# Biorelevant, Bioindicative and Biopredictive Dissolution: Current Perspectives and Future Challenges

**Patrick J. Sinko, PhD, RPh, FAAPS, FAAS, FCRS**

President, American Association of Pharmaceutical Scientists

Distinguished Professor & Parke-Davis Endowed Chair in Pharmaceutics and Drug Delivery, School of Pharmacy


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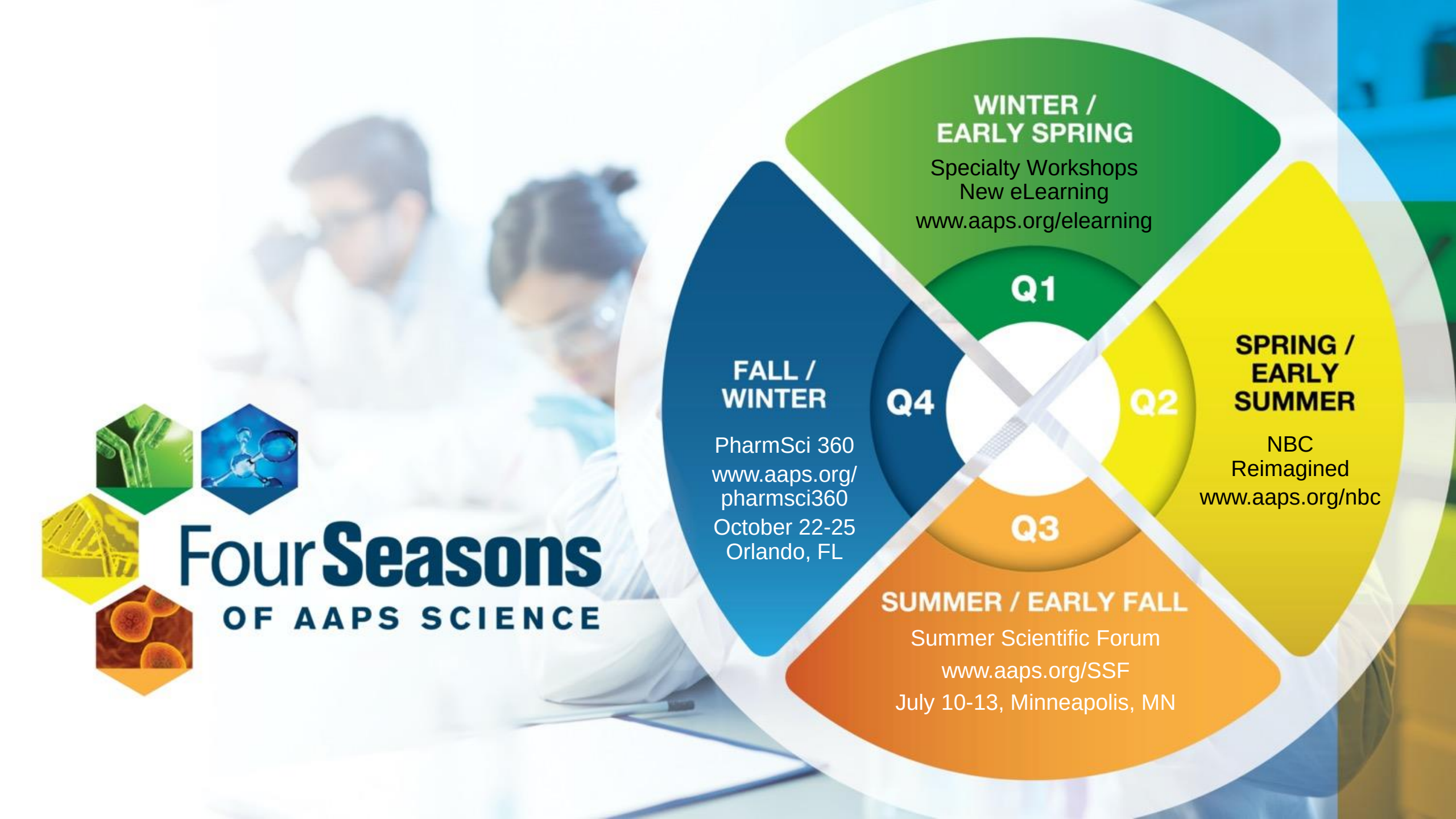
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# SPDS & AAPS

## Ongoing Cooperation & an Enduring Collaboration

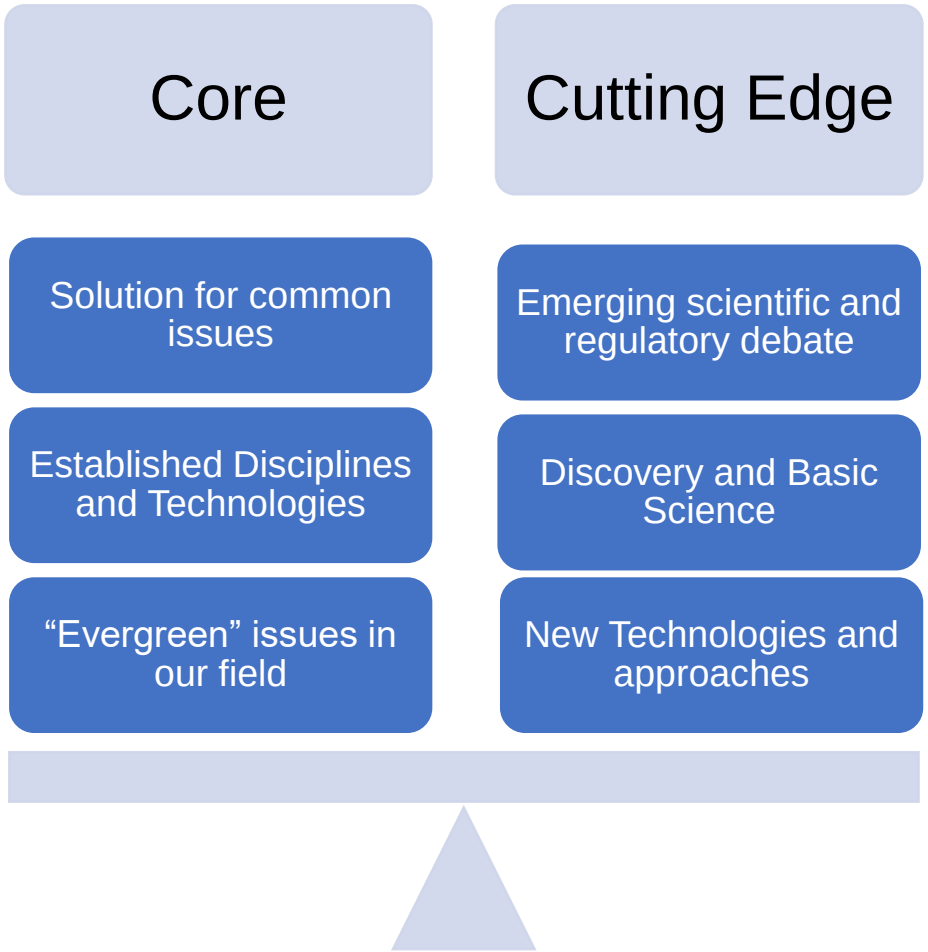
**Pharma 4.0**

**PAT**

**PBBM**

**ASD**

**Dissolution Safe Space**




**Continuous Manufacturing**

**BE Safe Space**

**Big Data**

**Population PBBM**

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# SPDS & AAPS

## Ongoing Cooperation & an Enduring Collaboration

- > 10% of AAPS members belong to the AAPS Dissolution Community.
  - Webinars
    - The Role of Dissolution in Continuous Manufacturing.
    - PBBM to Improve Drug Product Quality.
  - Co-organize workshops with SPDS-US.

DRPI
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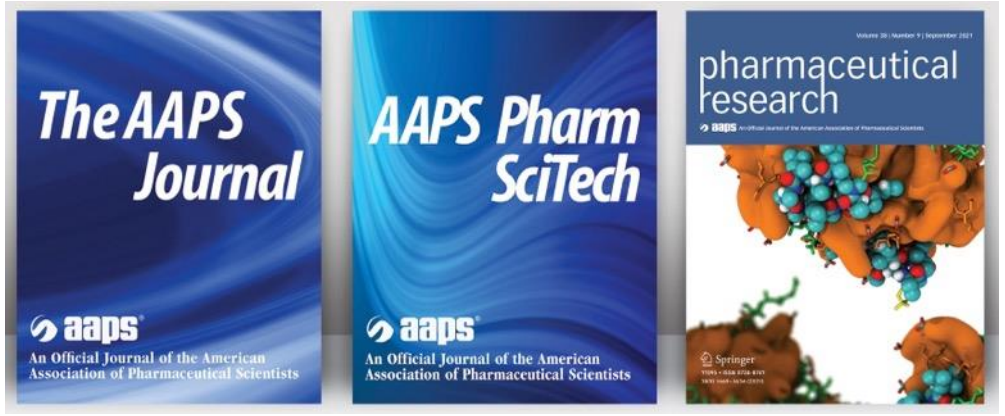
Dissolution Research Presentations International
IN ASSOCIATION WITH
aaps American Association of Pharmaceutical Scientists
US 2023

- Many Cutting-Edge Dissolution Papers Published in AAPS Journals

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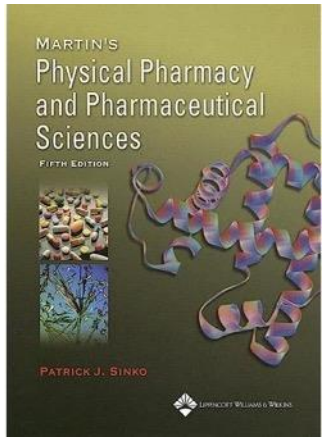
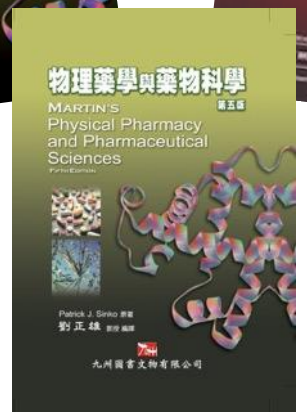
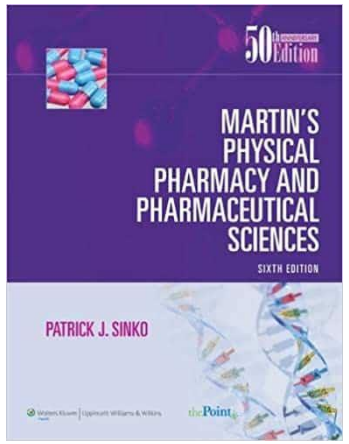
2006





