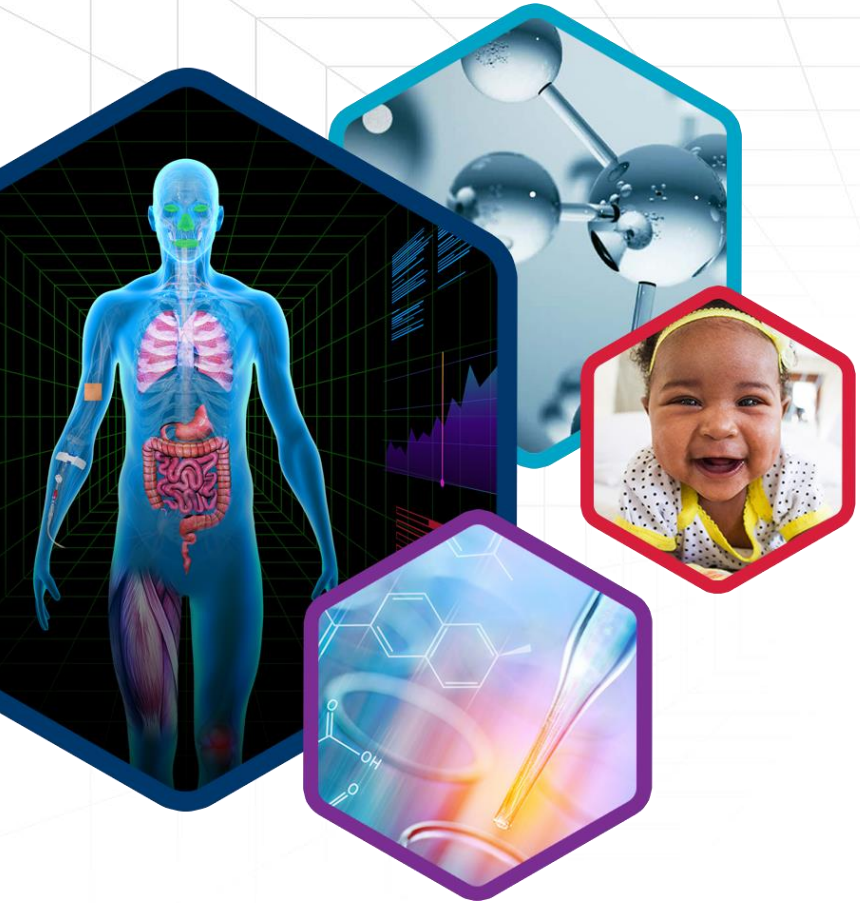


SimulationsPlus

Cognigen | DILIsym Services | Lixoft

# Predictive Dissolution Modeling with Clinically Relevant Specifications

**Sandra Suarez Sharp, PhD.**

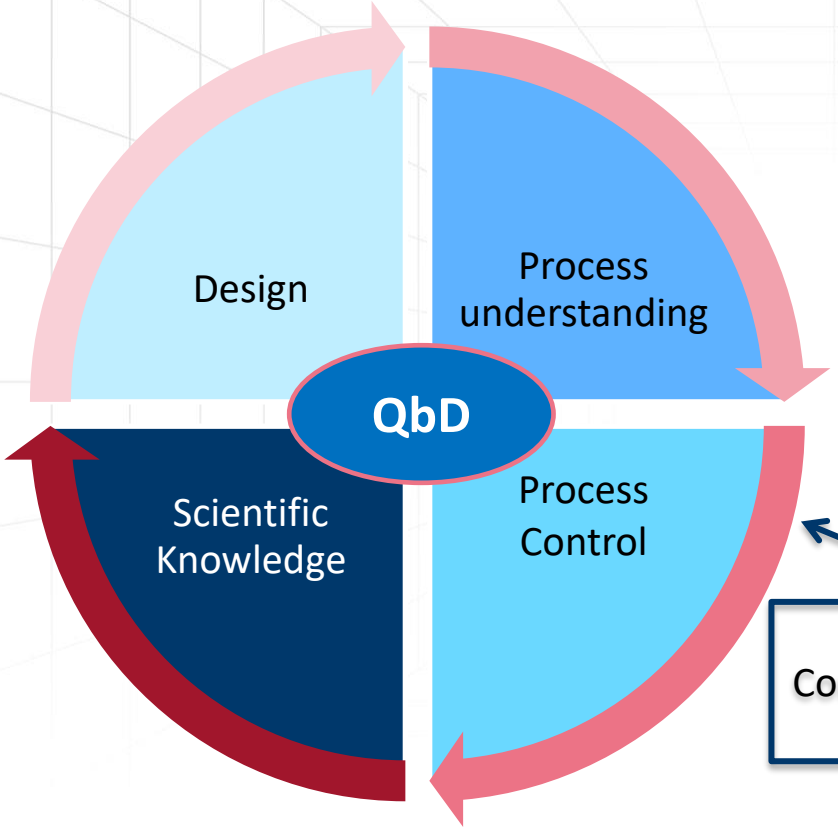
**IFPAC 2022**

**June 15, 2022**

# Outline

- Clinically relevant specifications: when is this important?
  - The role of biopharmaceutics risk assessment
- How do we build clinical relevance into RTRT dissolution models?
  - Conventional approaches
  - The relevance of mechanistic modeling and simulation (e.g., physiologically based biopharmaceutics modeling [PBBM])
- Take home message

# Quality by Design Purpose



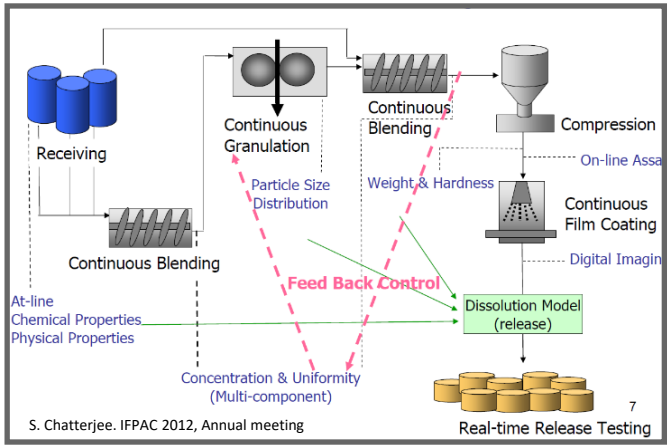

