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The Future of Clinically Relevant Dissolution Testing and Physiologically Based Biopharmaceutics Modeling (PBBM/PBPK) in Drug Product Development, Manufacturing Changes and Controls

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Outline

- Regulatory applications of dissolution testing as per published FDA guidance
- Current trends on the regulatory applications of dissolution testing
- What key data are needed to establish biopredictive/clinically relevant dissolution testing (CRDT)?
- PBBM/PBPK in drug product development: identification of Safe Space
- The future role of CRDT and PBBM/PBPK: A stepping-stone toward supporting:
  - Patient centric drug product development
  - Enhanced drug product control strategy
  - Regulatory flexibility
- Challenges with the implementation of CRDT and PBBM/PBPK
- Future directions and concluding remarks

Dr. Gottlieb's Speech to the Regulatory Affairs Professionals Society (RAPS) 2017 Conference

- "We're on an unsustainable path, where the cost of drug development is growing enormously, as well as the costs of the new medicines. We need to do something now, to make the entire *process less costly and more efficient*. Otherwise, we won't continue to realize the practical benefits of advances in science, in the form of new and better medicines"
  - ……we're also taking new steps to modernize how sponsors can evaluate clinical information, and how FDA reviews this data as part of our regulatory process.
    - ……**This includes more widespread use of modeling and simulation**, and high-performance computing clusters inside FDA.

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FDA's Vision: Advancing Product Quality

Patient-Centric Drug Product Development

----21st Century Cures and PDUFA VI

A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high quality drugs without extensive regulatory oversight"

-----Janet Woodcock MD, Director, CDER FDA

Establishment of acceptance criteria for CQAs based on clinical relevance instead of process capability or manufacturing process controls

---FDA Pharmaceutical Quality Oversight-One Quality Voice

What is the role dissolution and PBBM/PBPK?

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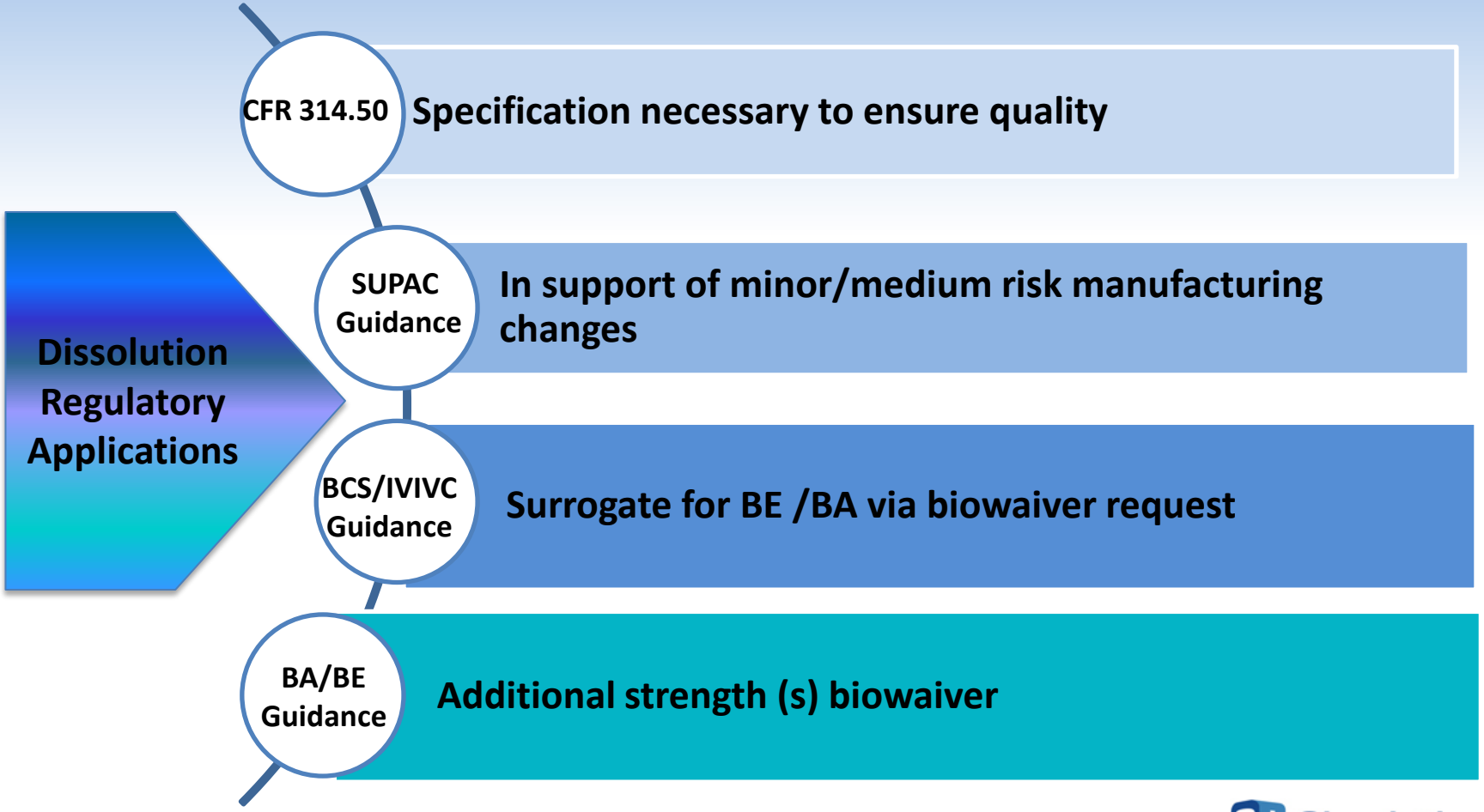
Regulatory Applications of Dissolution Testing: Current Published FDA Guidance



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Trends on the Application of Dissolution Testing

A Systematic Approach to Drug Product Development*

Predefined objectives	▪ Define Quality Target Product Profile (QTPP) ▪ Identify Critical Quality Attributes (CQA) based on science-driven development (scientific literature, prior knowledge, DOEs etc.)
Product and process understanding	▪ Identify critical material attributes (CMA*) and critical process parameters (CPP) ▪ Establish the functional relationships that link CMA/CPP to CQA
Process control	▪ Develop appropriate Control Strategy, including justifications
Quality risk management	▪ Risk-based development (ICH Q9)