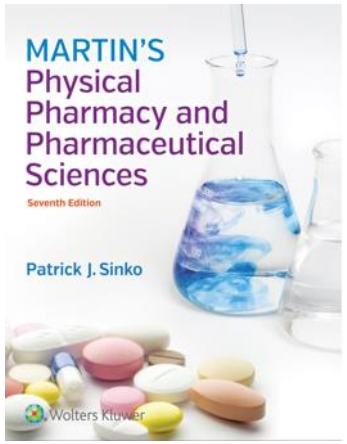



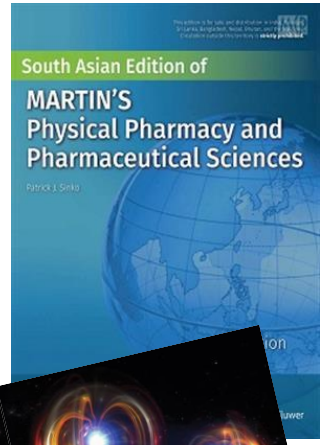

2011

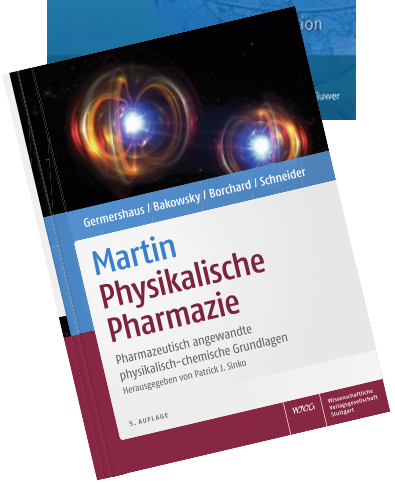





2016

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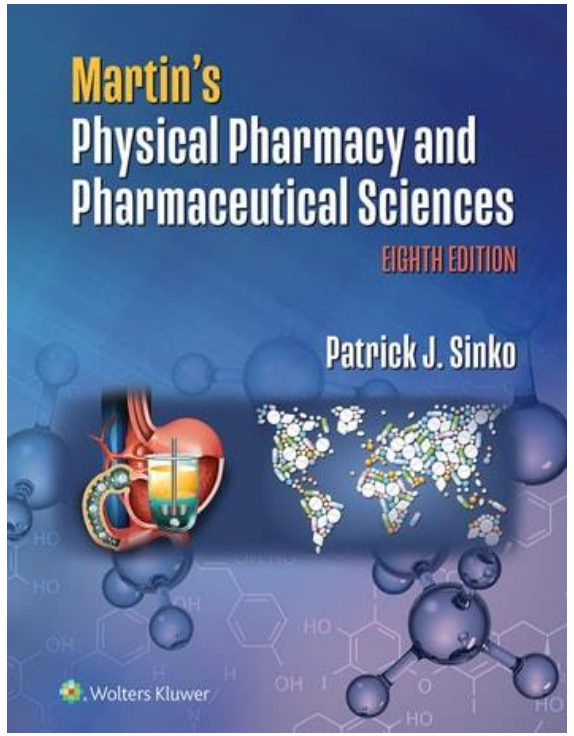


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# 13 DISINTEGRATION, DISSOLUTION, AND DRUG RELEASE

RAIMAR LÖBENBERG AND
DANIELA AMARAL SILVA

## CHAPTER OBJECTIVES

**At the conclusion of this chapter the student should be able to:**

1. Define dissolution and describe relevant examples in the pharmaceutical sciences and practice of pharmacy.
2. Understand the differences among immediate-, modified-, delayed-, extended-, and controlled-release delivery systems.
3. Differentiate between zero-order and first-order release kinetics.
4. Define and understand intrinsic dissolution rate and define the driving force for dissolution.
5. Understand the effect of surface area on dissolution rate.
6. Differentiate the Hixson–Crowell, Noyes–Whitney, Higuchi, and Power Law models of dissolution and release.
7. Understand the concept of sink conditions.
8. Understand how media properties can affect dissolution, for example, pH, lipids, surfactants.
9. Understand bicarbonate buffer kinetics and its importance for enteric-coated drug products.
10. Describe and understand the mechanics of the most used dissolution apparatuses.
11. Define the Biopharmaceutics Classification System and discuss the role of permeability and solubility.

## INTRODUCTION

Since only solubilized drugs can be absorbed, dissolution and the measurement of dissolution processes are important in the pharmaceutical sciences. Although simple in concept, the rate of dissolution can be affected by a variety of factors, including the type of media in which the drug is dissolving, temperature, pH, viscosity, agitation rate, and dosage form coatings. As an extension, drug release characteristics from various dosage forms and the manipulation of those rate processes are also of significant interest. This chapter covers the essential theoretical and analytical background for

KEY CONCEPT

### DISINTEGRATION

Disintegration is a physical process related to the mechanical breakdown of a tablet into smaller particles or granules, representing the breakage of interparticle interactions generated during tablet compaction or granulation.[1] After the immersion liquid wets the particle surface and penetrates the pores, disintegration occurs in two steps: first, disintegrating into smaller granules, and second, deaggregation or granule disintegration. The first step is essential to increase surface area. Gelling of a disintegrant, however, may slow this process down. If no disintegration occurred, only the API near the surface of the compact or granulate would dissolve. The increase in surface area compared to the intact tablet or granulate yields a higher dissolution rate. In the second step, an even faster drug dissolution rate is achieved due to the increased surface area in contact with the medium, as represented in the scheme shown in Figure 13-1.

KEY CONCEPT

### DISSOLUTION

Dissolution refers to the process by which a solid phase (e.g., a tablet or powder) goes into a solution phase, such as water. In essence, when a drug "dissolves," solid particles separate and mix molecule by molecule with the liquid and appear to become part of that liquid. Therefore, drug dissolution occurs when drug molecules are liberated from a solid phase and enter a solution phase. In general, only drugs in solution can be absorbed, distributed, metabolized, excreted, or even exert pharmacologic action. Thus, dissolution is an important process in the pharmaceutical sciences and is primarily used in the context of oral drug products. Differences in dissolution performance can cause products not to pass a bioequivalence test. Therefore, in vitro dissolution testing is an important performance test.

KEY CONCEPT

### DRUG RELEASE

Drug release occurs when a drug leaves a drug product and is subsequently available for processes such as dissolution, absorption, distribution, metabolism, and excretion, eventually becoming available for pharmacologic action. Drug release is generally described with reference to the rate at which the drug is available from a particular dosage form. Drug release from a drug product can be classified as modified release, including delayed and extended-release or immediate release. Drug release refers to oral drug products and other dosage forms, such as transdermal patches and drug-device combinations.

# Dissolution, Disintegration
## Methods, Media, & Apparatus

(A)

(B)

(C)


(D)

FIGURE 13-4 (A) USP dissolution apparatus 1 (Note the dye coming from the tablet in the basket); (B) USP dissolution apparatus 2; (C) USP dissolution apparatus 3; (D) USP dissolution apparatus 4.


TABLE 13-3

**Composition of Biorelevant Dissolution Media for In Vitro Dissolution Testing**

| USP SGF | USP SIF | FaSSIF V2 | FeSSIF V2 |
|---|---|---|---|
| HCl (7.0 mL) | NaOH (qs pH) | NaOH (34.8 mM) | NaOH (81.65 mM) |
| NaCl (2.0 g) | $KH_2PO_4$ (6.8 g) | NaCl (68.62 mM) | NaCl (125.5 mM) |
| Pepsin (3.2 g) | Pancreatin (10.0 g) | Bile salt (taurocholate) (3 mM) | Bile salt (taurocholate) (10 mM) |
| Deionized water qs 1 L | Deionized water qs 1L | Phospholipid (lecithin) (0.2 mM) | Phospholipid (lecithin) (2 mM) |
| pH 1.2 | pH 6.8 | Maleic acid (19.12 mM)<br><br><br>Deionized water qs 1L<br>pH 6.5 | Maleic acid (55.02 mM)<br>Glyceryl monooleate (5 mM)<br>Sodium oleate (0.8 mM)<br>Deionized water qs 1L<br>pH 5.8 |



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# What are some of the challenges?

- **Background:** Dissolution Profile Similarity Assessment.
  - **Challenge**: Global recognition of Clinically Relevant Diss Specs & Safe Space.

- **Clinically Relevant Dissolution Specifications & Safe Space**.

- **Bioequivalence Safe Space**

- **When is the Safe Space "Not Safe"?**
  - **Challenge:** PBBM Input Function & Variability in Predictions.

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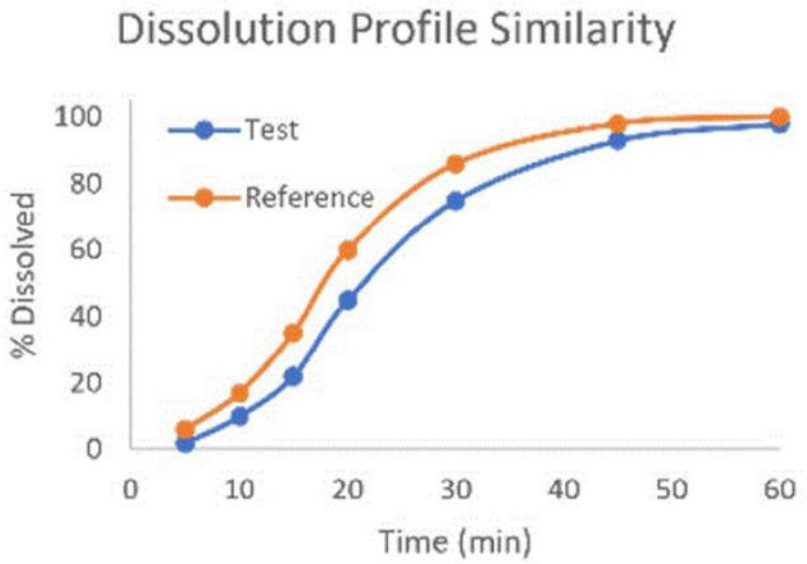
**CMC change / Biowaiver request**

