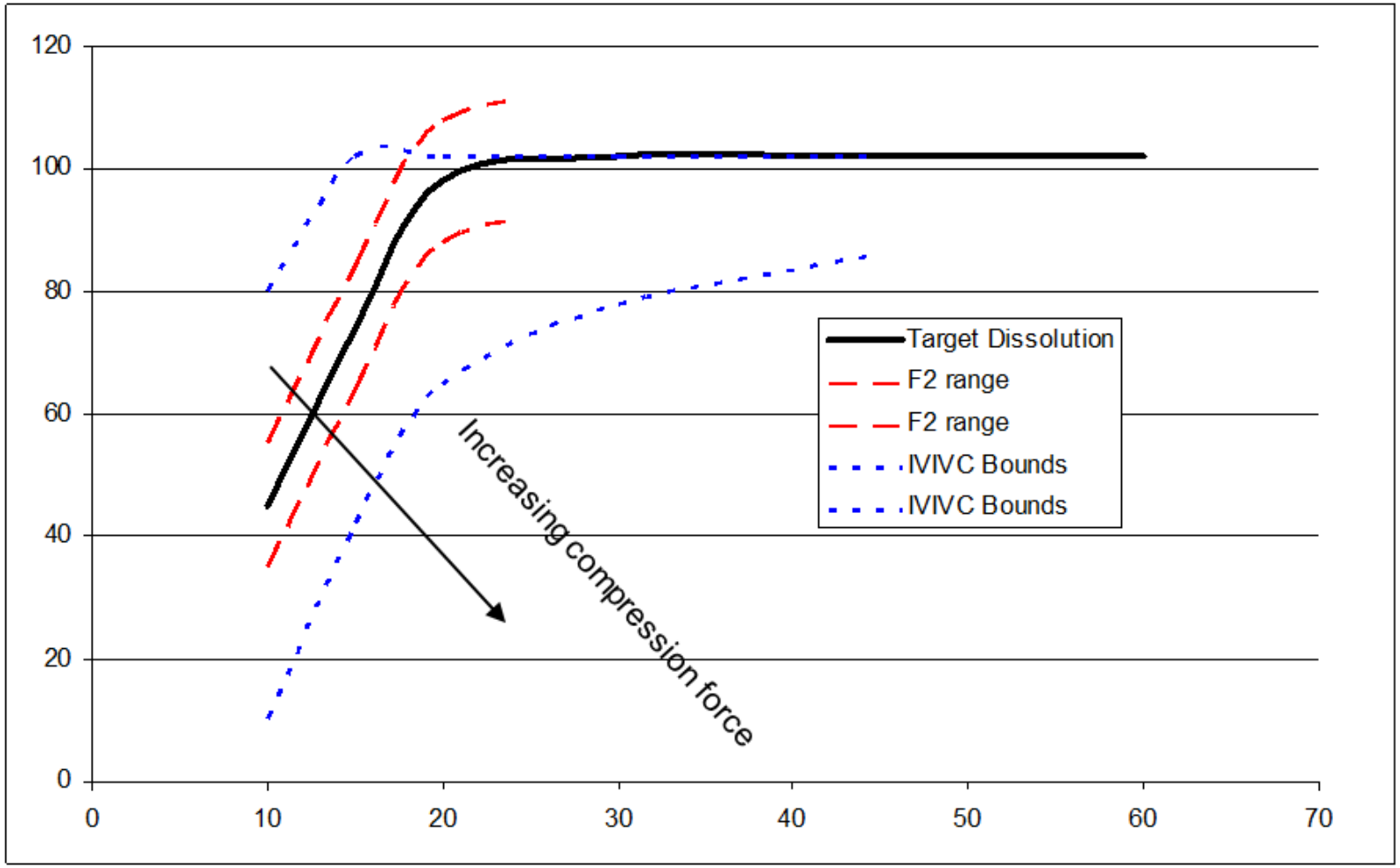


Multiple Level C IVIVC on Dissolution vs. C_{max} (AUC not sensitive)

Dissolution time point	lower dissolution range (% Claim)	upper dissolution range (% Claim)
10 min	10.3%	79.9%
15 min	42.2%	100%
20 min	64.9%	100%
30 min	77.8%	100%
45 min	86.0%	100%