Dissolution is usually identified as a CQA

Dissolution can be used to identify the CMAs/CPPs

Dissolution can be used to verify the design space limits

Dissolution can be used to support the establishment of clinically relevant drug product specifications

ICH guidance, Q9, Q8R2

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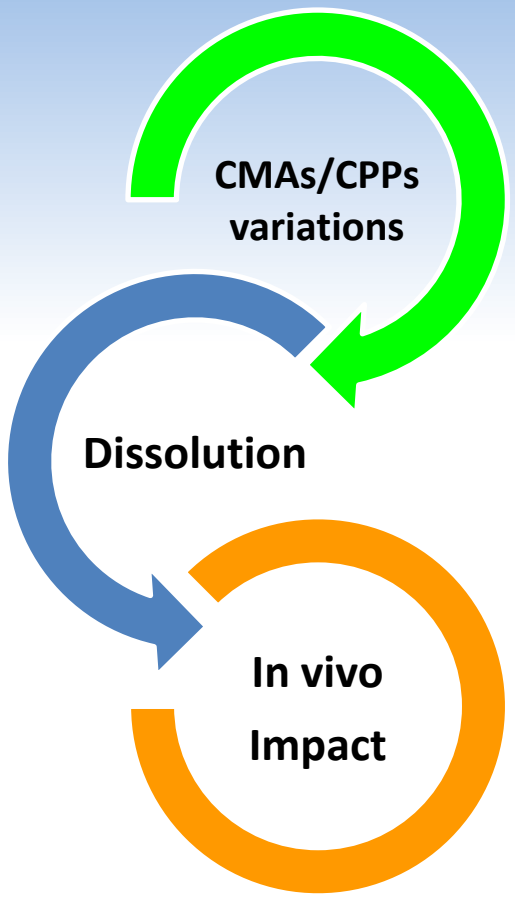
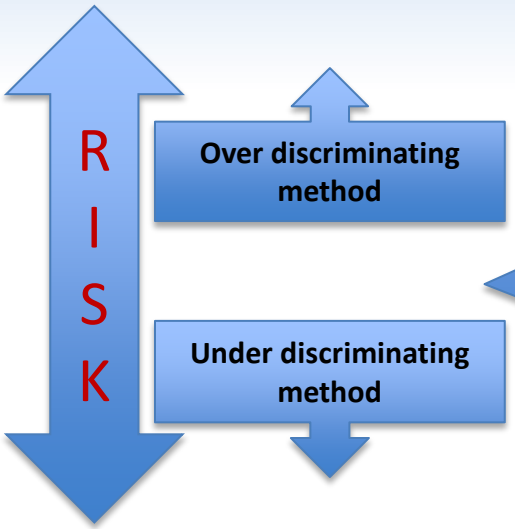
What Key Data are Needed to Establish the Predictive Ability/Clinical Relevance (CR) of Dissolution Testing?





Without an understating of the relationship between ***critical attributes/process parameters, dissolution and clinical outcome,*** the method could be under or over-discriminating.

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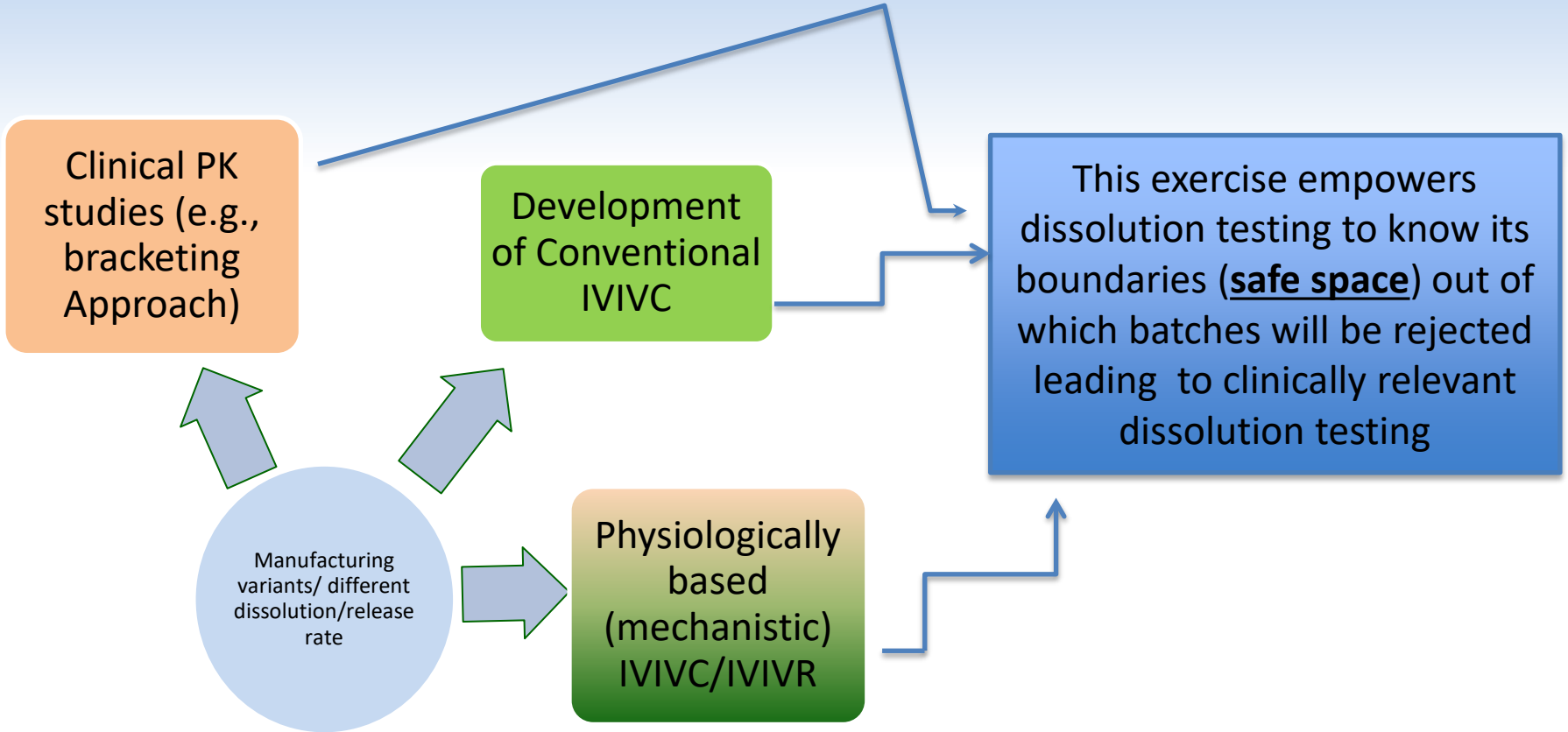
Understanding the Relationship Between Dissolution and Clinical Impact