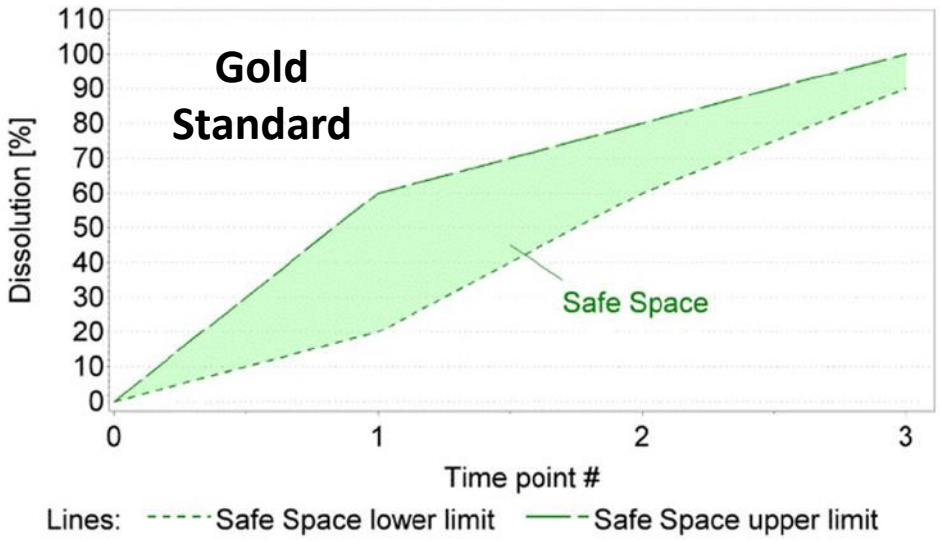
**UCR**

- no link between acceptance criterion and in vivo data
- REF and TEST profiles estimated
- two-sample equivalence testing problem

**CRDS**

- acceptance criterion supported by in vivo data
- only TEST profile estimated
- one-sample equivalence testing problem




**Similarity decision**

**Dissolution Profile Similarity Assessment—Best Practices, Decision Trees and Global Harmonization**

Andreas M. Abend[1] · Thomas Hoffelder[2] · Michael J. Cohen[3] · Leslie Van Alstine[4] · Dorys Argelia Diaz[3] · Emilija Fredro-Kumbaradzi[5] · James Reynolds[6] · Yanbing Zheng[6] · Krista Witkowski[7] · Tycho Heimbach[1]

The AAPS Journal (2023) 25:44
https://doi.org/10.1208/s12248-023-00795-5

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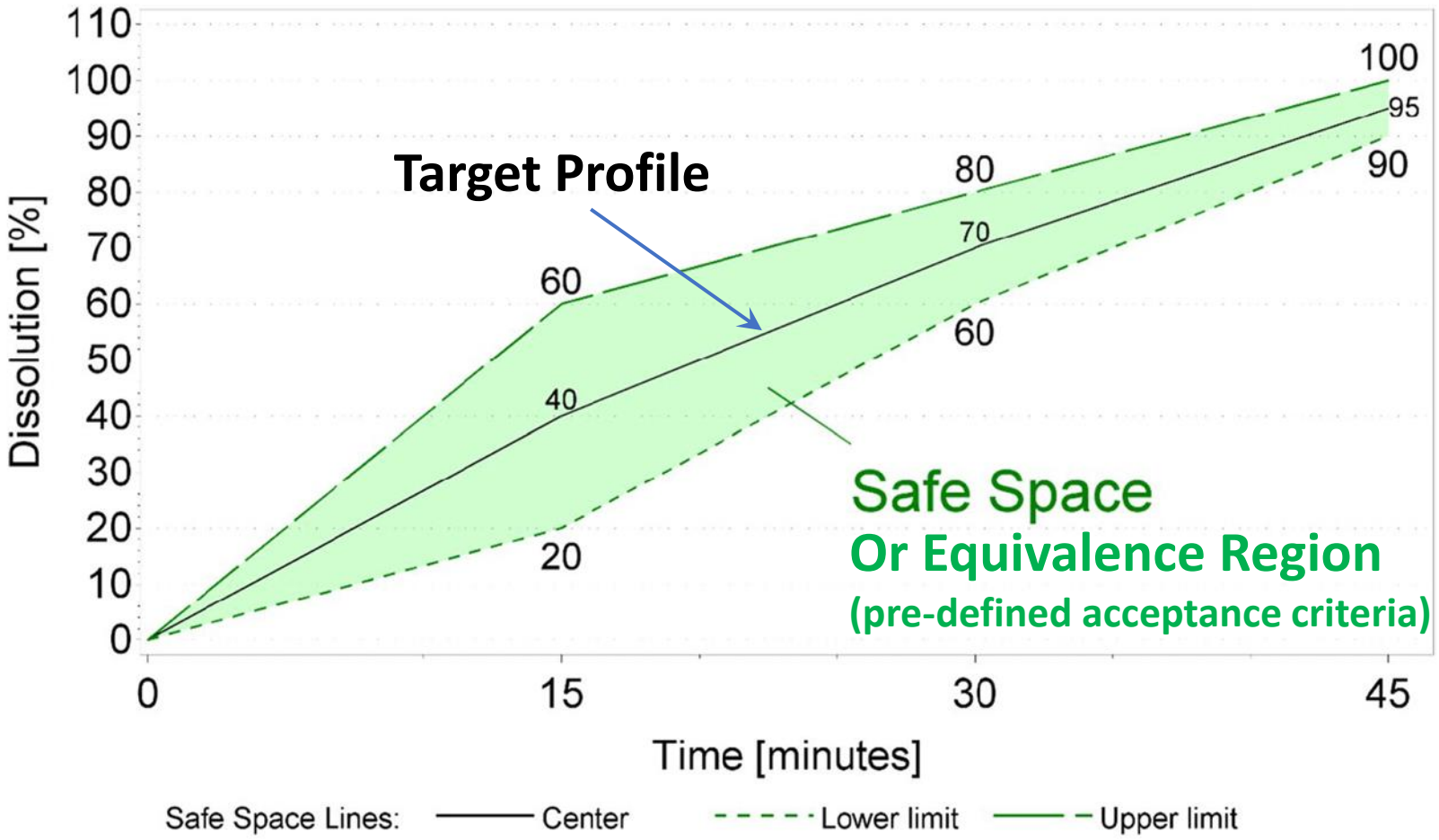
# Safe Space Concept: One-sample equivalence test.




**The dissolution profile of the TEST product should be generated under the same experimental conditions that was used to establish the safe space (QC or "biorelevant")**

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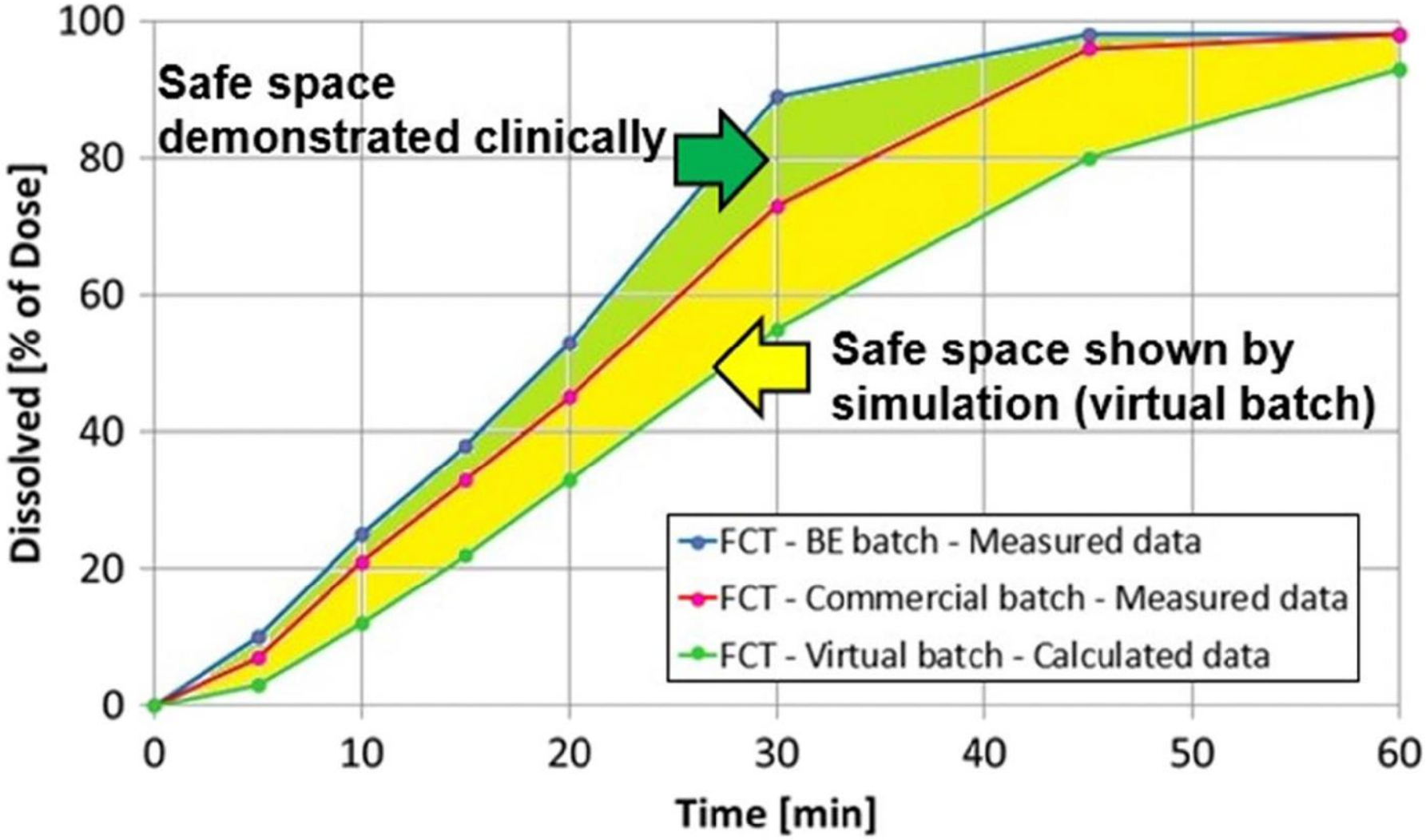
# Clinically Relevant Dissolution Specifications