Acceptable dissolution range based on IVIVC

Acceptable dissolution ranges based on IVIVC vs. traditional ranges (f_2) = SAFE SPACE



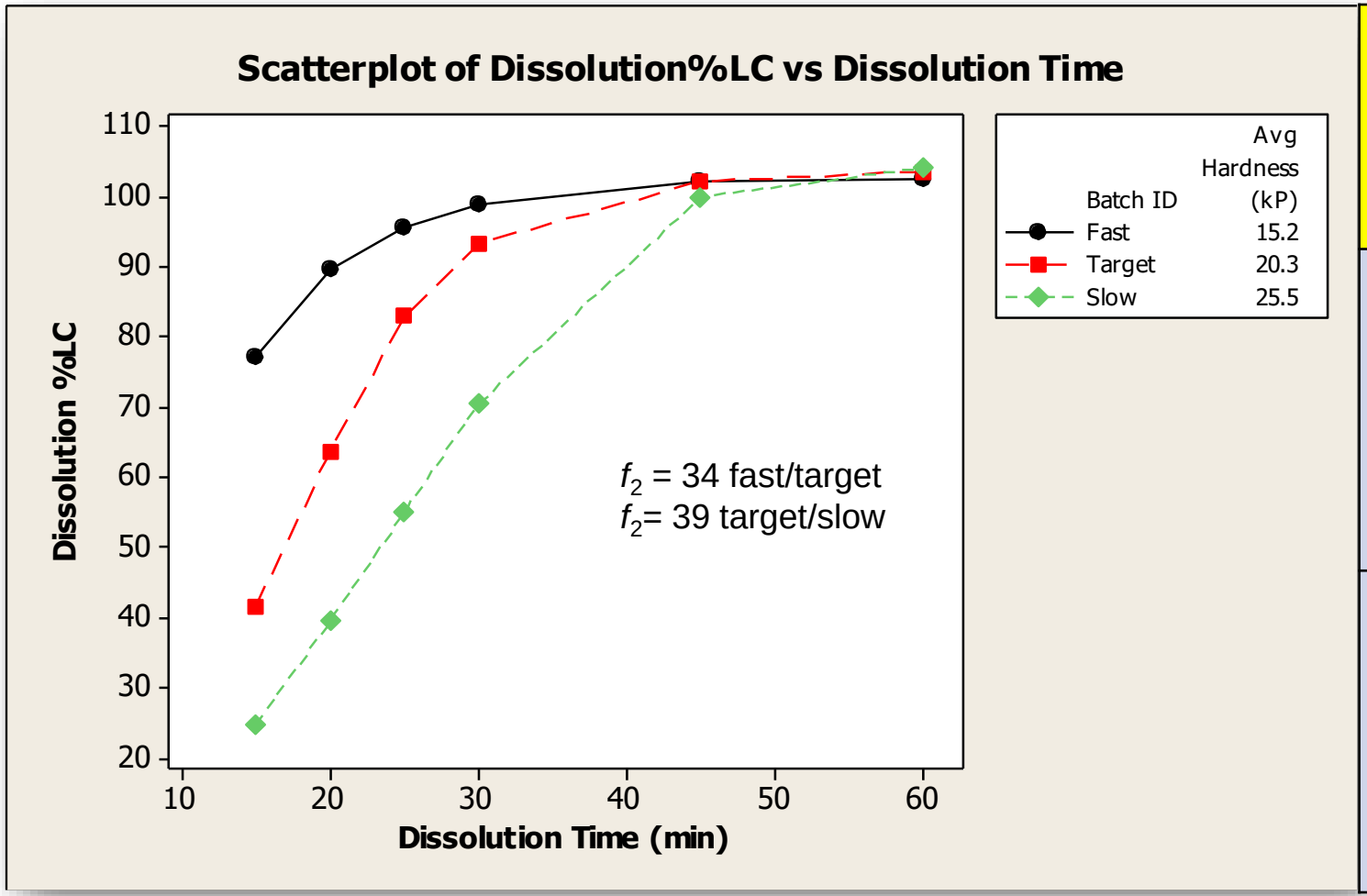
% dissolved vs. time (min)

