Strategic Considerations for Bridging Drug Delivery Devices: PBBM-Enabled Assessment of Formulation/Device Changes

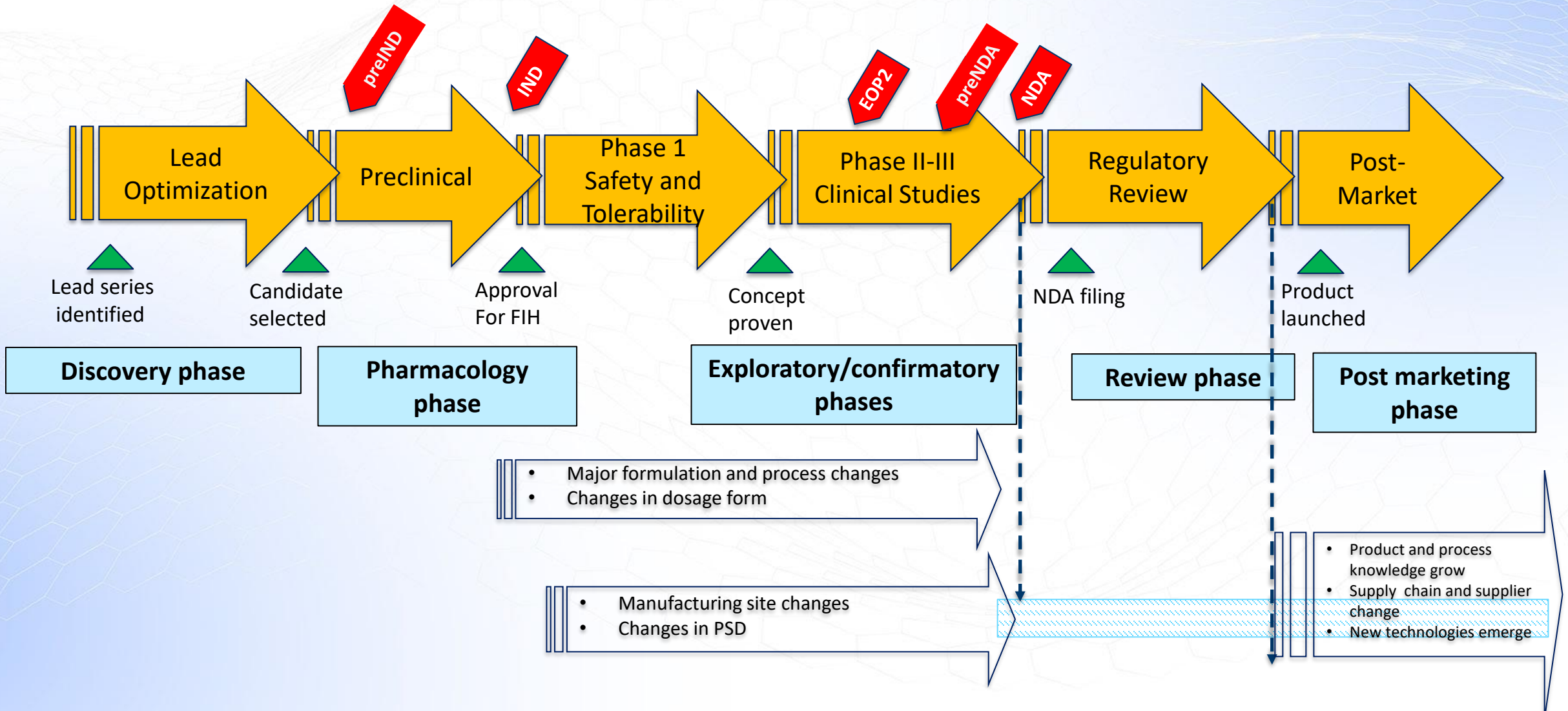
Sandra Suarez-Sharp
Global Head, Regulatory Strategies

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Advancing Clinical Care through Pharmacology
2026 ACCP Annual Meeting
"Harnessing Changing Clinical Pharmacology Paradigms to Improve Patient Outcomes"