- **CRDS**: links a product's performance to the *in vitro* dissolution specification.
  - Therefore, it has appropriate discriminating power.
  - **Alleviates major concern**: unknown sensitivity of the dissolution spec to detecting changes in the drug product (think – false positive & false negative).
    - **False Negative** = Not detecting changes in the drug product that could result in product batches released that are not consistent with pivotal batches used to establish product safety & efficacy.
- **Common Approaches for Establishing CRDS & Dissolution Safe Space**
  - "Traditional" in vivo bracketing (IVIVC Level A, IVIVC Level C, IVIVR)
  - Bioequivalence ("mapping and "side batch" approach)
  - **PBBM (Physiologically based Biopharmaceutics Models)**

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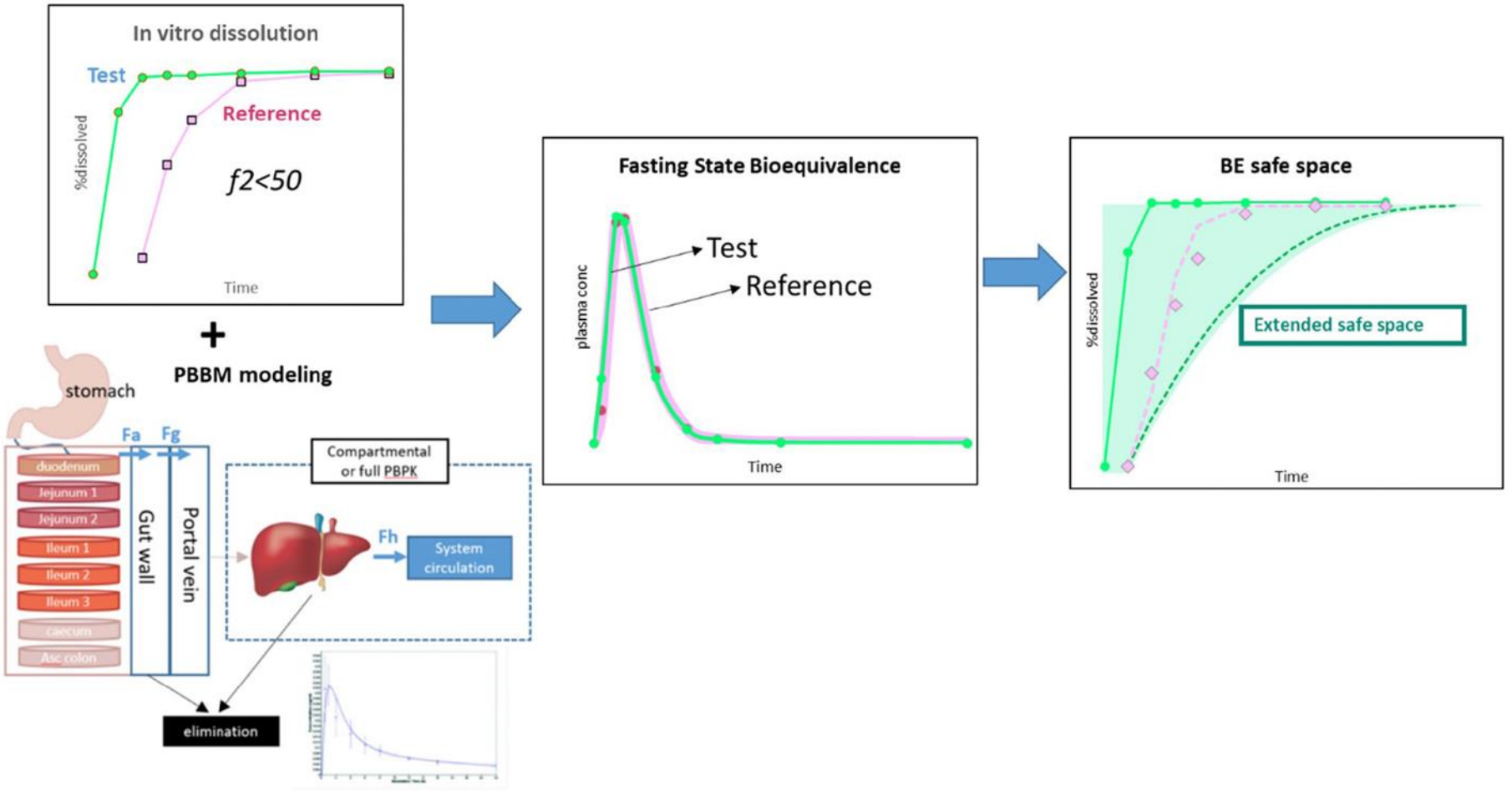
# PBBM BE safe space supersedes f2 similarity.




**Physiologically Based Pharmacokinetics Modeling in Biopharmaceutics: Case Studies for Establishing the Bioequivalence Safe Space for Innovator and Generic Drugs**

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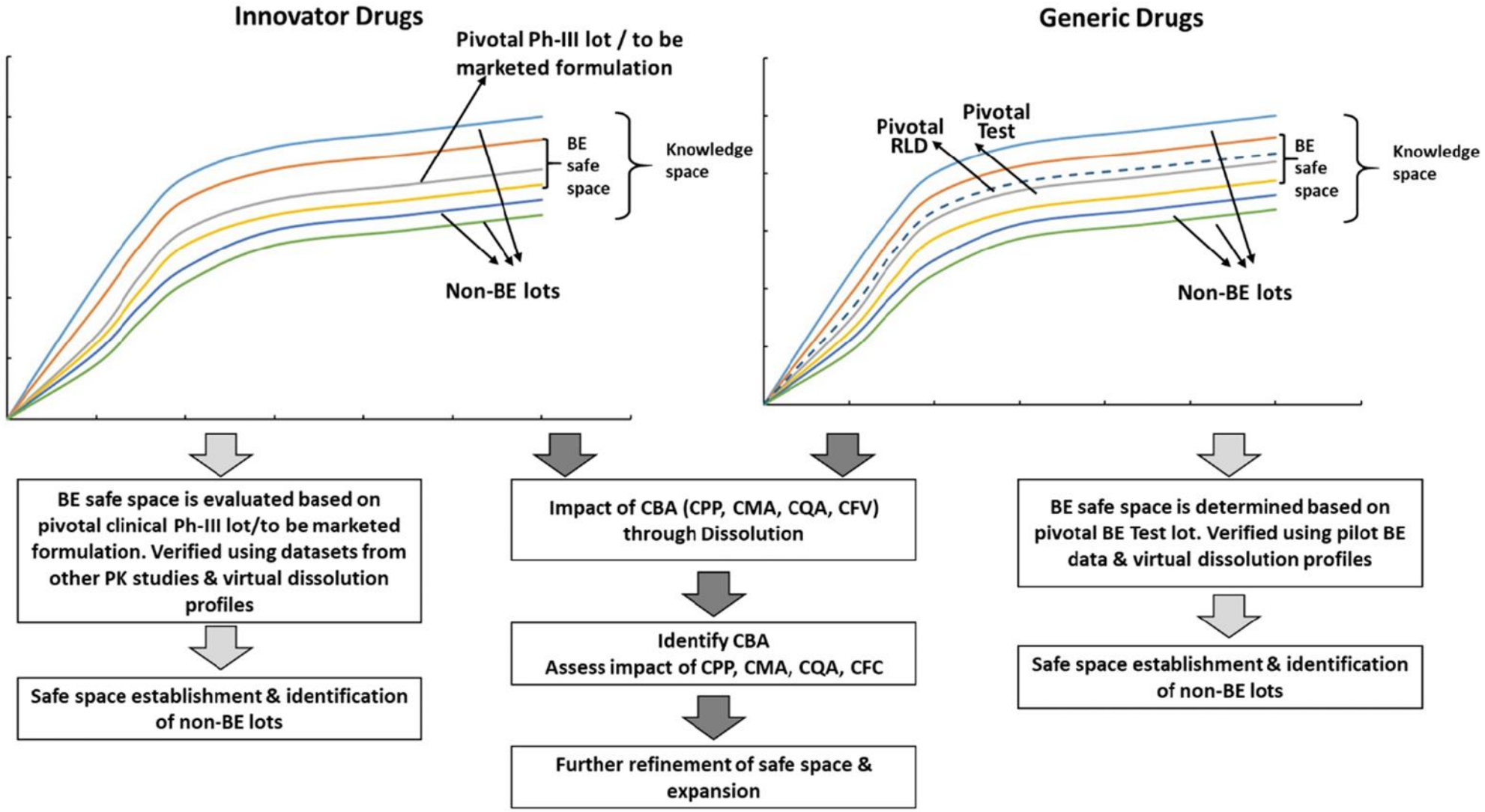


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# When is the Safe Space "Not Safe"?
## PBBM Inputs

### API

- **Dose**, Log P, **Particle Size**, **Solubility** (aqueous & biorelevant)