One can have QbD approaches without RTRT, but it may be very difficult to have RTRT without QbD

Control Strategy (PAT, **RTRT**)

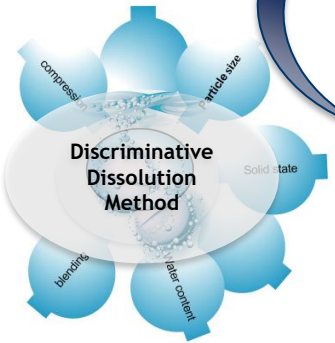
# Systematic Approach to Control Strategy

**Risk assessment to identify manufacturing parameters, material attributes**

**DoE studies**




Is a Control Strategy based on systematic controls of the CMAs/CPPs sufficient to ensure a robust control strategy and Patient Centric Drug Product Development/clinically relevant specifications?

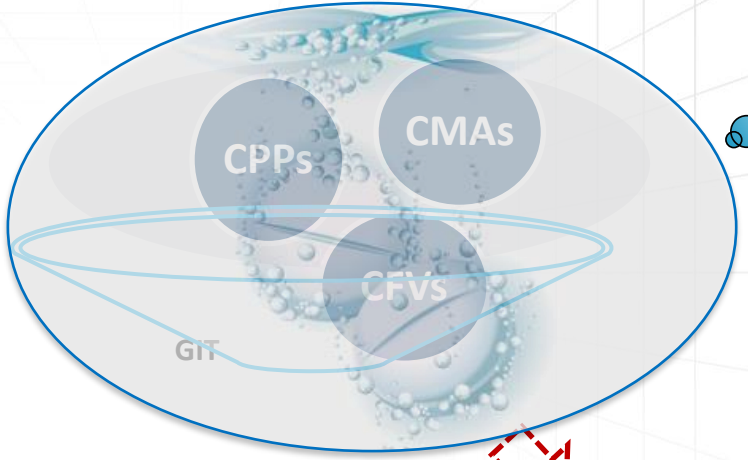



**Multivariate Model** → **RTRT Dissolution Model** → **Enhanced Control Strategy**

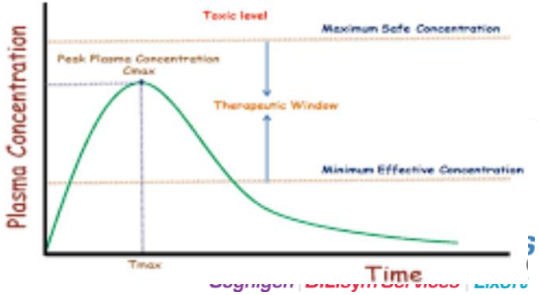
**Dissolution: f (CPP1, CPP2, CPP3,…. CMA1, CMA2, CPP1*CMA1…)**