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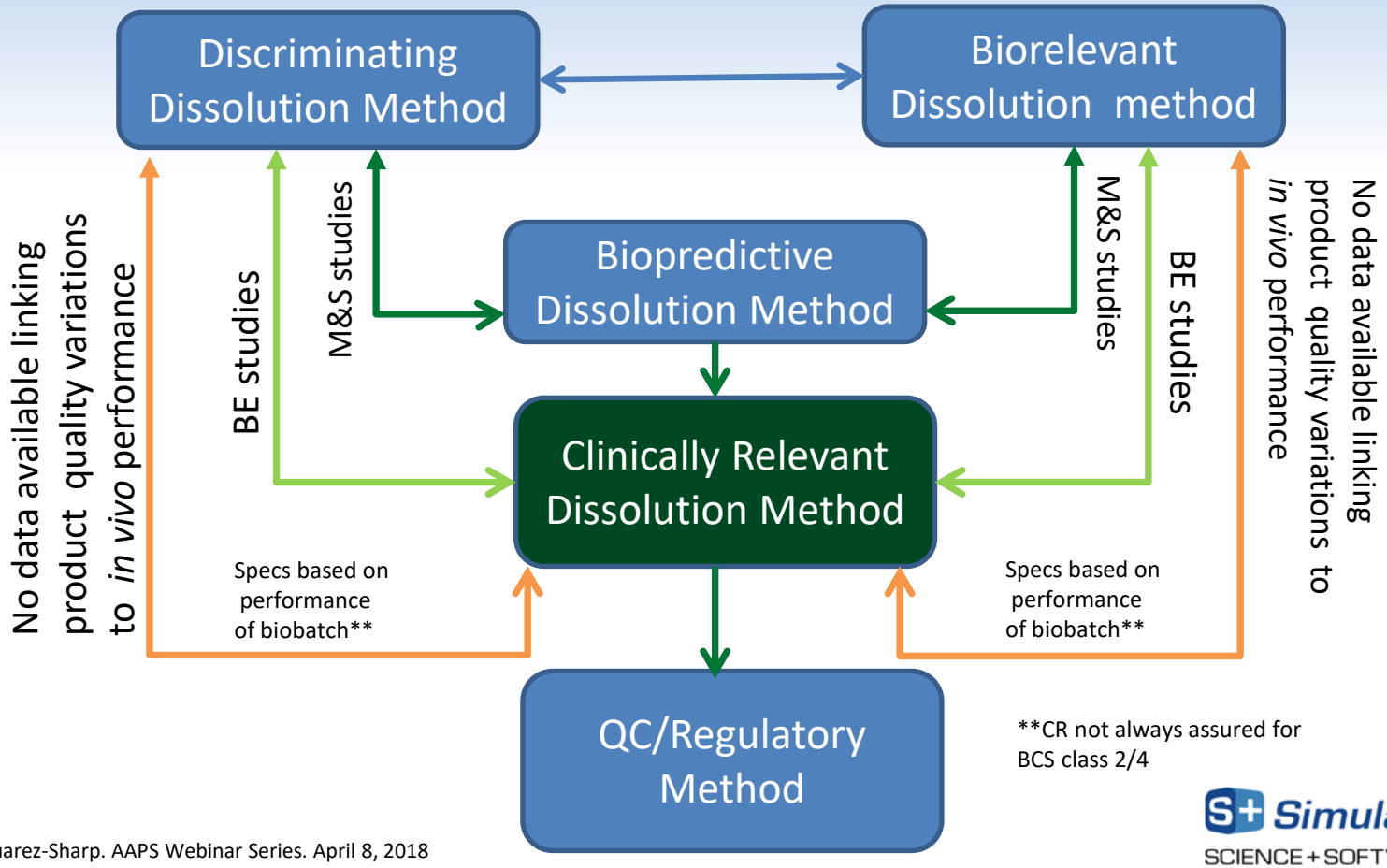
What is Biopredictive Ability/CR in Dissolution Testing?

Relationship between Various Dissolution Terminologies*



*Source: S. Suarez-Sharp. AAPS Webinar Series. April 8, 2018
Definitions: S. Suarez-Sharp et. al. AAPSJ 2018 Aug 27;20(6):93

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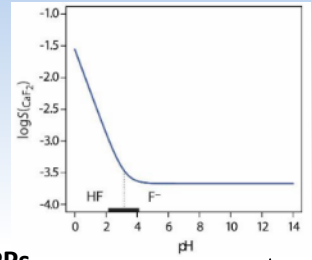
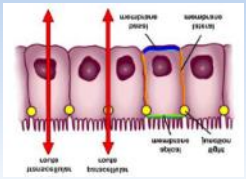
PBBM in Support of Drug Product Quality





Intestinal permeability

These models (i.e., physiologically based) are predicated on leveraging the scientific community's knowledge and experience through pooling existing/new physicochemical, in vitro characterization, preclinical/ clinical data, and formulation variants

Prior Knowledge, Risk assessment

CPPs

CMAs

Input Materials

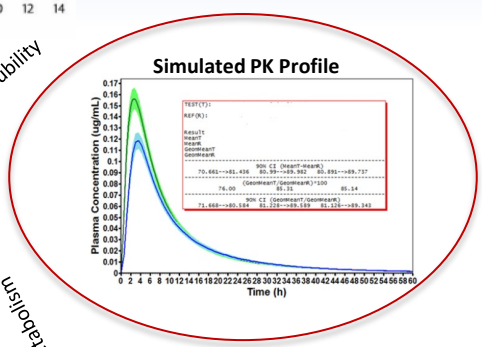
Dissolution: f (CPP1, CPP2, CPP3,…. CMA1, CMA2, CPP1*CMA1…)