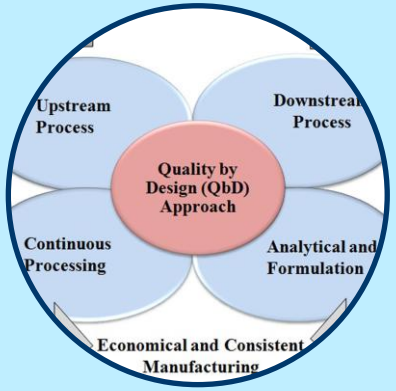
Outline

- Typical Phases of Drug Development and When Device Bridging Considerations Arise
- Possible Approaches to Reducing Regulatory Burden and Complexity
  - Concept of PBBM-Safe Space
    - Data Needed to Build a PBBM
    - Role of PBBM in Device/Formulation Bridging Across Product Lifecycle
- Case Studies for Formulation and Device Bridging
- Key Take Aways

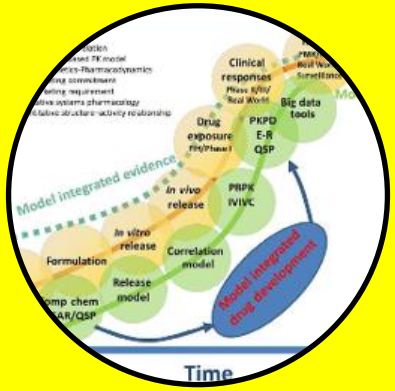
Phases of Drug Product Development – Regulatory Milestones



Possible Approaches to Reducing Regulatory Burden and Complexity



By building quality during drug product development rather than testing it into drug products (ICH Q8(R2)



By implementing tools that facilitate the establishment of an in vitro in vivo link


INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

BIOPHARMACEUTICS CLASSIFICATION SYSTEM-BASED BIOWAIVERS

M9

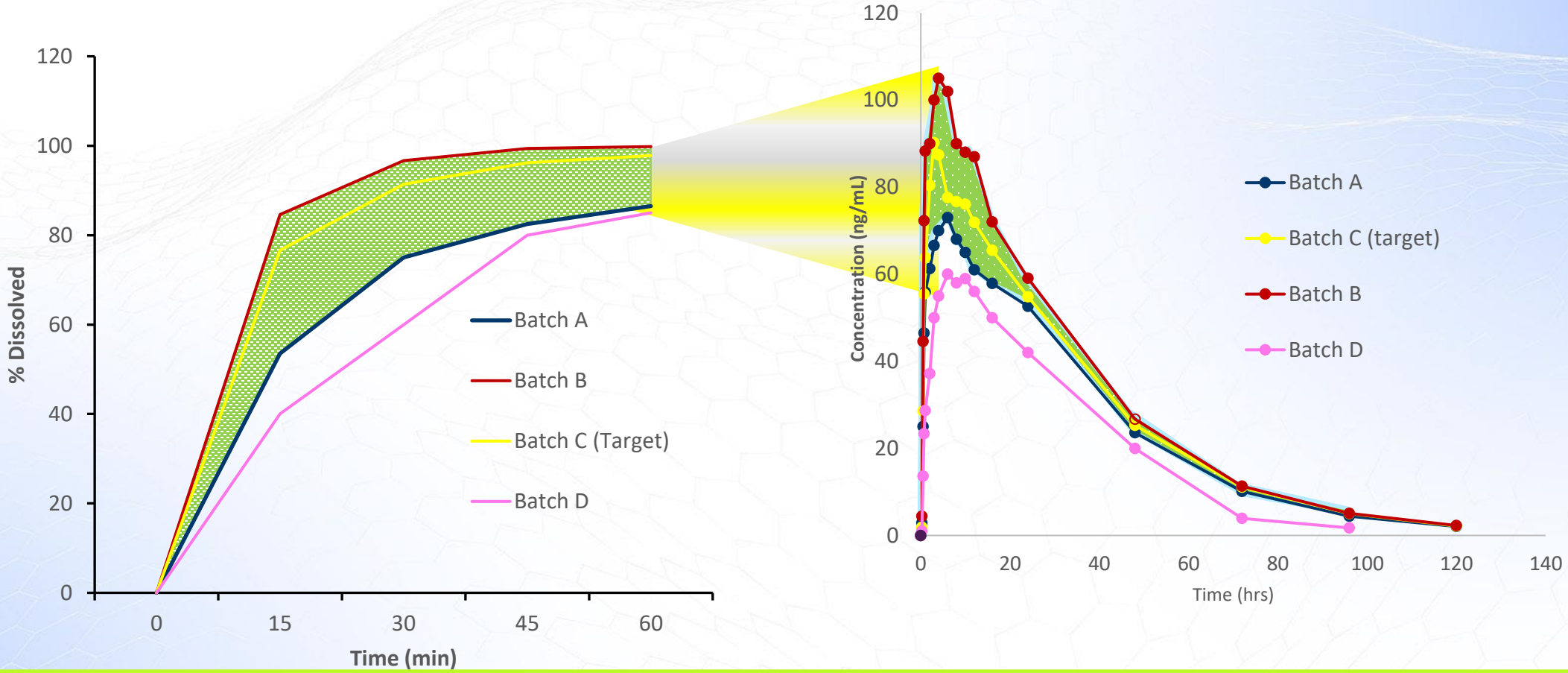
Final version

Adopted on 20 November 2019

By expanding the framework beyond traditional regulatory guidance

The Concept of Safe Space

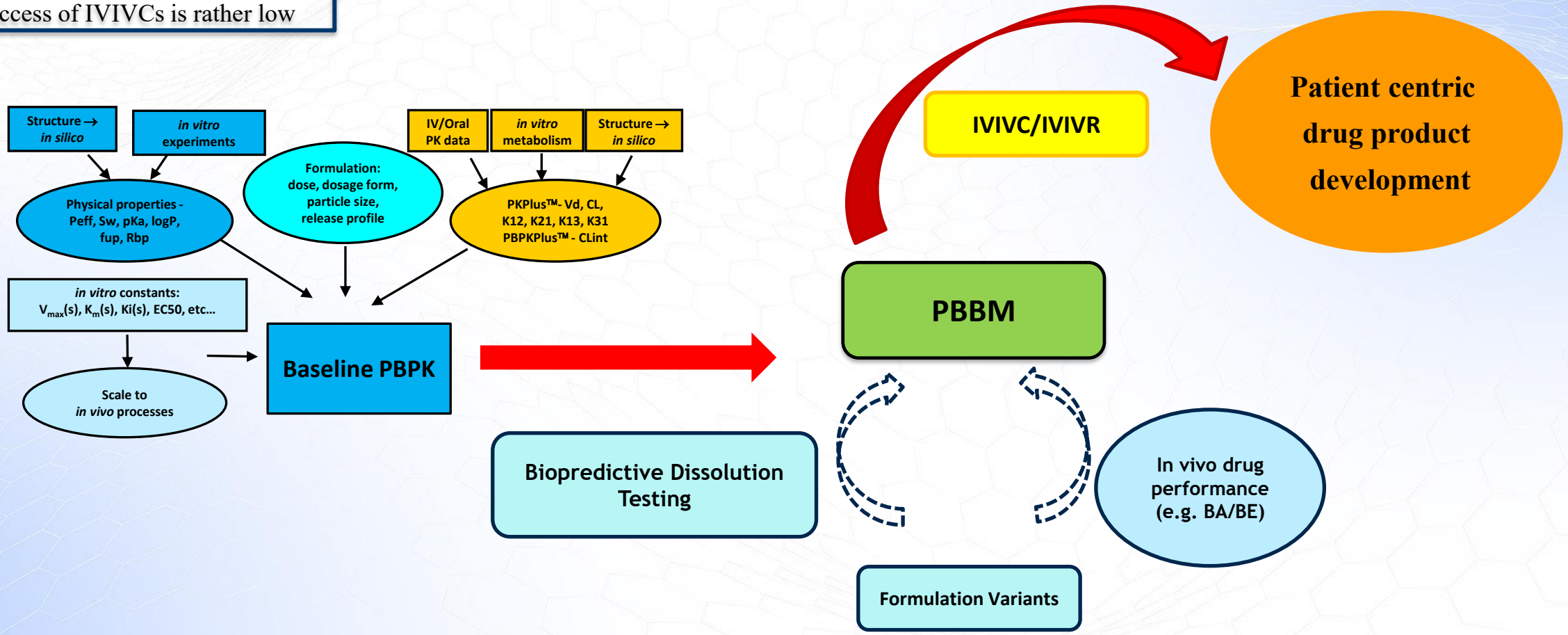
The Concept of Dissolution Safe Space



The limits defined by the extremes in dissolution profiles that have been shown to be BE to each other either by conventional approaches or using modeling and simulation such as PBBM