2c: CRDS based on acceptable BE outcome

- IVIVC attempted, non-BE not achieved!
  - Technically impossible to demonstrate non-BE empirically
  - Situation can be translated to a single BE study as well
- Overly sensitive dissolution method:
  - Risk of running BE studies for Post-Approval Changes (PAC) due to failing disso similarity
  - Erosion controlled dissolution
    - CMA → tablet hardness
- Three batches (slow, target, fast) manufactured and

Davit, B. (2017). Case Study: Use of In Vivo Pharmacokinetic Data to Develop a CRS for In Vitro Dissolution Testing. Dissolution and Translational Modeling Strategies enabling Patient-Centric Product Development. Baltimore, MD

Dissolution profiles of 3 process variants



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

General Advantages and Disadvantages of Approach 2

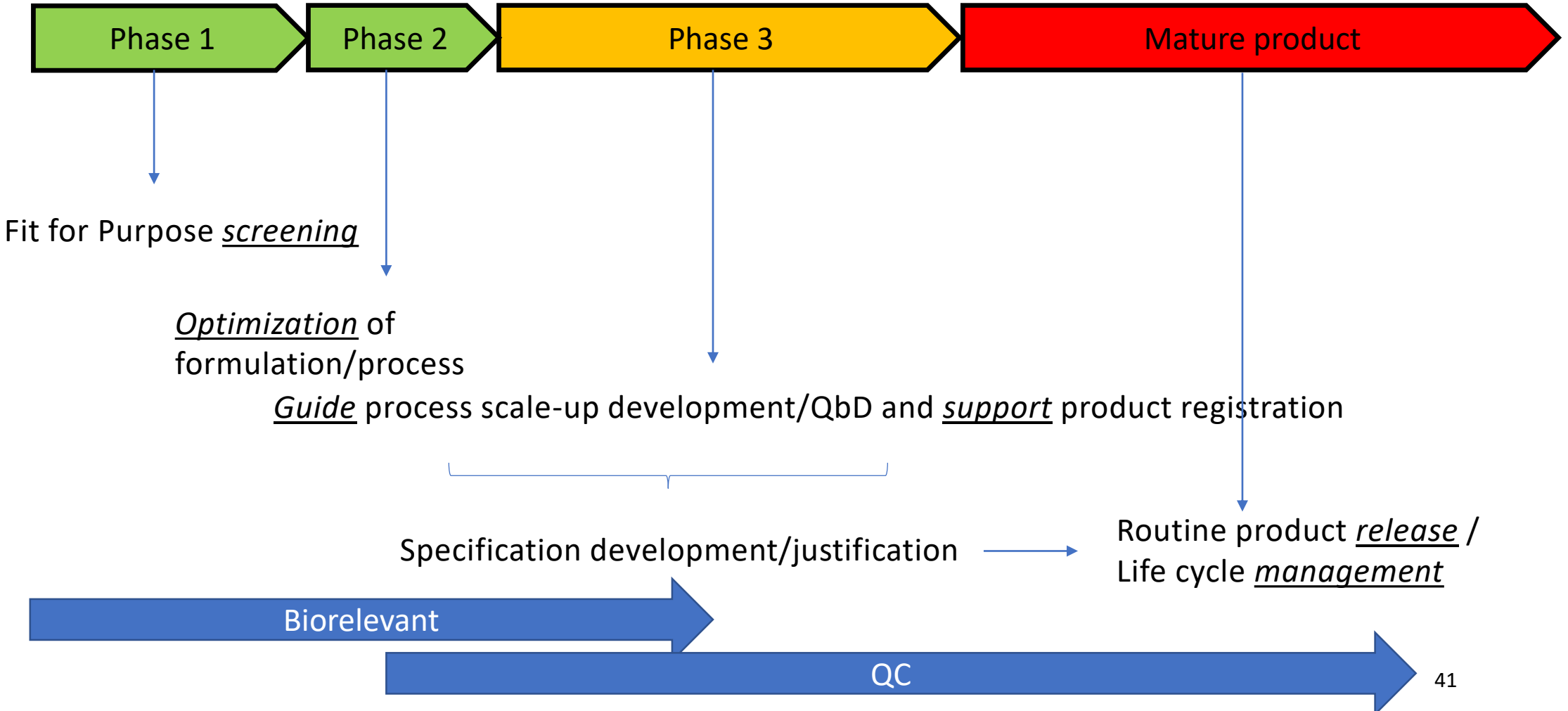
Advantage

- Confidence in the level of sensitivity of the disso specification
- Safe space should provide regulatory flexibility when needed