# Consequences of Lack of In Vitro In Vivo Link

When there is lack of understanding of the relationship between CMAs, CPPs, dissolution, and clinical performance, the **likelihood** of developing a robust, clinically relevant RTRT dissolution model and thus, robust control strategy is **low**



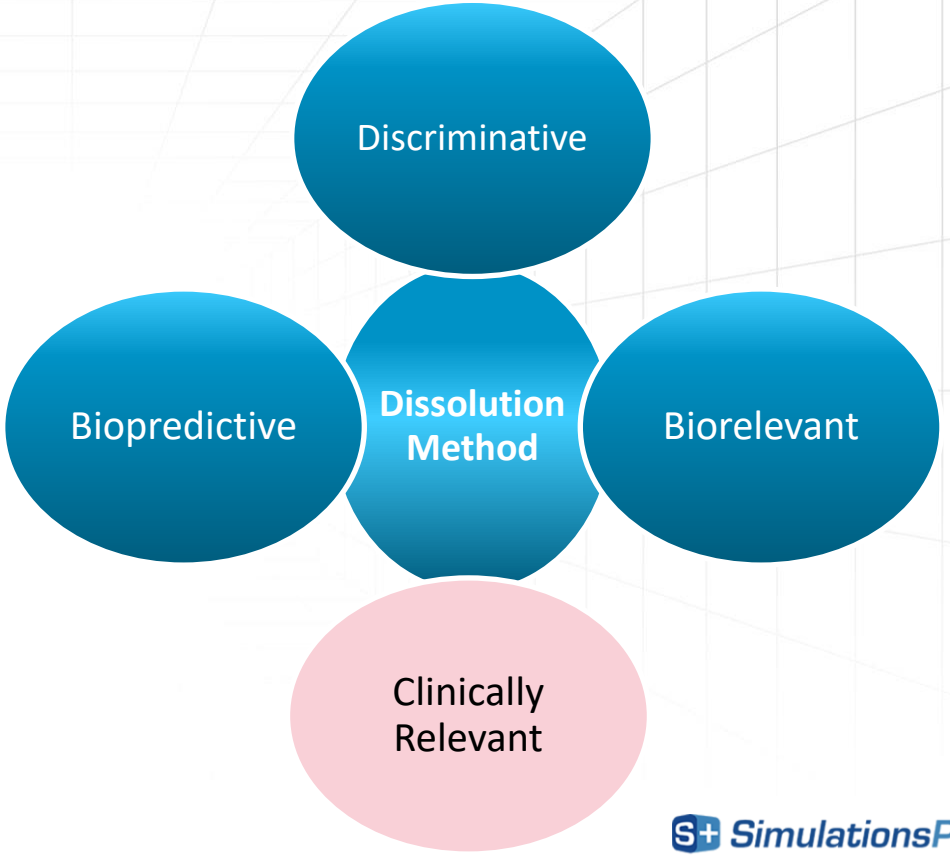

Fit for purpose dissolution method (FPDM)