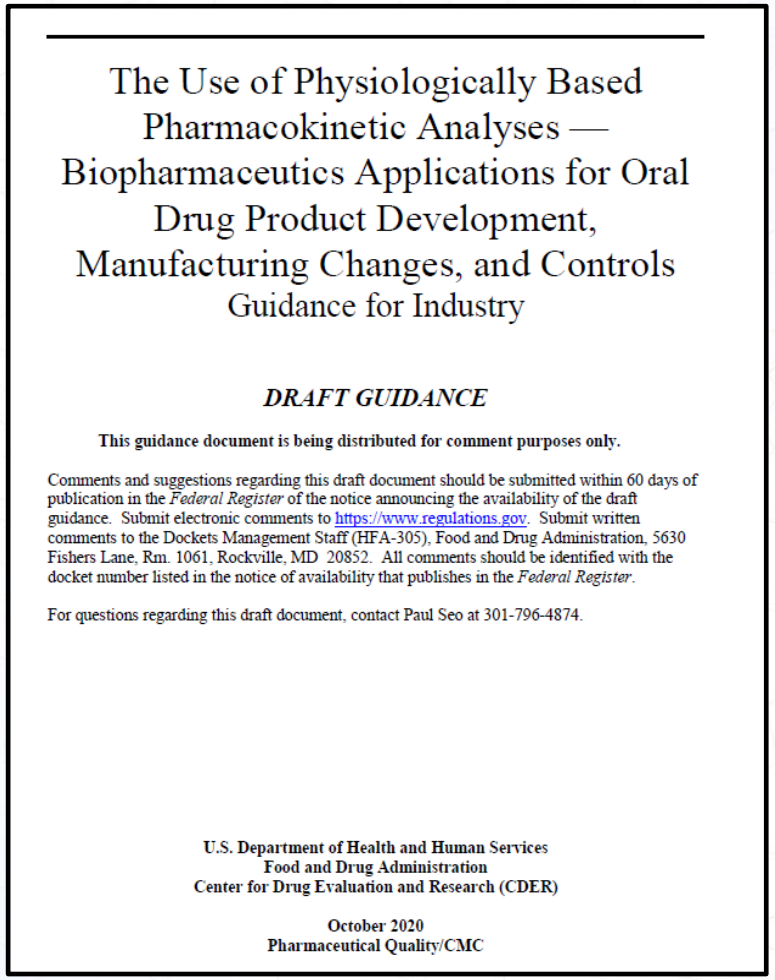
What is PBBM?

NOT confined to building an IVIVC, offering a simpler path to biowaivers specially for IR drug products for which the rate of success of IVIVCs is rather low



PBPK: Physiologically based pharmacokinetics
IVIVC: In vitro in vivo correlation
IVIVR: In vitro in vivo relationship

FDA Guidance: The Use of PBBM in Support of Product Quality



The Use of Physiologically Based Pharmacokinetic Analyses — Biopharmaceutics Applications for Oral Drug Product Development, Manufacturing Changes, and Controls
Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

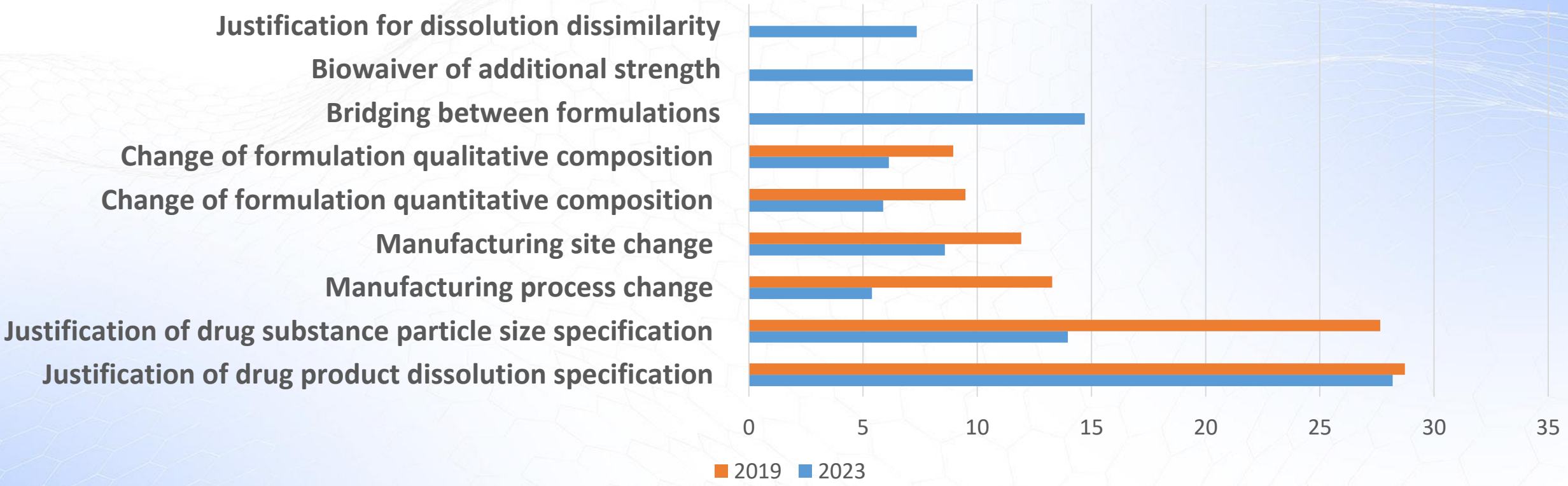
For questions regarding this draft document, contact Paul Seo at 301-796-4874.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