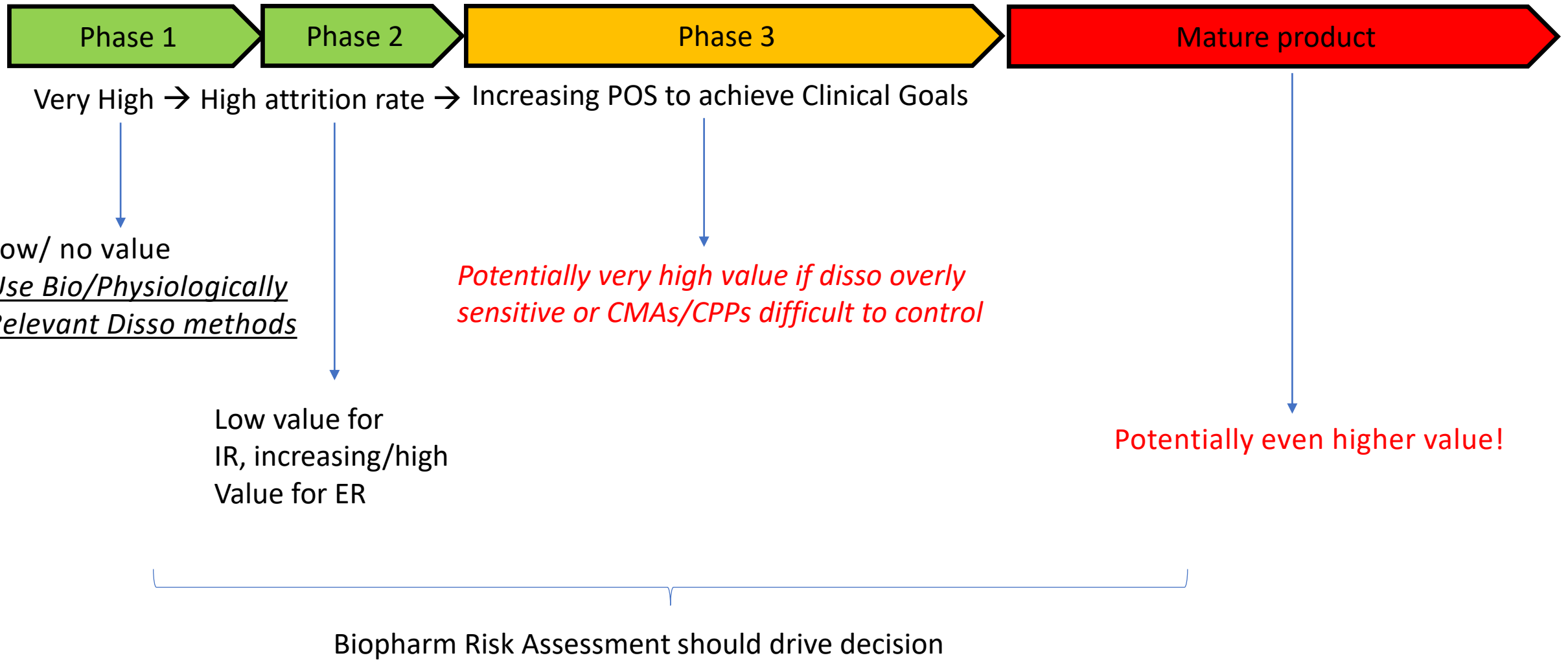
Disadvantage

- Additional cost/pre-investment
- Global acceptance of safe space based on Level C IVIVC, IVIVR or PBPK modeling unknown
  - → ROI