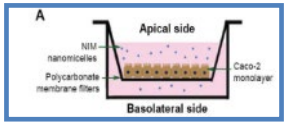
solubility

Dissolution

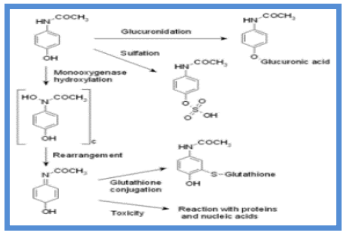
Metabolism

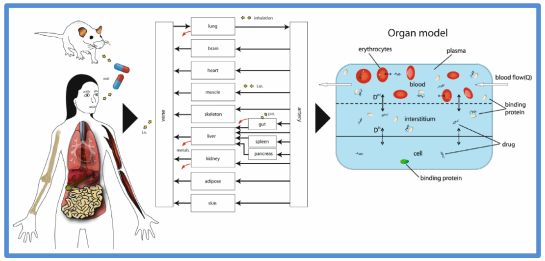
Transporter





PK





PBBM can be used to robustly *predict the in vivo performance* of drug products via identification of a safe space, reducing the number of in vivo studies needed

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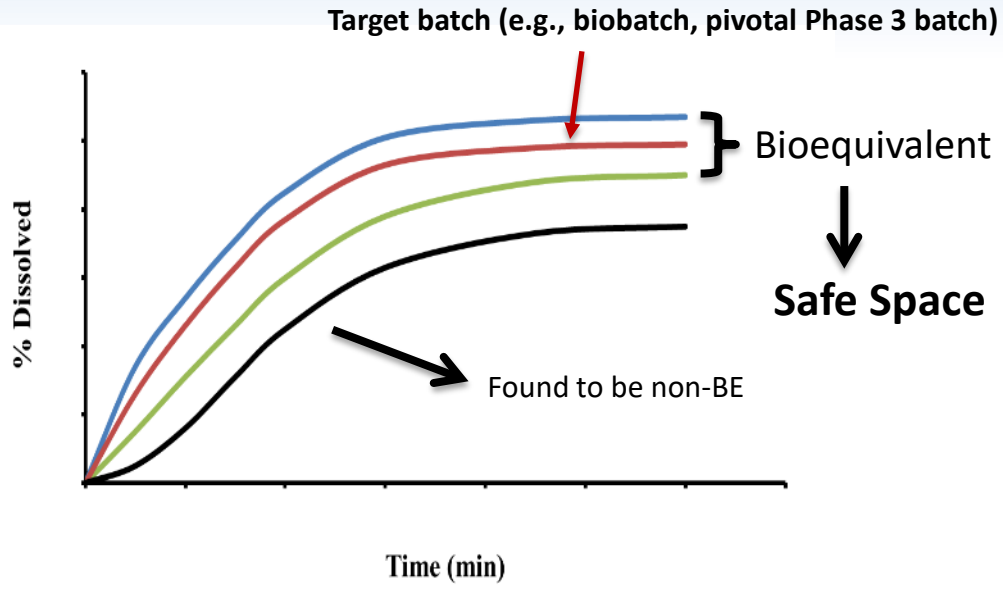
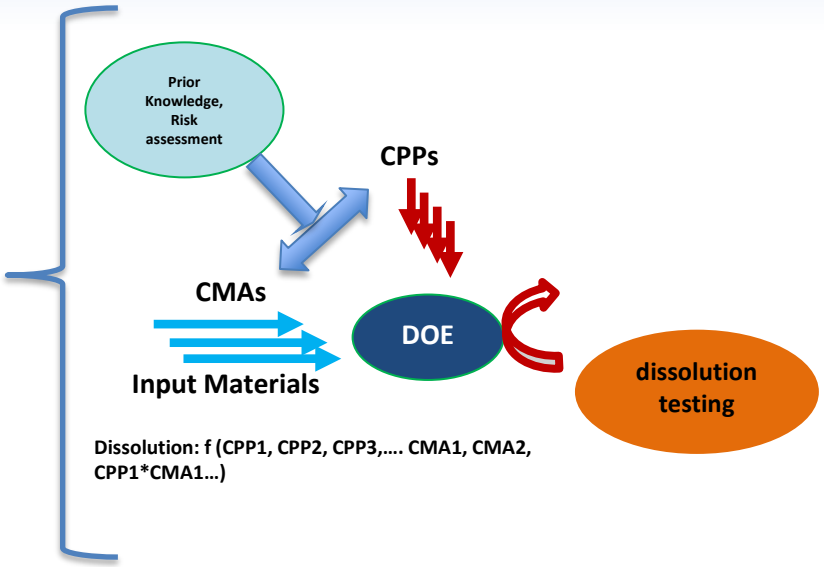
What is Safe Space?

- Boundaries defined by ***in vitro specifications*** (dissolution and other relevant drug product quality attributes), within which drug product variants are anticipated to be bioequivalent to one another*