October 2020
Pharmaceutical Quality/CMC

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/use-physiologically-based-pharmacokinetic-analyses-biopharmaceutics-applications-oral-drug-product

Common Applications: PBBM-Safe Space



2019 data from: Mitra, A., et al., Applications of Physiologically Based Biopharmaceutics Modeling (PBBM) to support Drug Product Quality: A Workshop Summary Report. Journal of Pharmaceutical Sciences, 2021. 110: p. 594-609. https://doi.org/10.1016/j.xphs.2020.10.059

2023 data from: https://www.pharmacy.umaryland.edu/centers/cersievents/PBBM2023/

Role of PBBM in Device Bridging Across the Product Lifecycle

Development Phase	Typical Device Changes	Role of PBBM
Discovery / Preclinical	Device selection, prototypes	Assess formulation–device compatibility and identify risks
Phase I	Minor device refinements	Predict impact on dose delivery and exposure
Phase II–III	Device redesign, component changes	Predict in vivo performance and guide bridging strategy
Pre-Approval	Commercial device, late-stage changes	Demonstrate comparability and support regulatory justification
Post-Marketing	Supplier, manufacturing, or device updates	Evaluate lifecycle changes and support post-approval submissions

Case Study 1:

Development and Validation of a PB-IVIVC Safe Space to support Manufacturing Changes and PSD Changes for a Long-Acting-Injectable (LAI)

Drug Product Background

Problem Statement — **Change in PSD and Site Changes post-approval**

- Site changes and PSD specification changes for an extended-release (ER) product are considered major requiring BA/BE studies
- The sponsor's strategy was to request a biowaiver supported by modeling and simulation