### Formulation

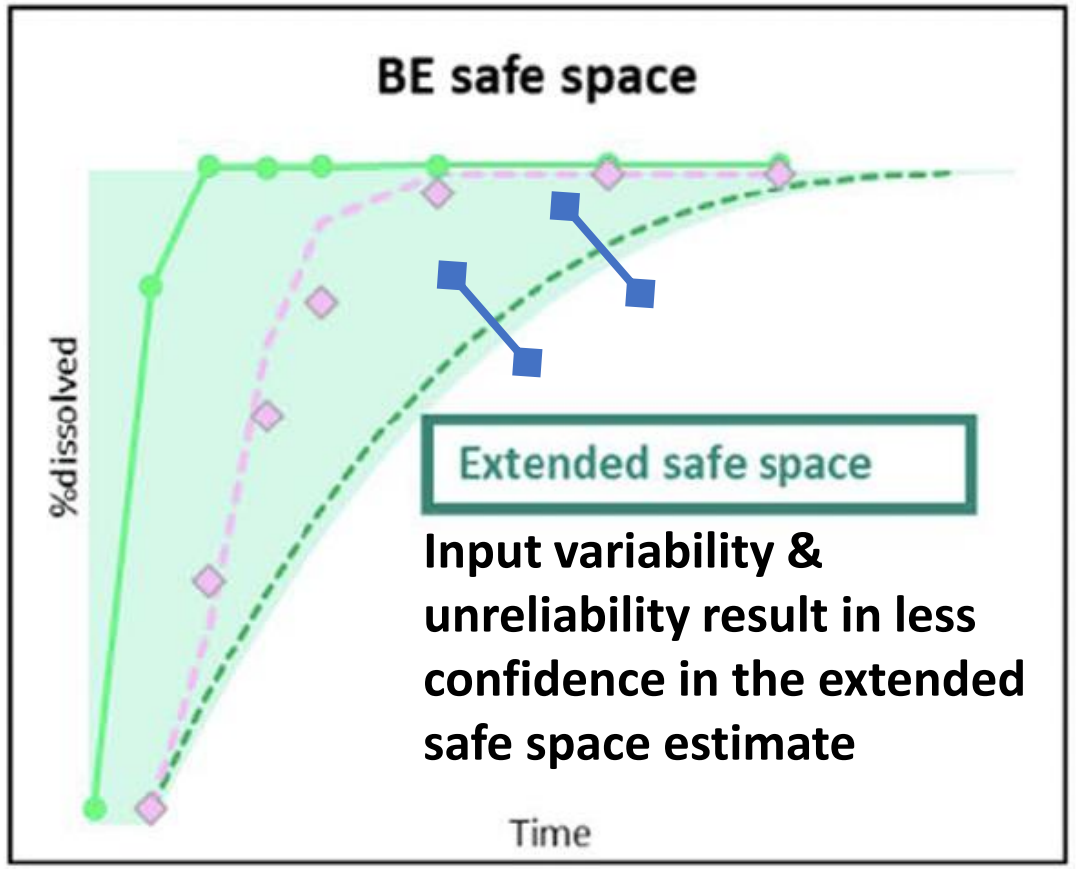
- **Dissolution**, hardness, **disintegration** time, **precipitation time.**

### Physiology

- "default" parameters
- Gastric transit time, pH, water content

### Pharmacokinetics

- Disposition = Intravenous Data.

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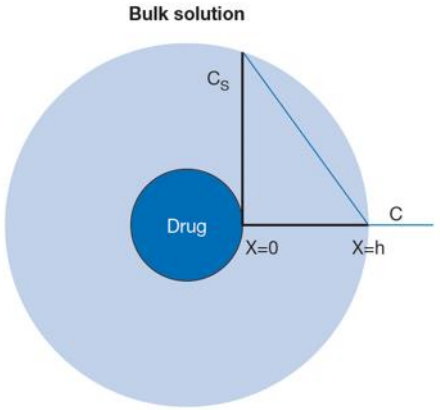
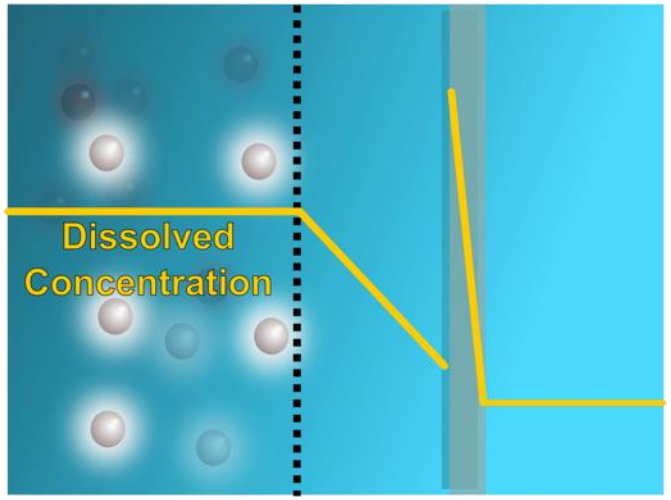
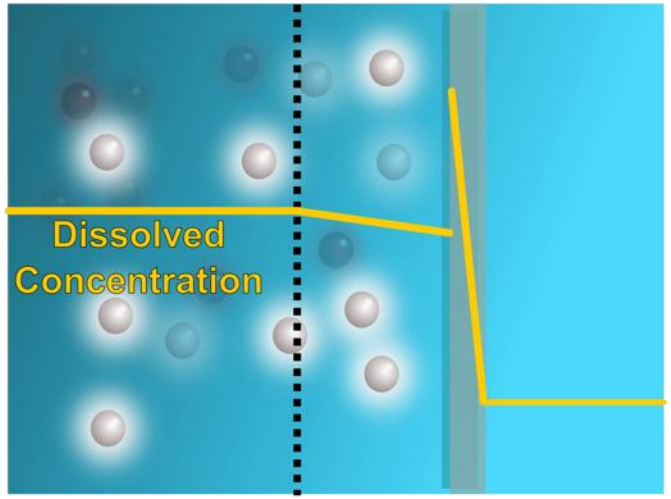
# Effect of Particle Size and Dose
## Non-Sink Dissolution Conditions




- **Confinement** = dissolved drug accumulates closer to the undissolved particle than some infinite distance in the bulk, allowing for a buildup of local concentration to form around each solid particle, i.e., non-sink conditions.




$$\Delta_{conf} = \frac{\gamma}{1-\gamma}$$

$$\gamma = \frac{3}{2}\frac{\left(\frac{V_c}{V_p}\right)^{2/3} - 1}{\frac{V_c}{V_p} - 1}$$

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**Particle-Size, Dose, and Confinement Affect Passive Diffusion Flux Through the Membrane Concentration Boundary Layer.** P.D. Sinko, N. Salehi, T. Halseth, P.J. Meyer, G.L. Amidon, R.M. Ziff, G.E. Amidon (submitted).

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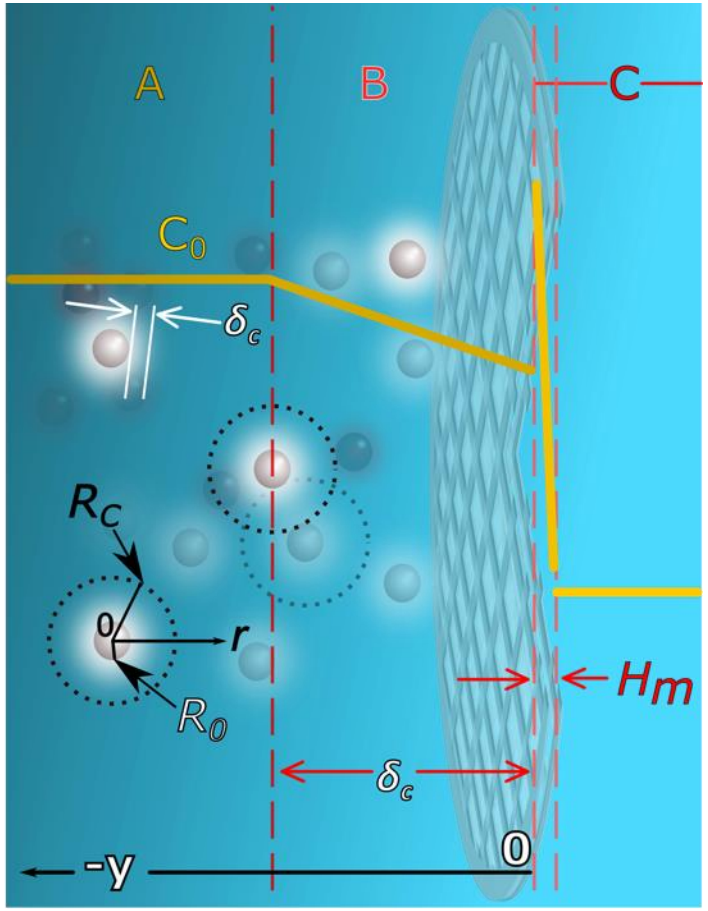