*Source: Sandra Suarez Sharp et al. AAPSJ 2018

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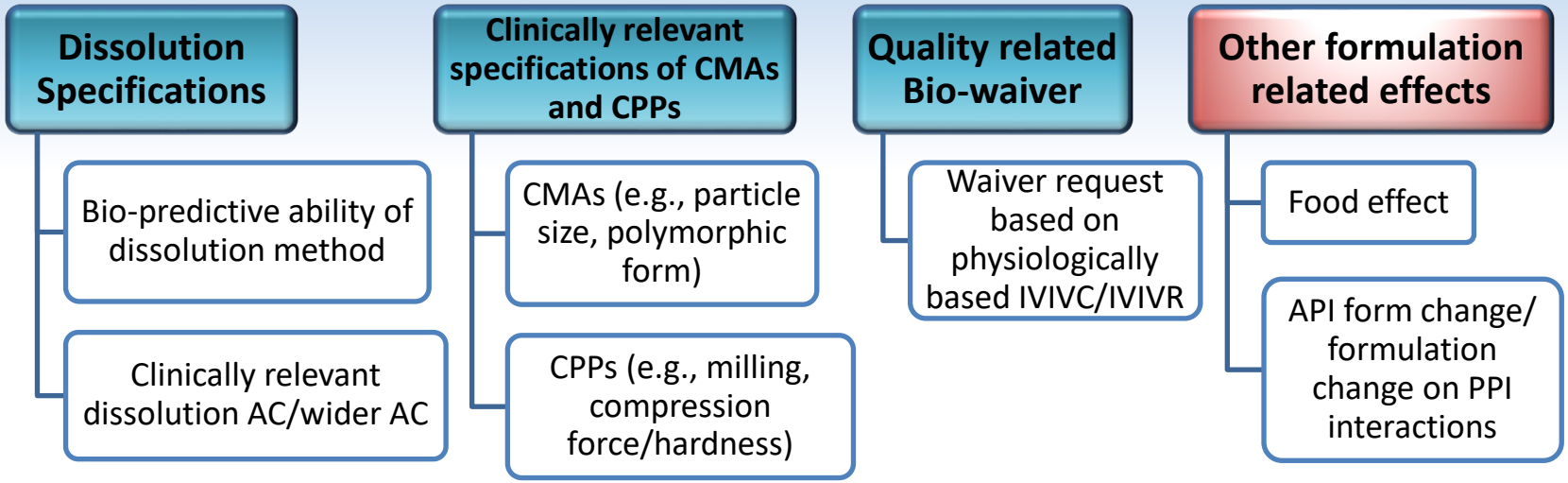
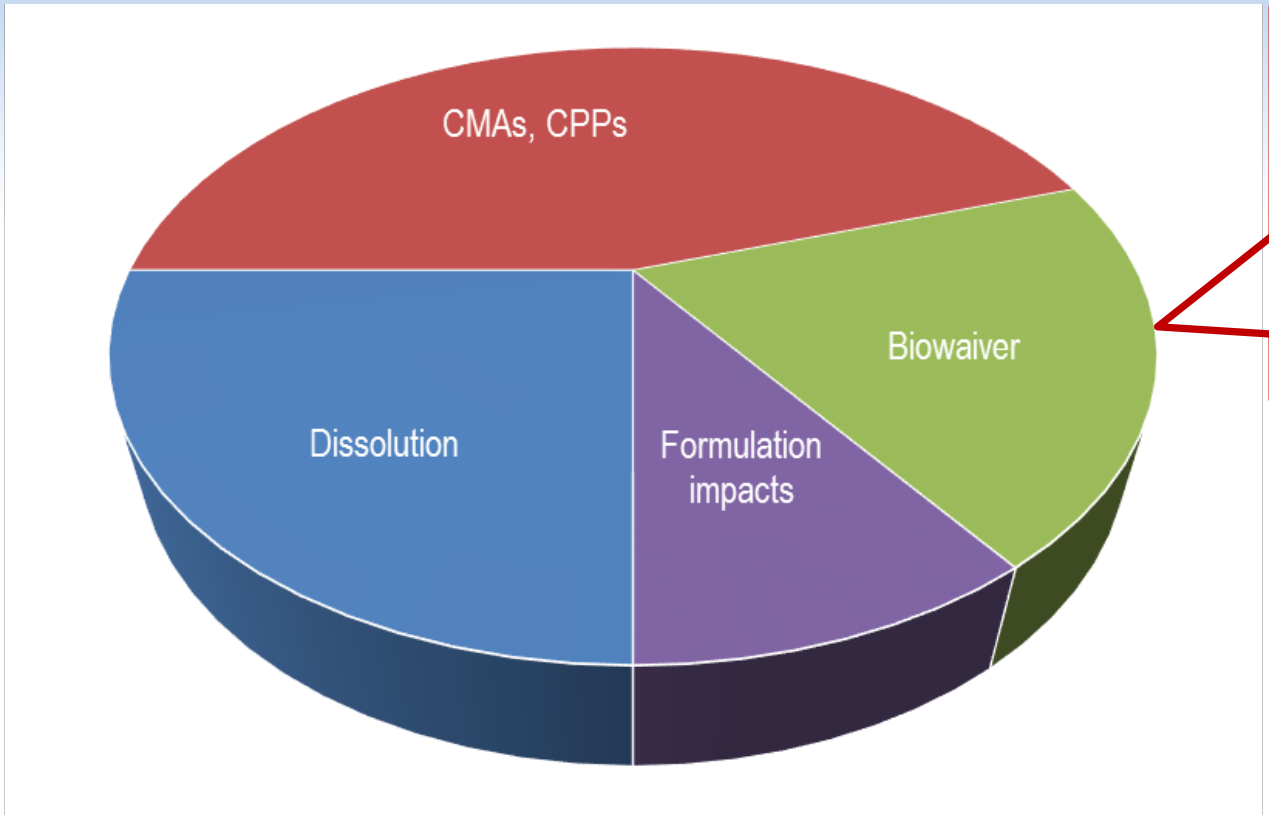
Common Applications of PBBM in Support of Drug Product Quality



AC=Acceptance criteria

FDA Experience in PBBM in Support of Drug Product Quality (2008-2018)



~ 30 submissions included in INDs and NDAs from 2008-2018 (22 submitted from 2015- 2018) (three of which attempted IVIVC)

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General Expectations on Submissions Containing PBBM

- **Summary report**
- **M&S objectives**
  - Questions/Issues to be addressed by the model
  - Rationale for conducting the M&S exercise
- **Model Development**
  - *Model structure*
    - Disposition model
    - Mechanistic framework of absorption model
      - Combination of a mechanistic absorption model with a simplified compartmental disposition model (e.g., classic compartment PK model; models that lumps tissue/organ compartments from whole-body PBPK models) may be acceptable with justification
    - Approaches taken to integrate dissolution data
    - Justification for model modifications
  - *Model Assumptions*
    - Assumptions underlying model structure and parameters should be clearly presented (e.g., drug disintegration, dissolution, precipitation, degradation, transport, first-pass effect, distribution, and clearance)
  - *Model Parameters*
    - Rationale and supportive information on model parameters

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General Expectations on Submissions Containing PBBM