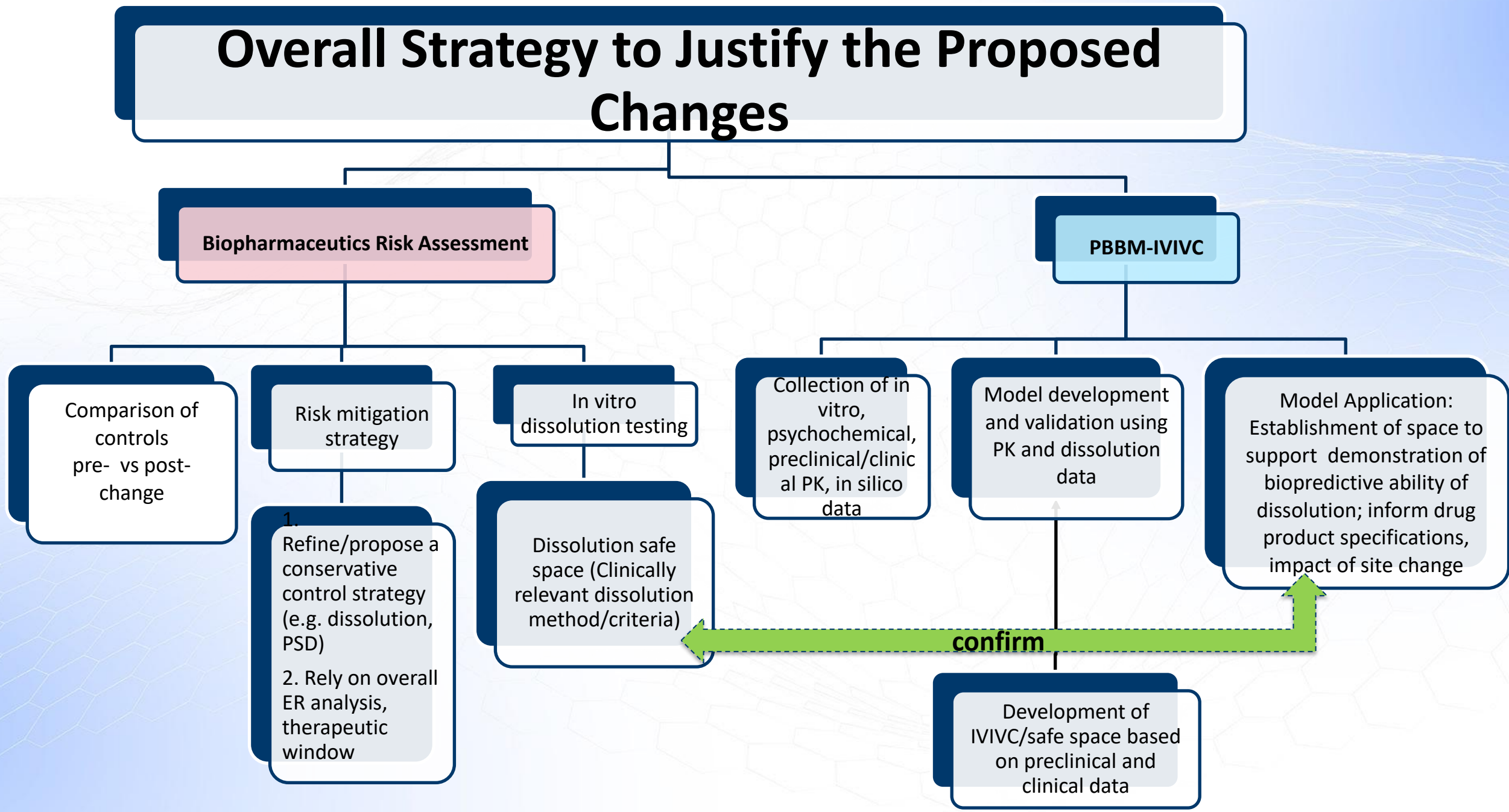
Drug Product Characteristics — **Long-Acting injectable: Suspension for IM administration (Pre-filled Syringe)**

- Drug product was evaluated in preclinical studies to determine the impact of particle size distribution (PSD) on systemic exposure
- Two formulation variants with different dissolution profiles were evaluate in PK/efficacy and safety clinical trials
- Linear and dose proportional PK