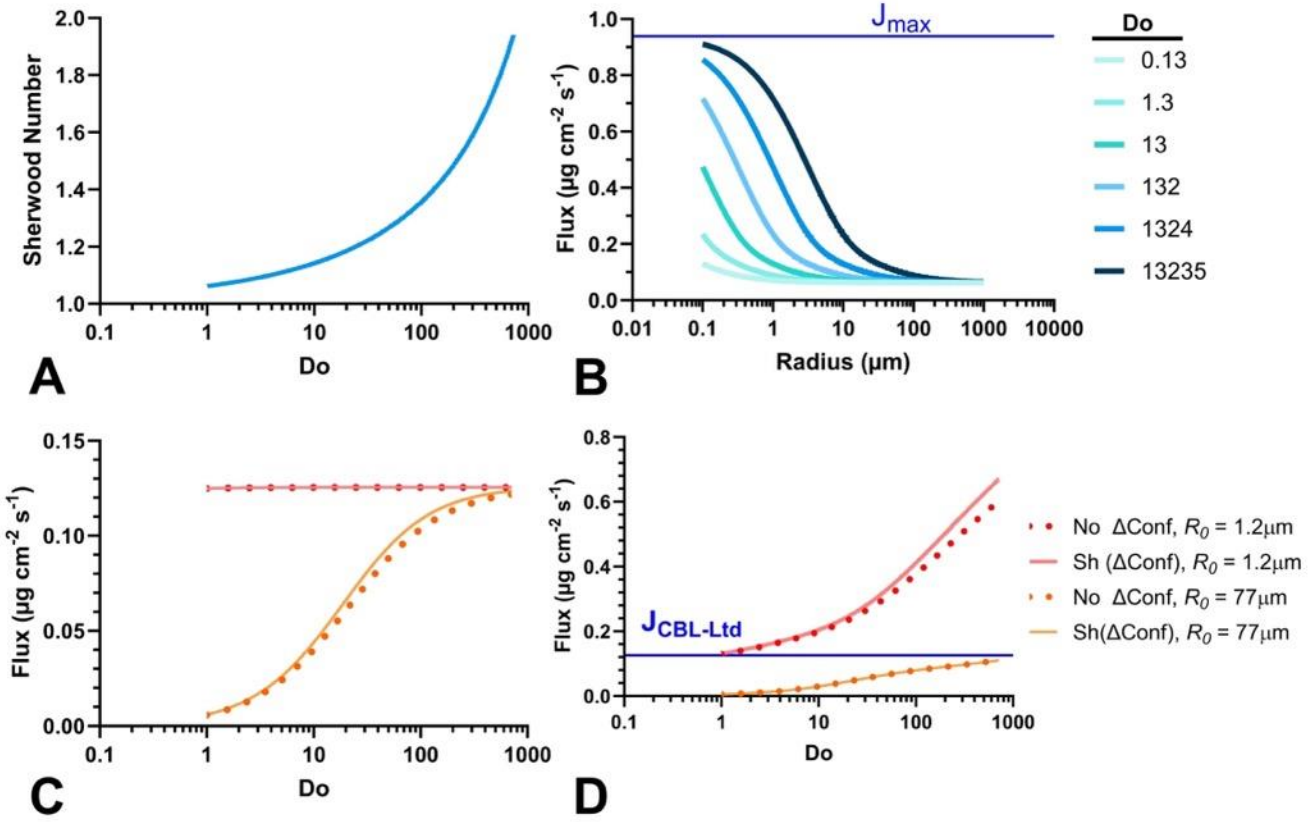


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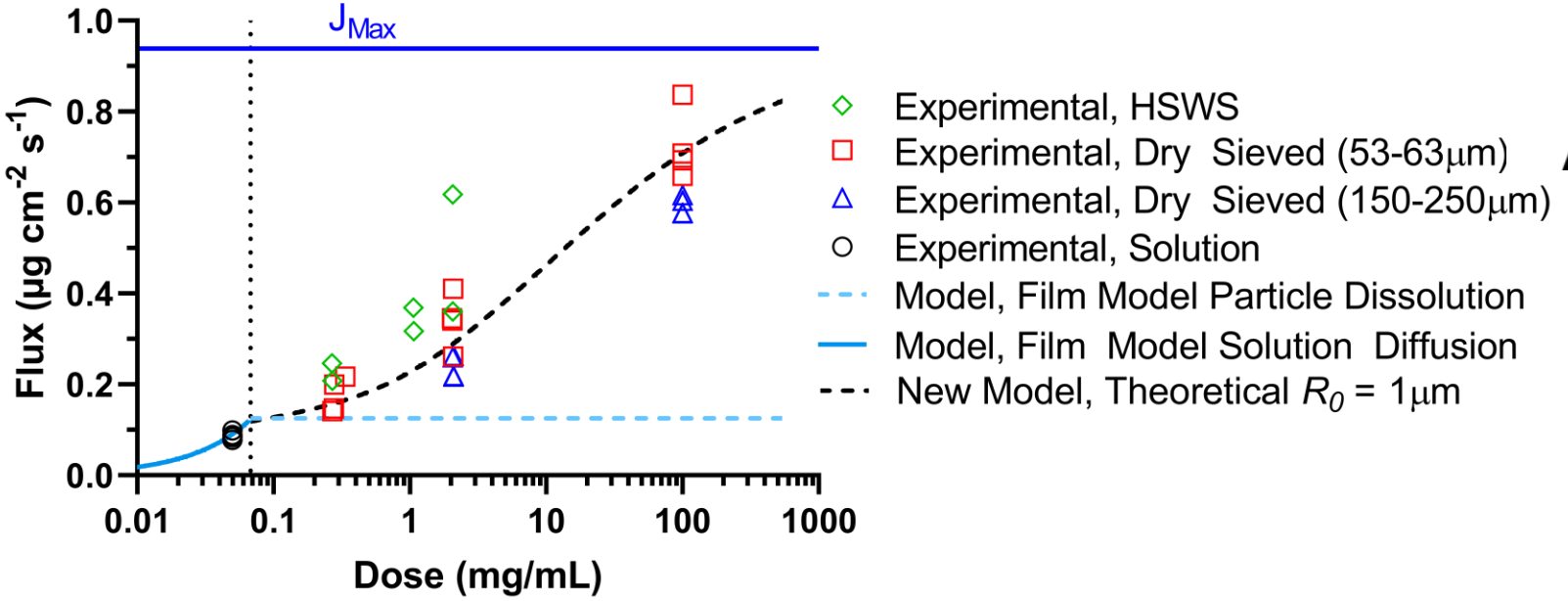


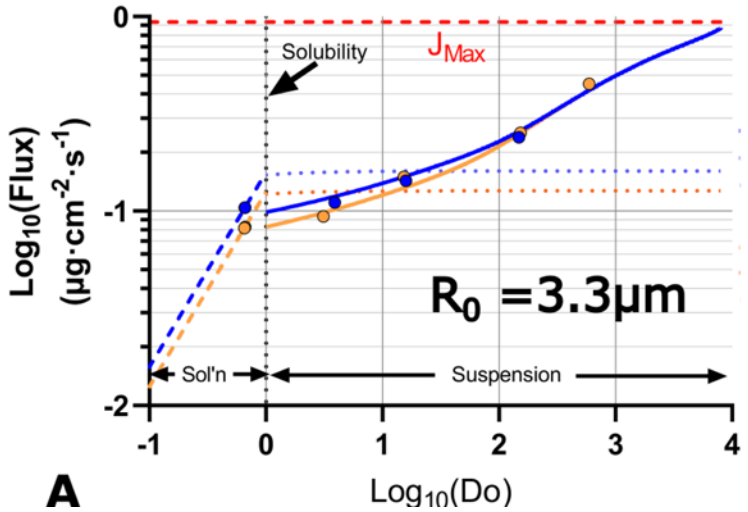


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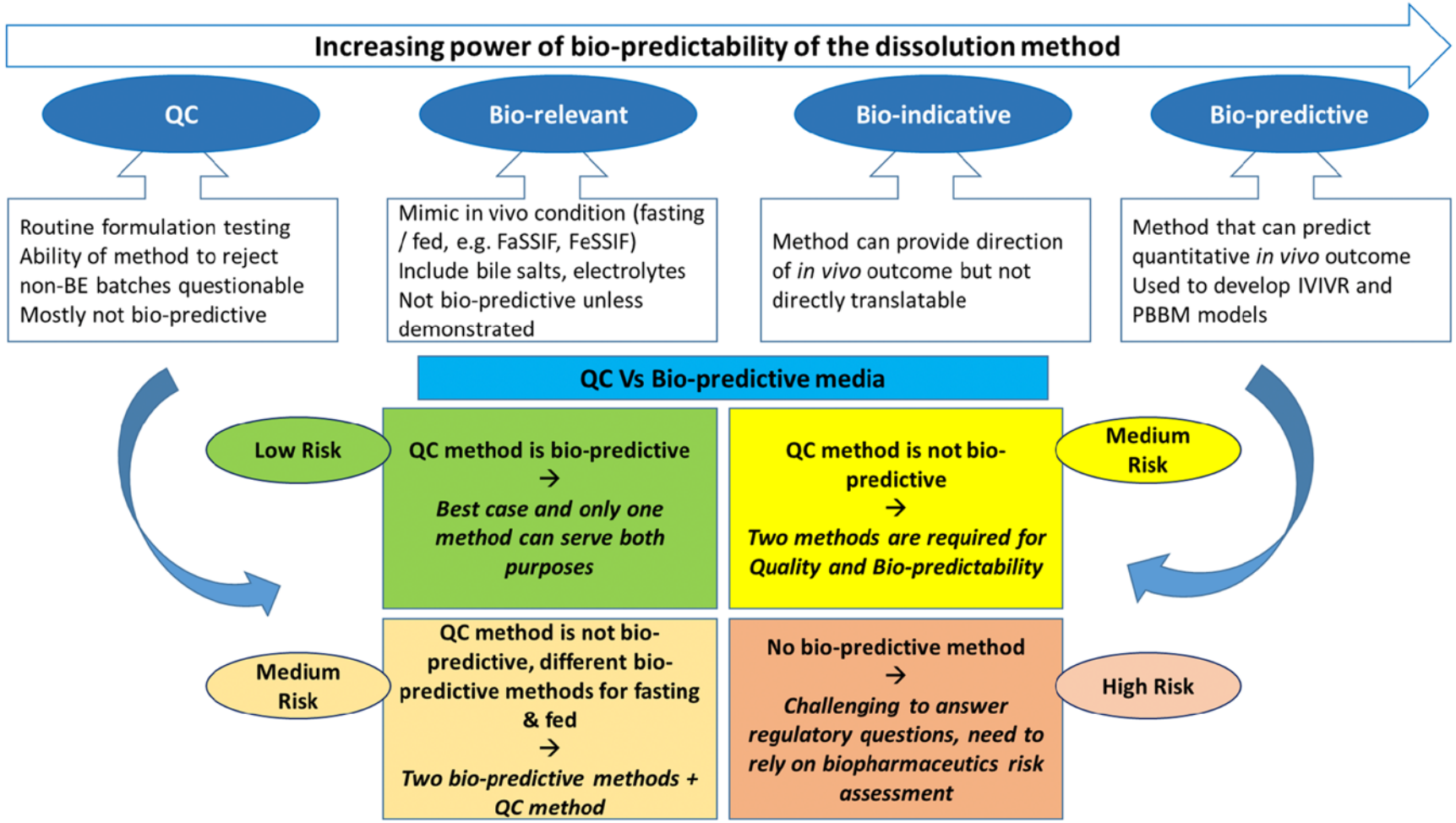
# Bio-Predictive Dissolution is Required for PBBM to Ensure the Integrity of the Safe Space Prediction