- **Model Verification/Validation**
  - The predictive performance of a model should be validated for its intended purpose
    - Graphical and numerical comparisons of the predicted and observed drug concentration versus time as well as PK parameter estimates and statistical analysis (e.g., confidence intervals) should be provided
  - Independent datasets not used in model development are recommended to challenge the predictive performance of the model
    - Preferably the use non-BE data
  - Model validation acceptance criteria should be established a priori
    - The acceptance criteria for IVIVC model to support biowaivers should comply with the criteria provided in the IVIVC guidance

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PBBM Specific Expectations: Dissolution Data Input

- Dissolution data must be incorporated as part of PBBM model development and validation for supporting manufacturing/controls changes
  - The data should show a clear rank-order relationship between in vitro testing (e.g., in vitro release/dissolution) and PK

- Incorporation of biorelevant dissolution data are not required
  - However, it is recommended to conduct biorelevant testing alongside QC testing to support major CMC changes and bridging studies. PBBM could then be very useful in assisting the bridging process

- Selection of a dissolution modeling approach should be based on drug product understanding and not on the best fit of the dissolution data
  - Use of “raw” dissolution data is not recommended; may only be appropriate for high soluble compounds
  - For MR products the use of empirical functions is justifiable

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PBBM Specific Expectations: Virtual BE Trials

- The estimated intra- and inter-subject variability for PK parameters (such as Cmax and AUC) should be comparable to the observed intra- and inter- subject variability
- The numbers of subjects for virtual BE trials should be justified and comparable to in vivo BE trials
- The number of virtual BE trials used to estimate the probability of concluding bioequivalence should be justified
- Description of the methods/algorithms used to determine intra-subject variability in virtual BE should be included

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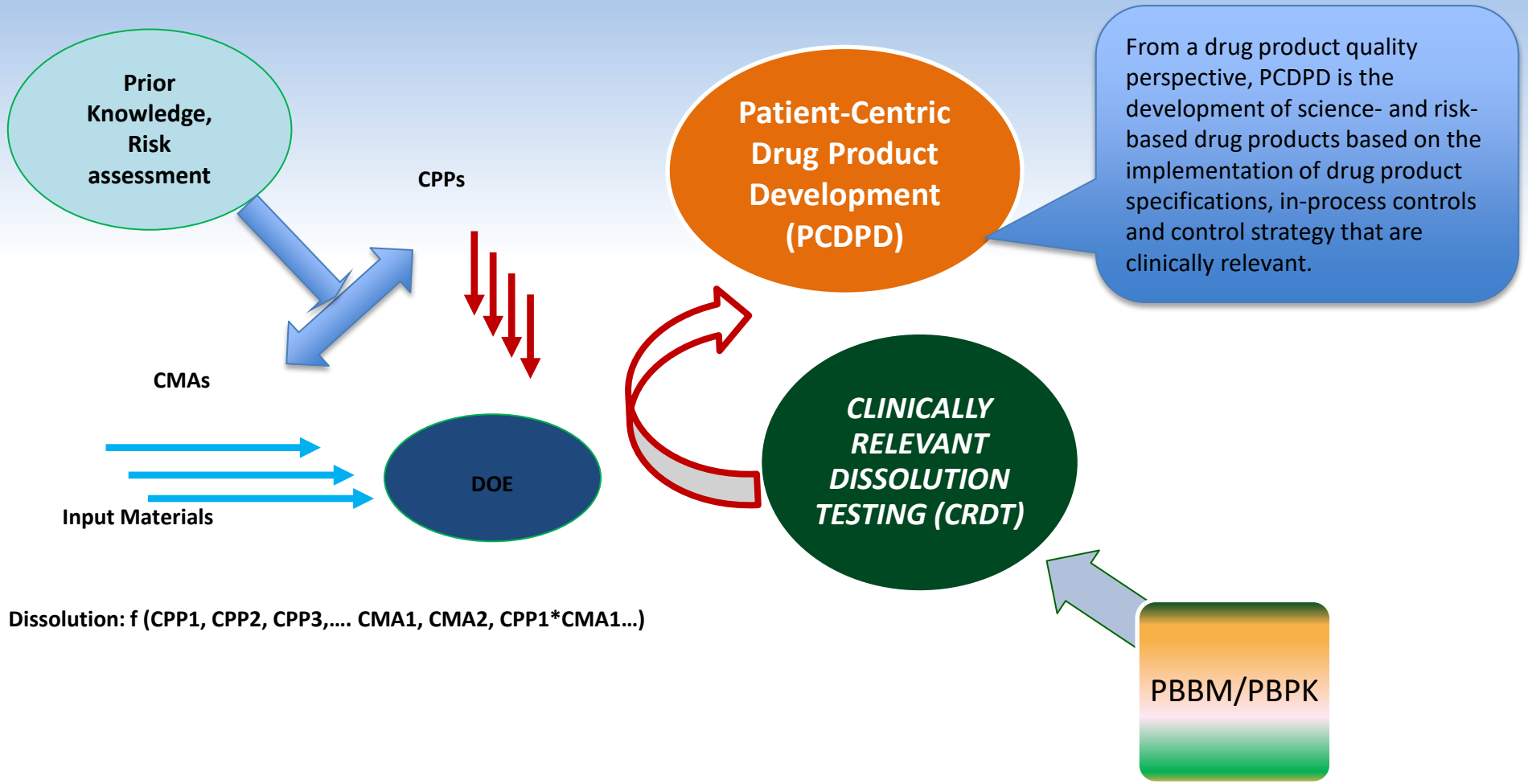
Current Challenges/Limitations in PBBM

- **Model structure information is insufficient**
  - No mechanistic framework accounting for impact of quality attributes on absorption
  - No justification for input parameter values selected in drug, PK, formulation, physiology
  - Insufficient data/program files
  - Parameter sensitivity analysis (constrained around experimental data) not always provided.