Dissolution specification development timeline

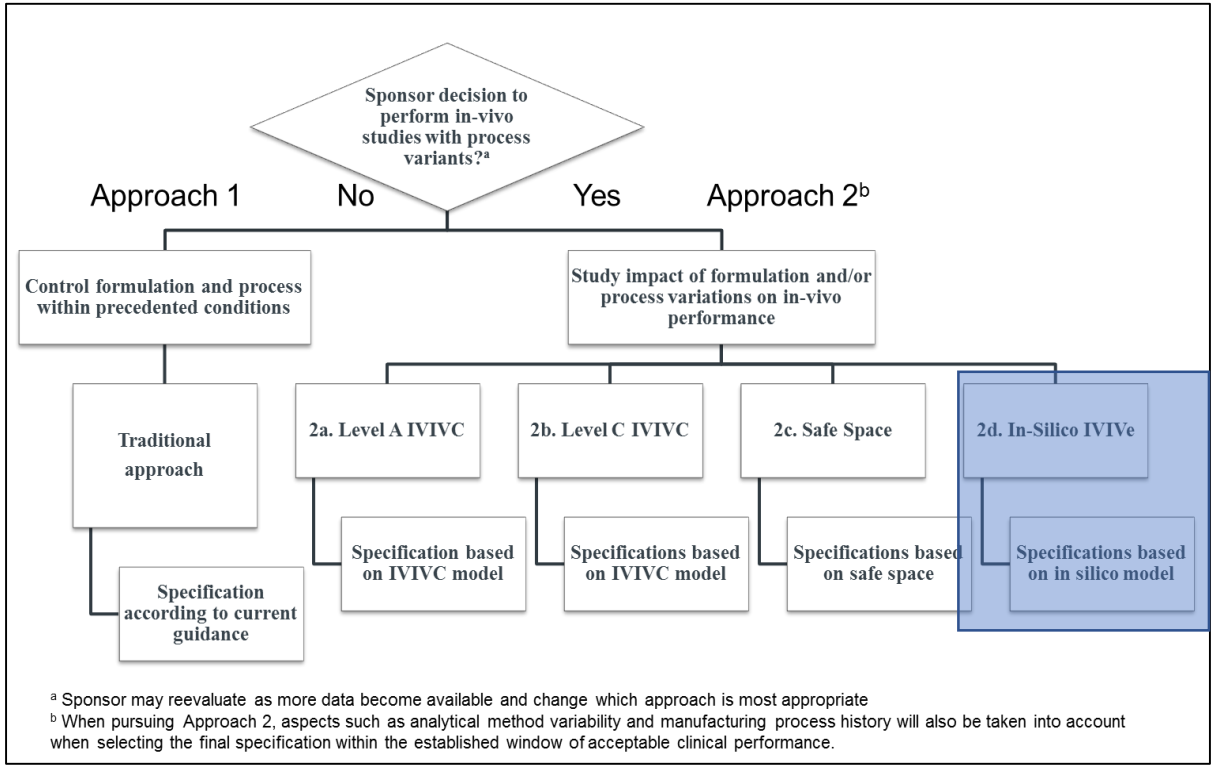


Timing and role of CRDS



Conclusions: Why are we doing all of this?

- Enhanced product understanding! Benefits all !
  - *Only product with acceptable in vivo performance is released to the patient*
- All products will eventually experience “change” – ultimately, CRDS can take the guess-work out of “Product life cycle management”
  - Even the most advanced stats to underpin “profile similarity” with analytical methods of unknown sensitivity towards *in vivo* behavior are pointless
  - Elimination of the ambiguity of *in vitro* bridging approaches based on methods with unproven ability to assess potential *in vivo* impact
  - Clarity when BE studies are really needed based on appropriate understanding of biopharmaceutics risks



Webinar 2. Introduction to PBPK/PBBM. How to build a PBBM model and why?

Speakers: Andrea Moir- AZ and Susan Cole – MHRA

2nd March 2021

- Background to PBPK/PBBM
- The approach to developing and building a model
- Different approaches to model dissolution within Industry (PSD approach, PBDT approach)
- Benefits of PBBM modelling approach
- Best practices in approaches to modelling and model evaluation.
- Regulatory thoughts on assessing predictive performance and qualification of models- the guidelines.
- Introduction to examples which will be presented in subsequent webinars


Thank You!

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