# *What is a FPDM?*

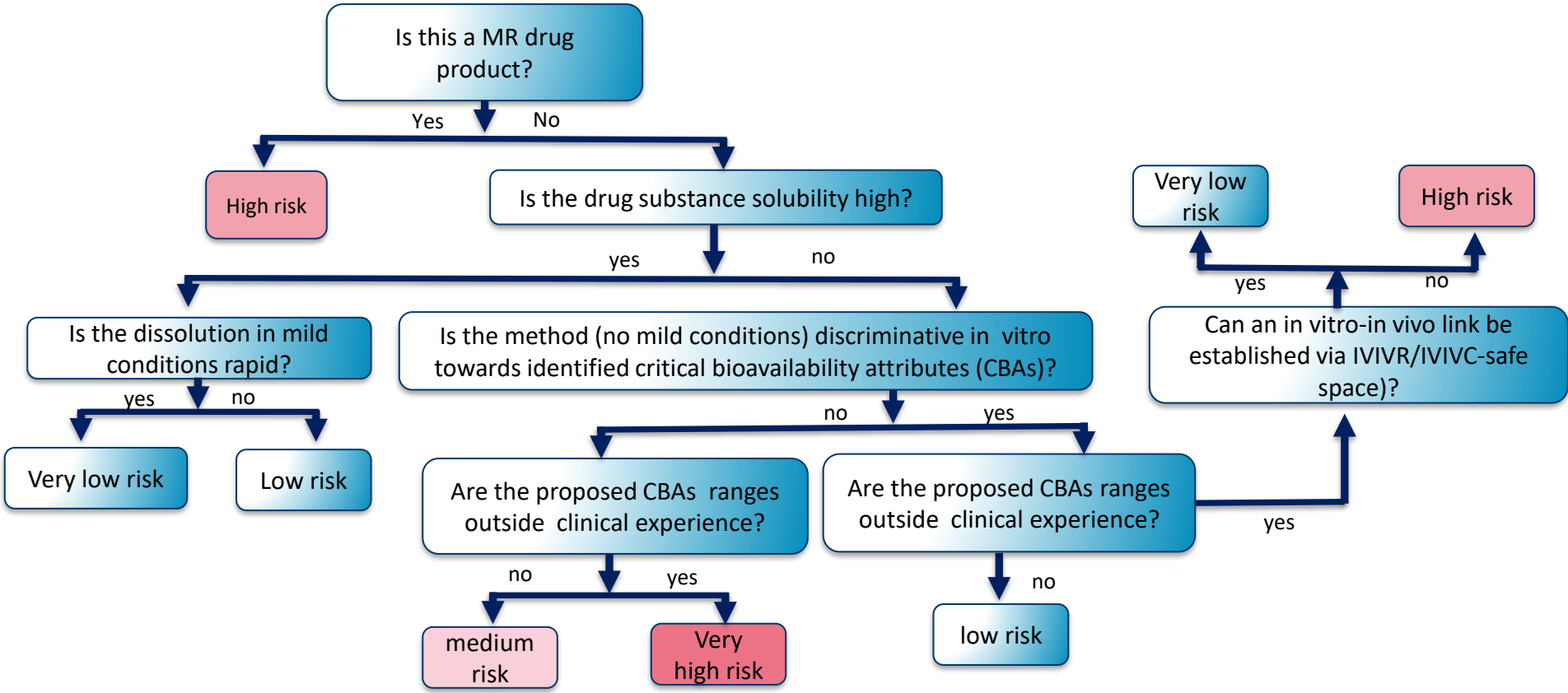
# Fit for Purpose QC Dissolution Method

- A method for which its level of **discerning ability/scrutiny** has been established <u>based on biopharmaceutics risk assessment</u>