- **Validation data are insufficient**
  - Not objective oriented model verification/validation
  - Inappropriate data selection for model validation
  - Additional validation needed for the intended purpose

- **Reliability of simulation results is questionable**
  - Uncertainty of subject variability

The Future of CRDT & PBBM/PBPK: Patient-Centric Drug Product Development



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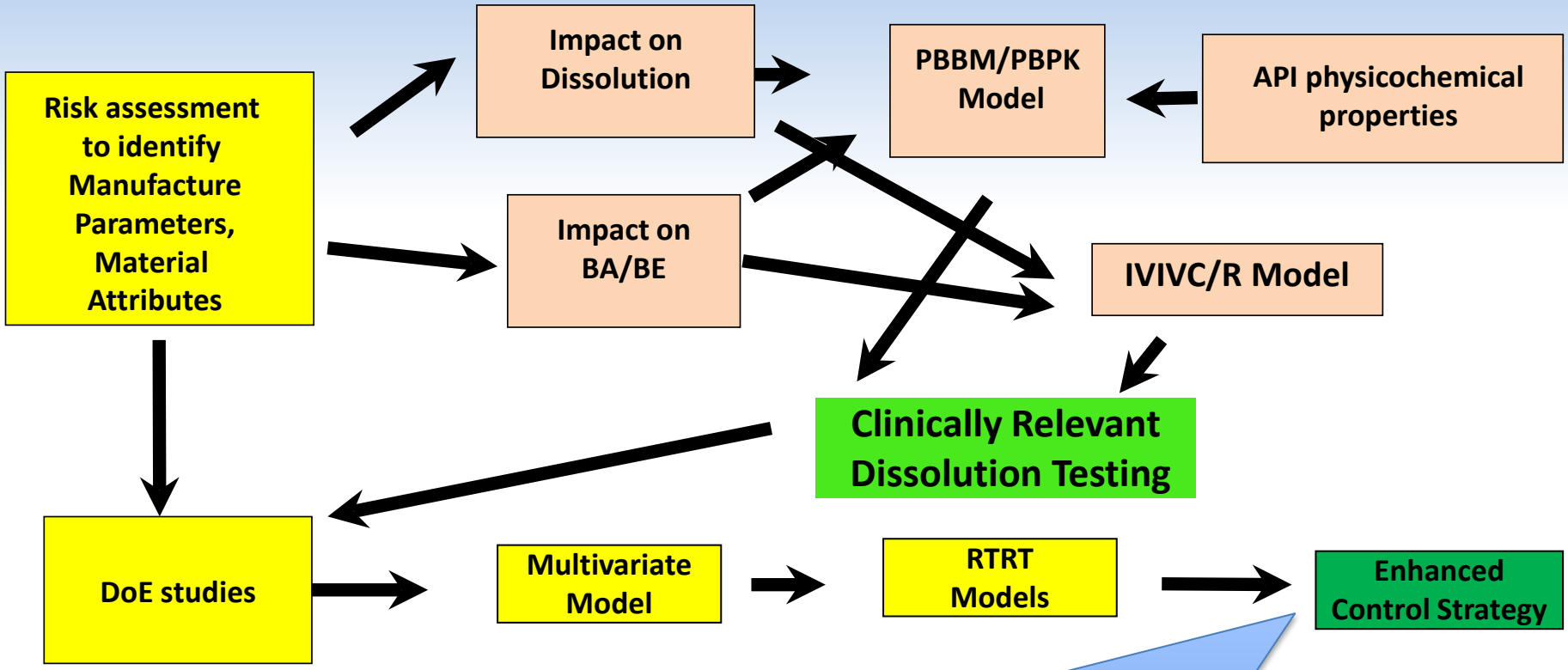
The Future of CRDT and PBBM/PBPK: Enabler of Enhanced Control Strategy



Relying on a control strategy that does not include dissolution as an endpoint, poses a risk to the patient since dissolution is the only in vitro test that proves the rate and extend of systemic exposure.

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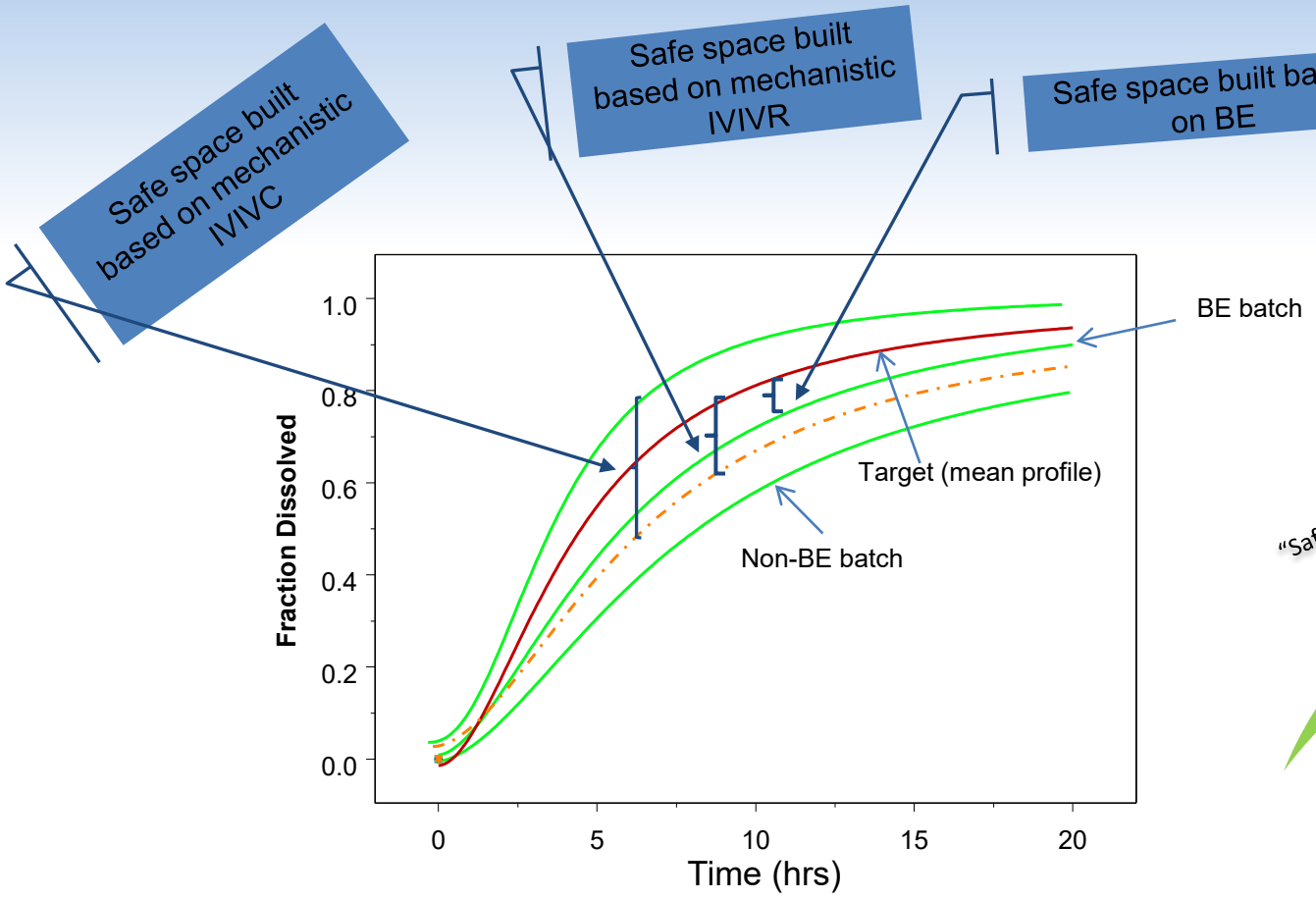
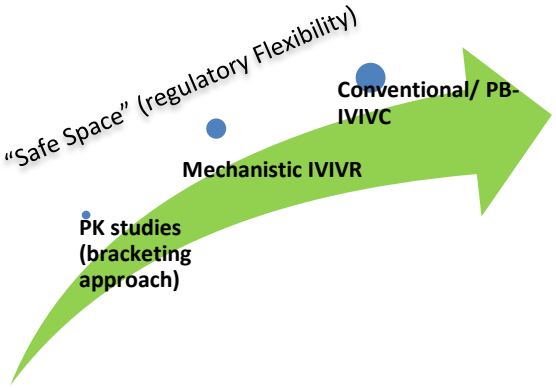
The Future of CRDT and PBBM/PBPK: Enabler of Regulatory Flexibility via Safe Space