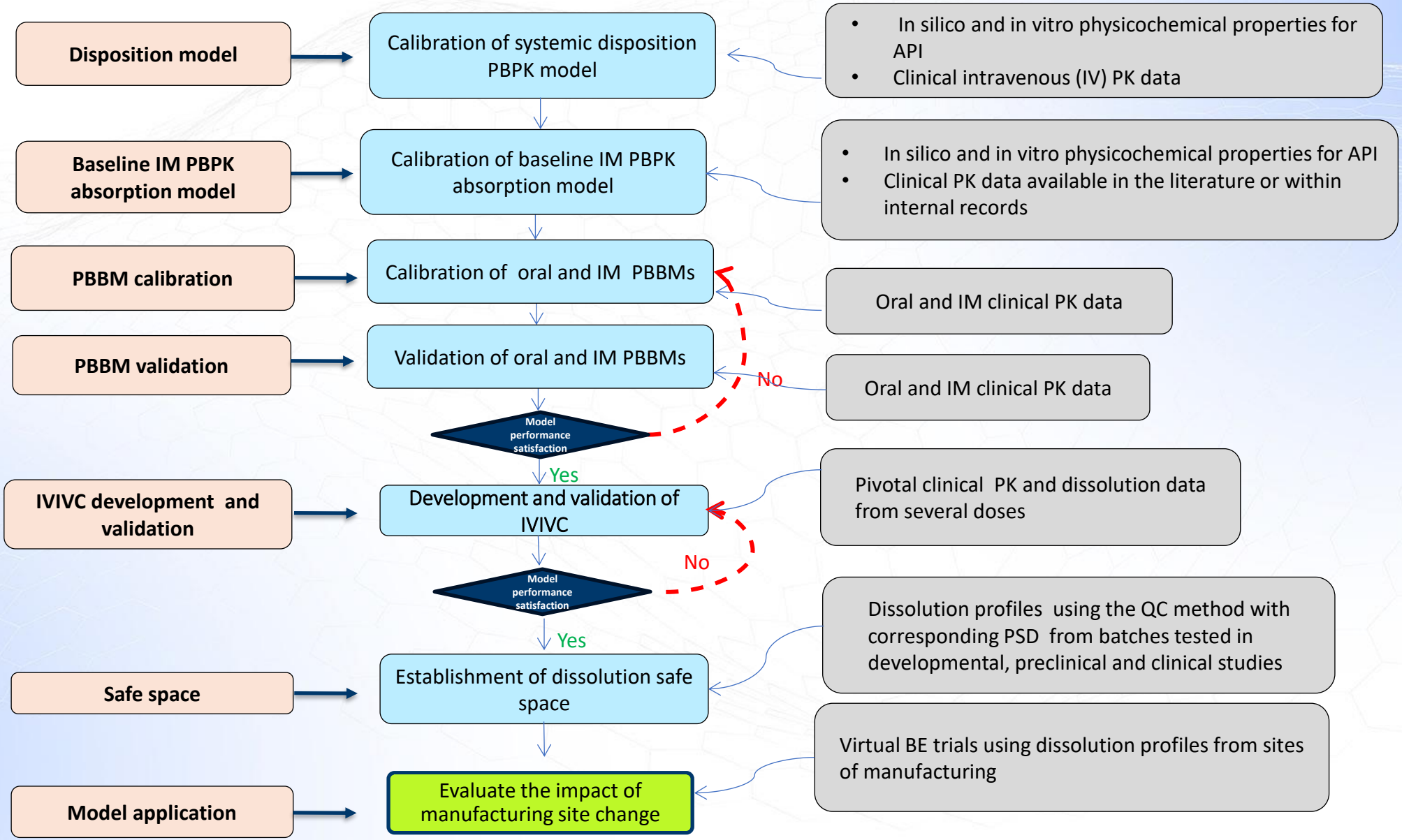
Dissolution method characteristics — **Compendial US method (no surfactant)**

- The method discriminates PSD and viscosity

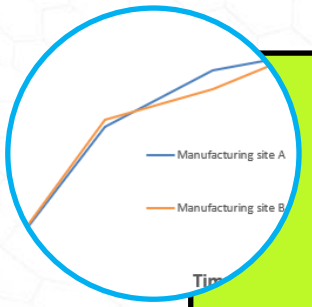
Overall Strategy to Justify the Proposed Changes



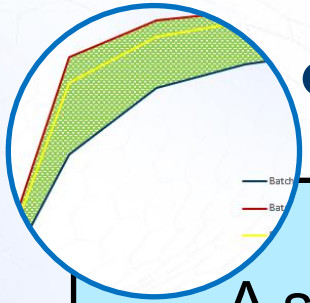
PB-IVIVC Development and Validation Flowchart: Clinical Model



Model Application: Justification for a Manufacturing Site Change/ Change in PSD Specs.



The predicted Cmax, Cmin and AUC comparing both manufacturing sites met the requirements for BE after single and multiple dosing



A safe space was established via VBE comparing the upper and lower bounds

Case Study 2:

PBBM to Support Device Bridging: Transition from Nebulizer to Dry Powder Inhaler During Clinical Development

Drug Product Background

Problem Statement

- Early clinical studies used a continuous-output nebulizer
- Commercial development transitioned to a spray-dried DPI
- Objective: maintain comparable systemic exposure despite different lung deposition