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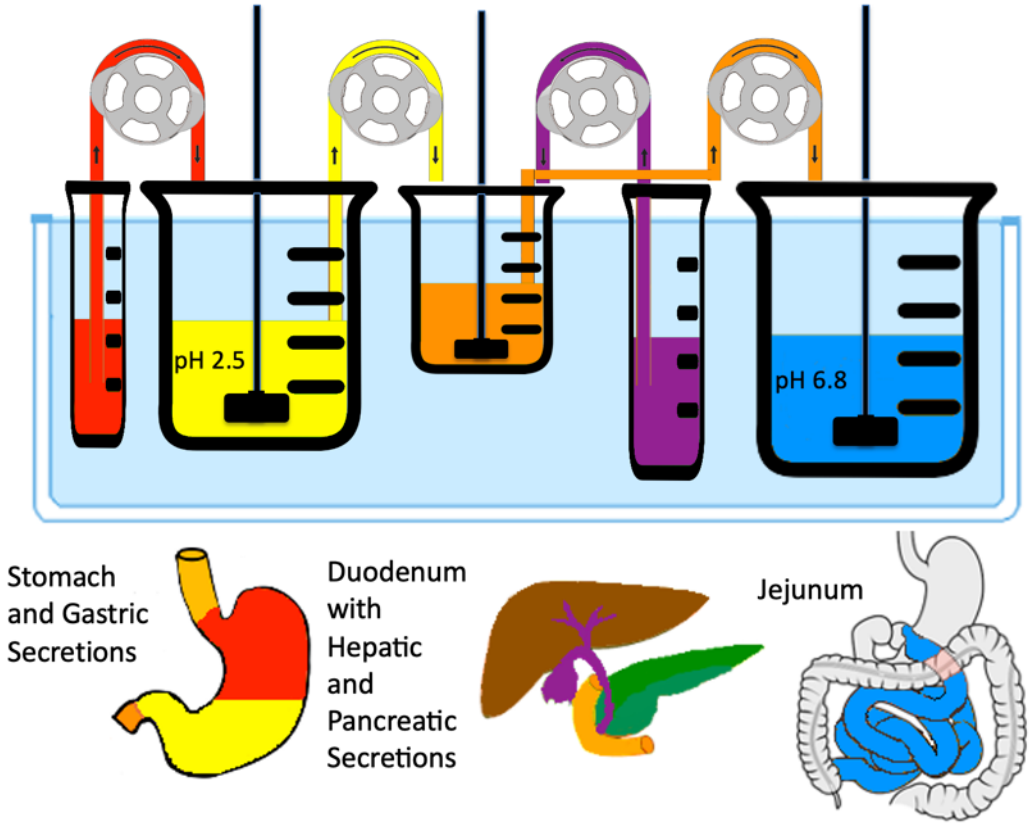
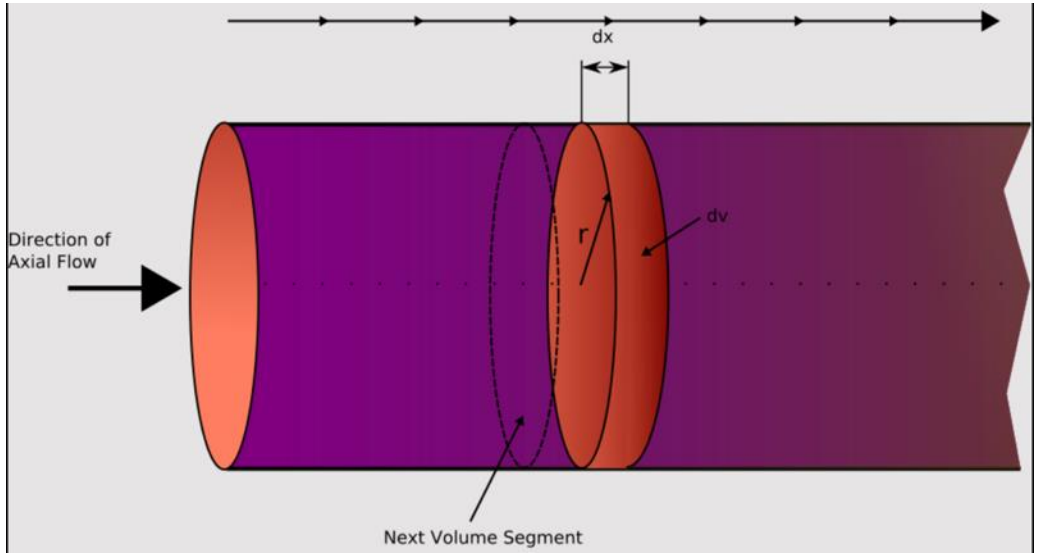
# Precipitation Time



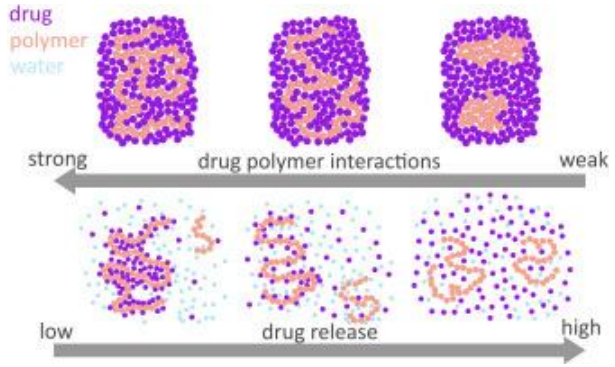

**Transfer Dissolution Model – GI Simulator System**



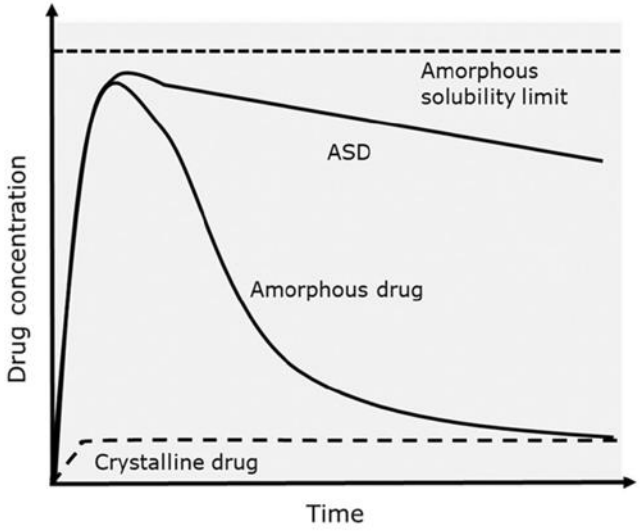

What if no accumulation of drug occurs in any one plug and critical supersaturation never occurs?

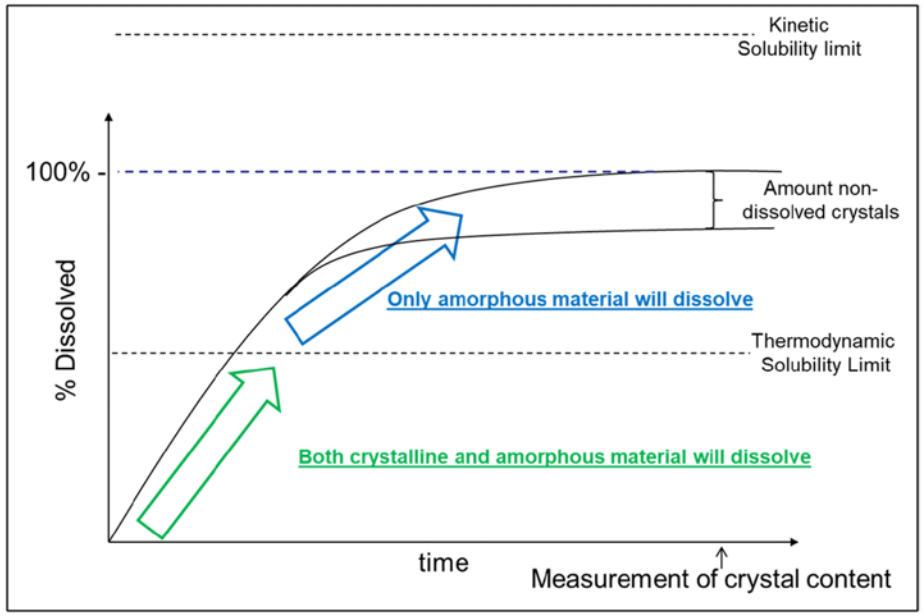
# Solubility

## Formulation Dependency: Amorphous Solid Dispersions




**Spring & Parachute Approach**




**Challenges and Strategies for Solubility Measurements and Dissolution Method Development for Amorphous Solid Dispersion Formulations**

Andre Hermans[1] · Johanna Milsmann[4] · Hanlin Li[3] · Christian Jede[7] · Andrea Moir[2] · Bart Hens[6] · James Morgado[1] · Tian Wu[8] · Michael Cohen[9]

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# Other Challenges & Future Opportunities (I)

**Pharma 4.0 (data driven manufacturing)**.

- Real Time Release Testing (RTRT) within the Process Analytical Technology framework or use of Machine Learning methods (e.g., ANNs).
  - Goal: reducing tests in standardized instruments that are labor- and time-intensive.
  - Example: NIR and/or Raman spectra with regression analysis predict dissolution.
    - Moisture content, compression force, mixing shear forces, feed frame and blender speeds, API content.
  - Challenge: Applying a single PAT tool may not be sufficient to predict dissolution.
    - May need multiple inputs, which requires something more sophisticated (e.g., ANNs) than linear regression models

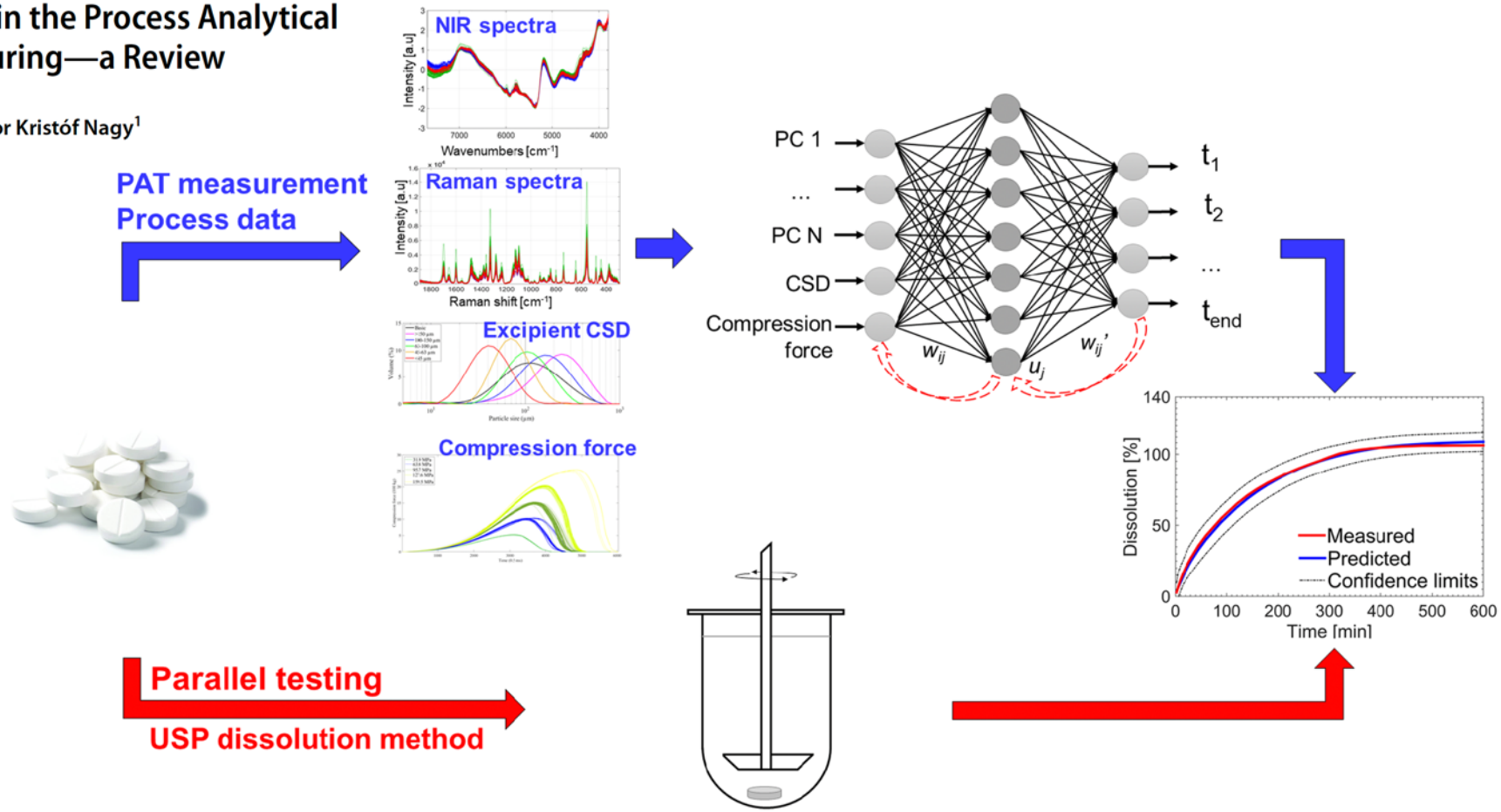
The AAPS Journal (2022) 24: 74
https://doi.org/10.1208/s12248-022-00706-0