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Concluding Remarks

- There are no regulatory hurdles for the use of innovative modeling approaches in support of drug product quality

- The development of conventional/mechanistic IVIVCs are considered the “gold standard” for gaining regulatory flexibility throughout the drug product’s life cycle
  - When these paths fail, the data generated during drug product development along with the conduct of dedicated PK studies (whenever possible) may be leveraged to define a safe space via the following approaches:
    - IVIVR with bracketing approach
    - Mechanistic IVIVR/IVIVC via virtual BE

- Building a safe space is not only relevant for gaining regulatory flexibility, but a steppingstone toward setting clinically relevant drug product specifications and towards “Patient-centric” Drug product development

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Backup Slides

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Dissolution Testing Dilemma

- Despite of the overall well known value of dissolution testing in drug product development, its recognition as a key enabler of "enhanced" drug product understanding is precluded in many cases by the uncertainty of its predictive ability/clinical relevance
  - Specially for drug product comprising BCS class 2/4 compounds and modified release formulations

How can be "remove" this uncertainty; What data are needed?

The development of clinically relevant dissolution testing for IR drug products with rapid dissolution and comprising BCS class 1/3 drugs is not necessary.

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PBBM Specific Expectations: Data Submission

- Complete M&S report, definition files, and datasets in module 5.3.1.3 of the eCTD. Datasets can be submitted in .zip format
- Include the definition file(s) listing all input and output files, and the use or purpose of each of these files in an appropriate format (e.g., .pdf, .xpt)
- Submit complete datasets used for model development, optimization, validation, and application (e.g., GastroPlus® compatible files including but not limited to *.mdb, *.cat, *.dsd, *.opd, *.spd, *.stc files)
  - Include raw data used for model development, optimization, validation, and application including (but not limited to) physicochemical parameters, in vitro dissolution profiles, in vivo plasma drug concentration time profiles, and virtual BE trials.

- FDA does not request the use of a specific software
  - Due to substantive differences in software/versions, clear identification of software is critical
    - E.g., name and version of the software, and (for custom modeling software) schematics of model structure and differential equations.

What Are Some of the Challenges in the Implementation of CRDT and PBBM/PBPK?

- PK studies addressing effect of product variants not always part of drug product development.
  - The resulting safe space may not lead to desire regulatory flexibility

- The success rate of conventional/mechanistic IVIVC is relatively low
  - Partially due to lack of biopredictive dissolution methods
  - Biorelevant dissolution testing which may increase the success rate of IVIVC/IVIVR, is usually not implemented during drug product development and/or as regulatory method.
    - If implemented, there is not currently a defined path for transitioning from biorelevant to a "simpler" method to be used as QC/regulatory method
    - Their superior "ability" toward achieving IVIVC/IVIVR is yet to be demonstrated

- Culture change
  - Patient-centric drug product development (from quality perspective) should rely heavily on a deep understating of the relationship between ***critical attributes/process parameters, dissolution and clinical outcome.***

- The Application of PBBM/PBPK into drug product development is still evolving
  - Promising but underused tool for risk assessment and establishing CRDT
  - Refinement of commercial in silico platforms is needed
  - No regulatory guidance applied to drug product quality

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What to expect for the future?

- **Refinement of PBBM/PBPK Models:**
  - Develop new models to better capture the disintegration, dissolution erosion processes specially for modified release dosage forms
    - The tools are not ready to accurately model extended release formulations, specially for colonic absorption
  - Build better mechanistic understanding to be able to model the effect of excipients
  - Mechanistic IVIVC needs to be more clearly defined
  - Integration of intra subject variability into predictive simulations

- **Use of models (e.g., PBBM) to:**
  - Guide the development of a biopredictive dissolution method
  - Increase the rate of success of IVIVC
  - Risk assessment for the selection of CMAs and CPPs
  - Verification of the Design Spaces via safe space
  - Setting clinically relevant drug product specifications via safe space
  - Bridging across dissolution methods (e.g. biorelevant vs. discriminating methods)

- **Culture change**
  - Building clinical relevance into continuous manufacturing and Real Time Release Testing (RTRT) models via the use of biopredictive/clinically relevant dissolution testing