Drug Product Characteristics

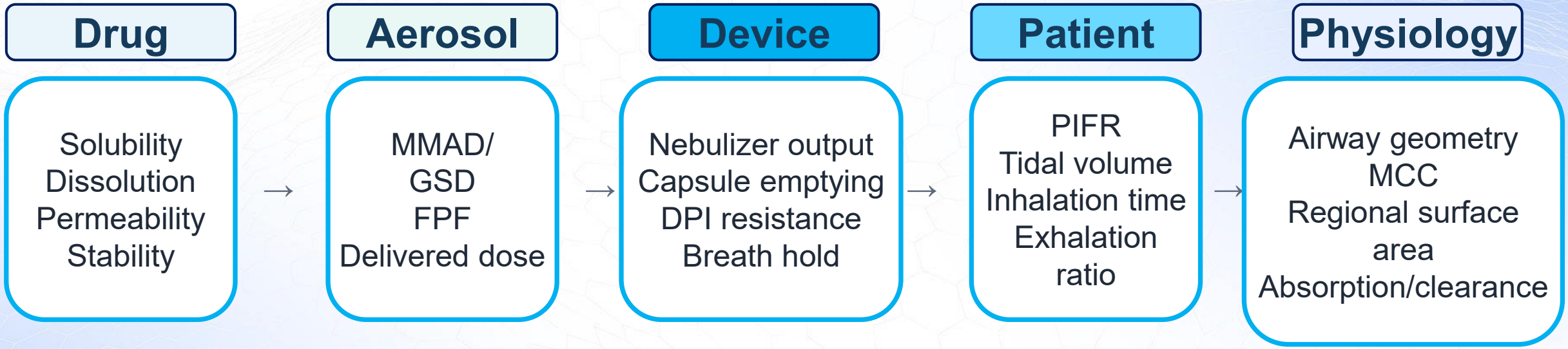
- Novel inhaled biologic protein (DPA)
- Solution (nebulizer) and spray-dried powder (DPI)

Key Question

Can PBBM predict equivalent exposure and support device bridging?

Critical Inputs

PBBM is most useful when experimental product data and realistic inhalation scenarios are integrated before clinical dosing decisions.



MMA: Mass Median Aerodynamic Diameter
GSD: Geometric Standard Deviation
FPF: Fine Particle Fraction
PIFR: Peak Inspiratory Flow Rate.
MCC: Mucociliary Clearance

Source: Franek et al., Molecular Pharmaceutics 2025

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What the Model Showed: Similar Total Lung Dose, Different Regional Pattern

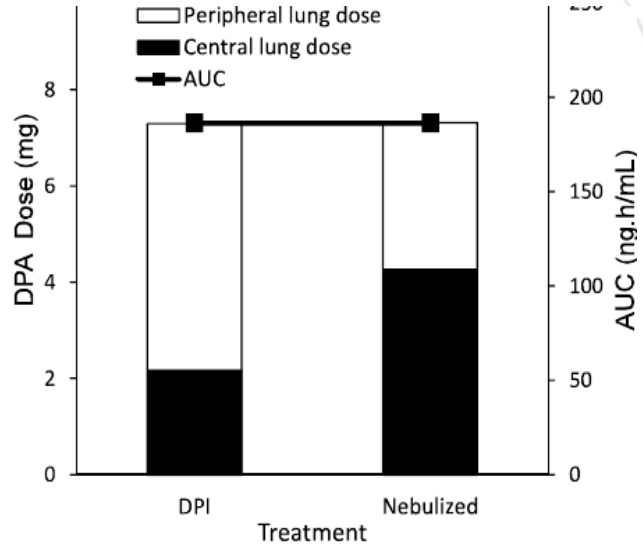


Figure 3. Estimated DPA central, peripheral, and total lung (= cer + peripheral) dose and observed AUC.

Figure 3 crop: estimated DPA central/peripheral lung dose and observed AUC

Model-based interpretation

Total lung dose

DPI and nebulizer were set to achieve approximately the same predicted total lung dose (~7.3 mg)

Regional shift

Nebulizer was predicted to deliver more central lung dose; DPI more peripheral lung dose

Clinical link

Observed systemic exposure was comparable despite predicted regional differences

Mechanistic conclusion

For DPA, systemic PK appeared more driven by total lung dose than by regional distribution

Relevance

This is the central value of PBBM for device transition: it helps determine whether a regional deposition change is clinically meaningful or primarily a modeling/quality attribute to track

Source: Franek et al., Molecular Pharmaceutics 2025 | Prepared for discussion

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Key Takeaways & Strategic Recommendations

- Start bridging strategy early
- Align model purpose with regulatory question
- Validate models with relevant variants
- Frame PBBM as a transparent risk-based communication tool
- Use PBBM with fit-for-purpose data to strengthen regulatory confidence in device and formulation bridging.
- Use safe space to support lifecycle flexibility

Questions



Please come up to one of the floor microphones



Introduce yourself



Ask your question



Stay at the microphone until the faculty have finished answering your question