REVIEW ARTICLE

Theme: Process Analytical Technology (PAT) in Pharmaceutical and Biopharmaceutical Industry

# Application of Artificial Neural Networks in the Process Analytical Technology of Pharmaceutical Manufacturing—a Review

Brigitta Nagy[1] · Dorián László Galata[1] · Attila Farkas[1] · Zsombor Kristóf Nagy[1]

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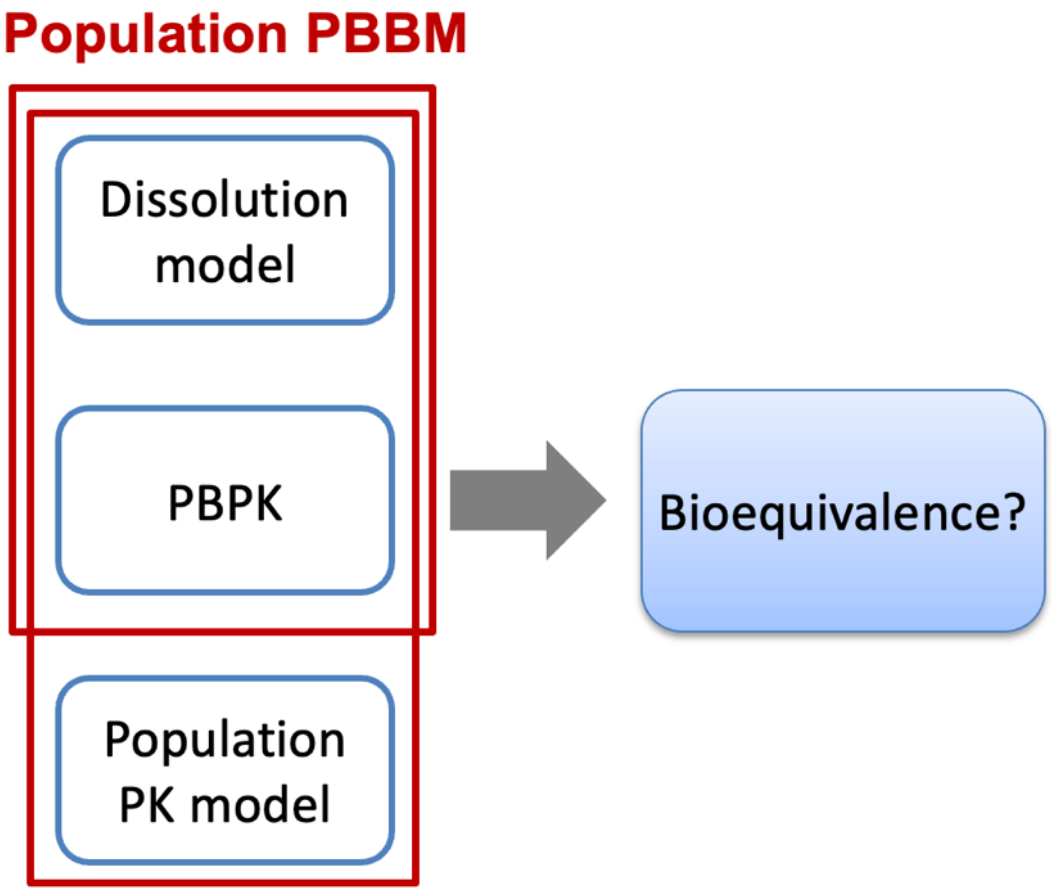
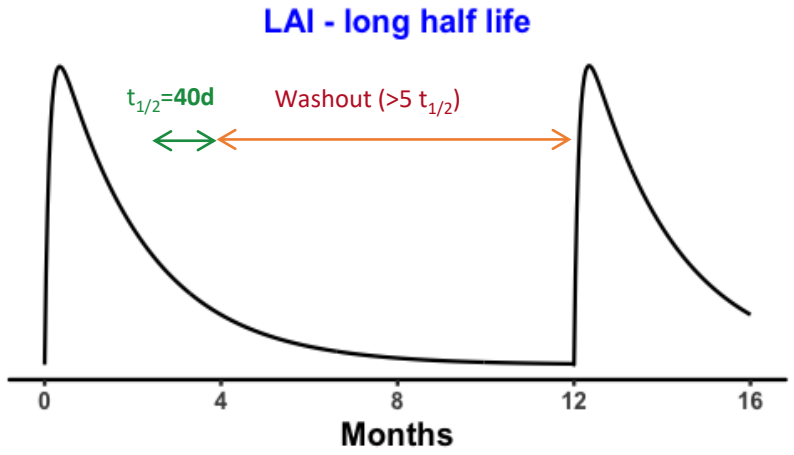
# Other Challenges & Future Opportunities (II)
## Model-Integrated Bioequivalence Evaluation

- **Complex generic drugs**
  - Implants
  - Long-acting injectables
  - Oral (IR, MR).
- **Goal**: To untangle complicated input functions (absorption, release, dissolution rate), considering flip-flop kinetics & diverse patient populations.

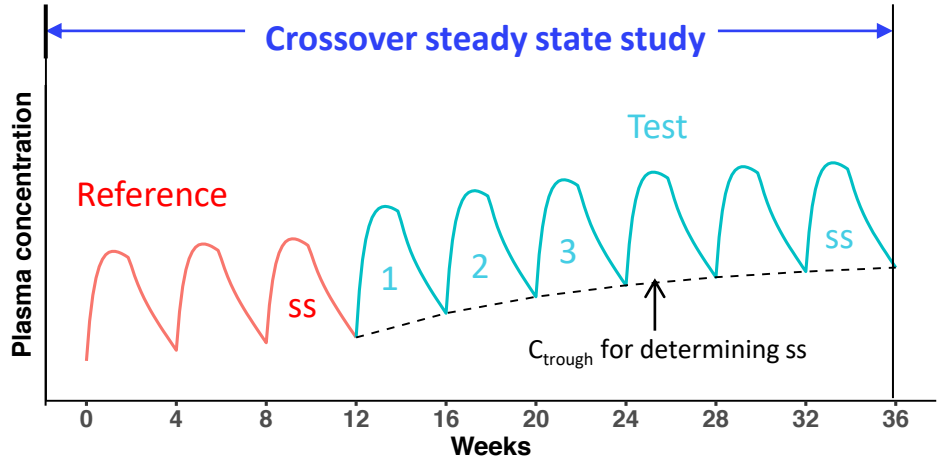


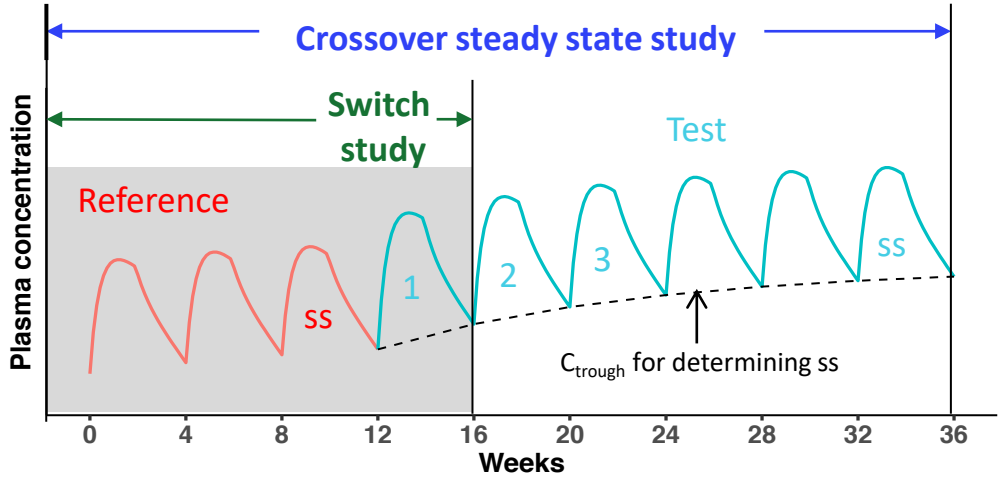
# Other Challenges & Future Opportunities (II)

## Model-informed BE evaluation strategies for long-acting injectable products




**It is not practical to perform a single-dose crossover BE study on LAI.**




**Source**: X. Chen, Uppsala University.

# Takeaways

- AAPS and SPDS should continue to explore ways to collaborate and strengthen our ties.
- Improve global regulatory recognition of Clinically Relevant Dissolution Specifications & the concept of Safe Space (the gold standard equivalence region).
- Need to balance sensitivity analysis (a sort of fudge factor) with more robust models of inputs and the variability of API (dose, solubility, particle size distribution) and formulation (dissolution, hardness, disintegration time, precipitation time).
- For complex generics, more sophisticated population-based PBBM model-informed approaches should be developed & utilized.

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