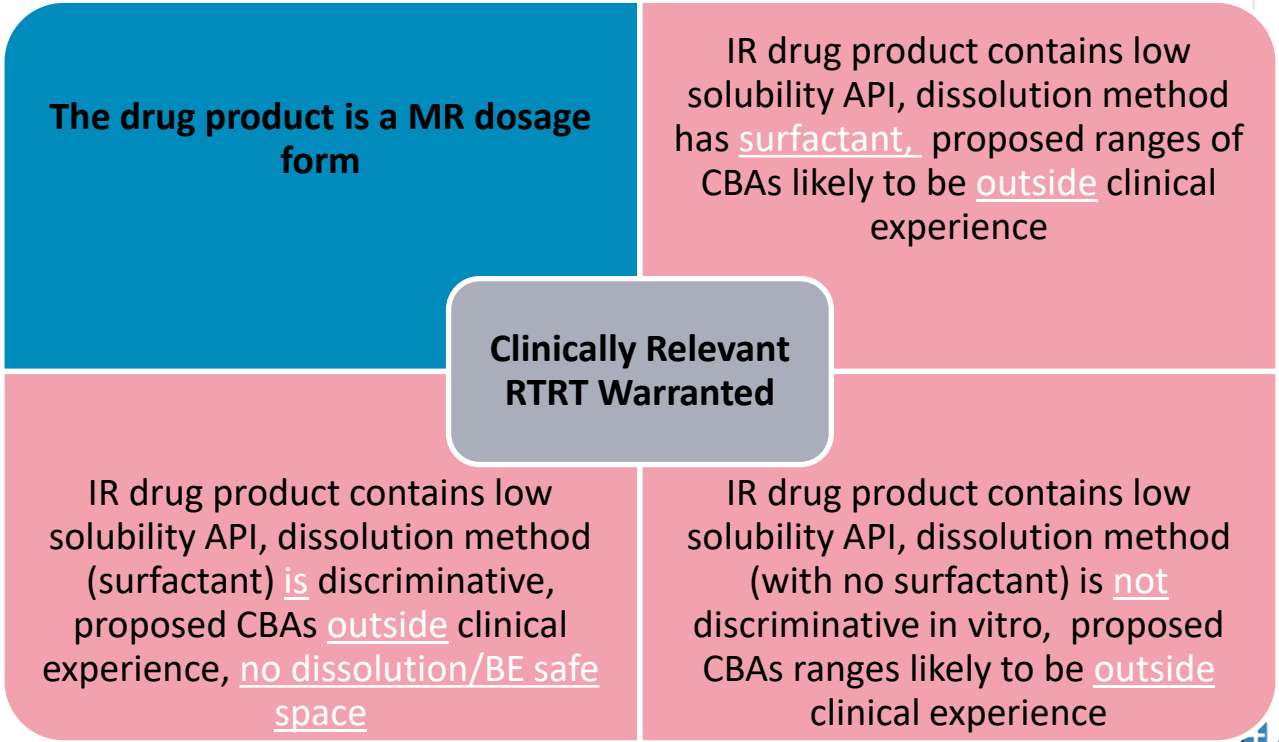


# *Biopharmaceutics Risk Assessment*

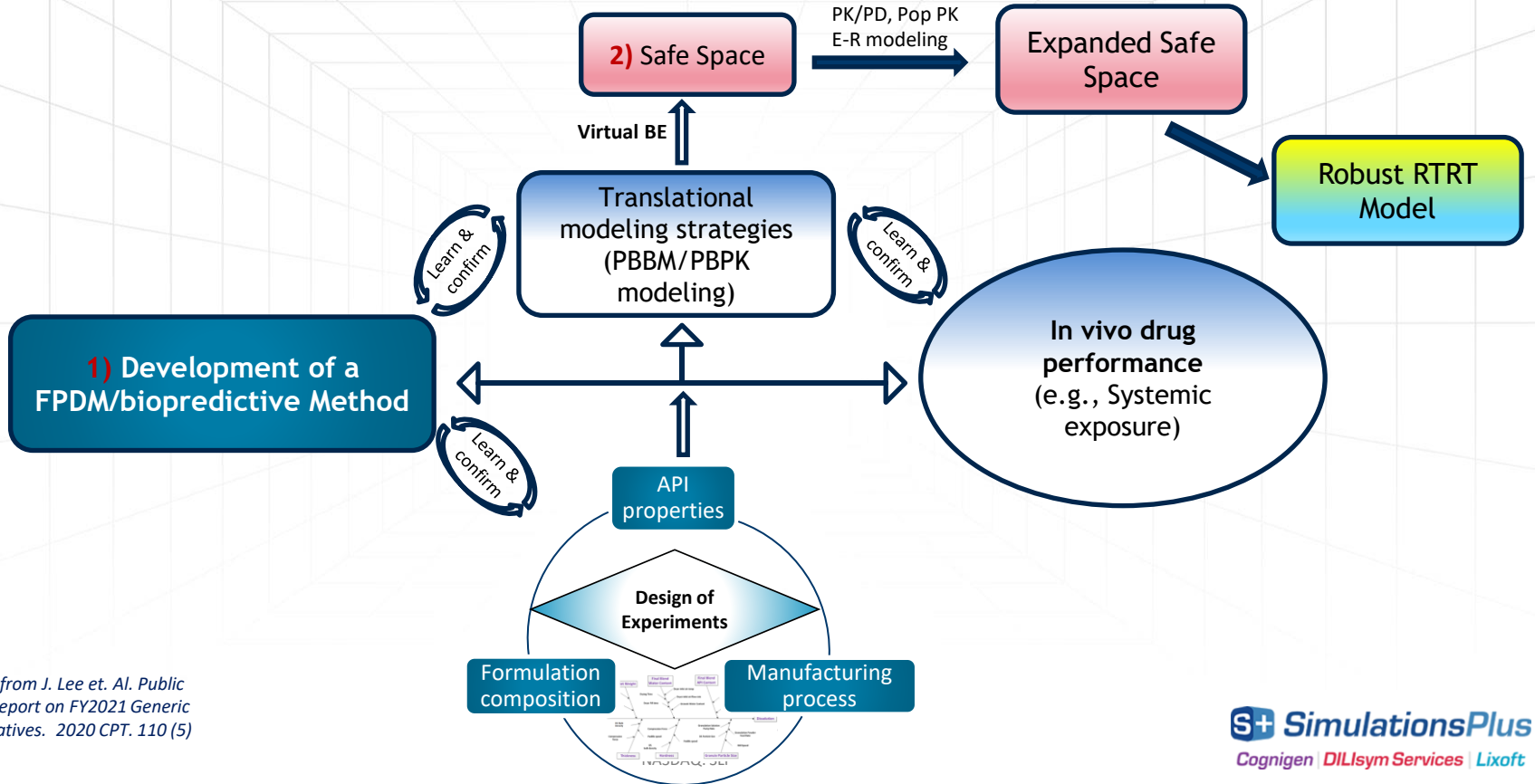
# Initial Biopharmaceutics Risk Assessment for IR Solid Dosage Forms (Non-NTI) with RTRT Strategy



# Clinically Relevant RTRT – When is it Warranted (Examples)?



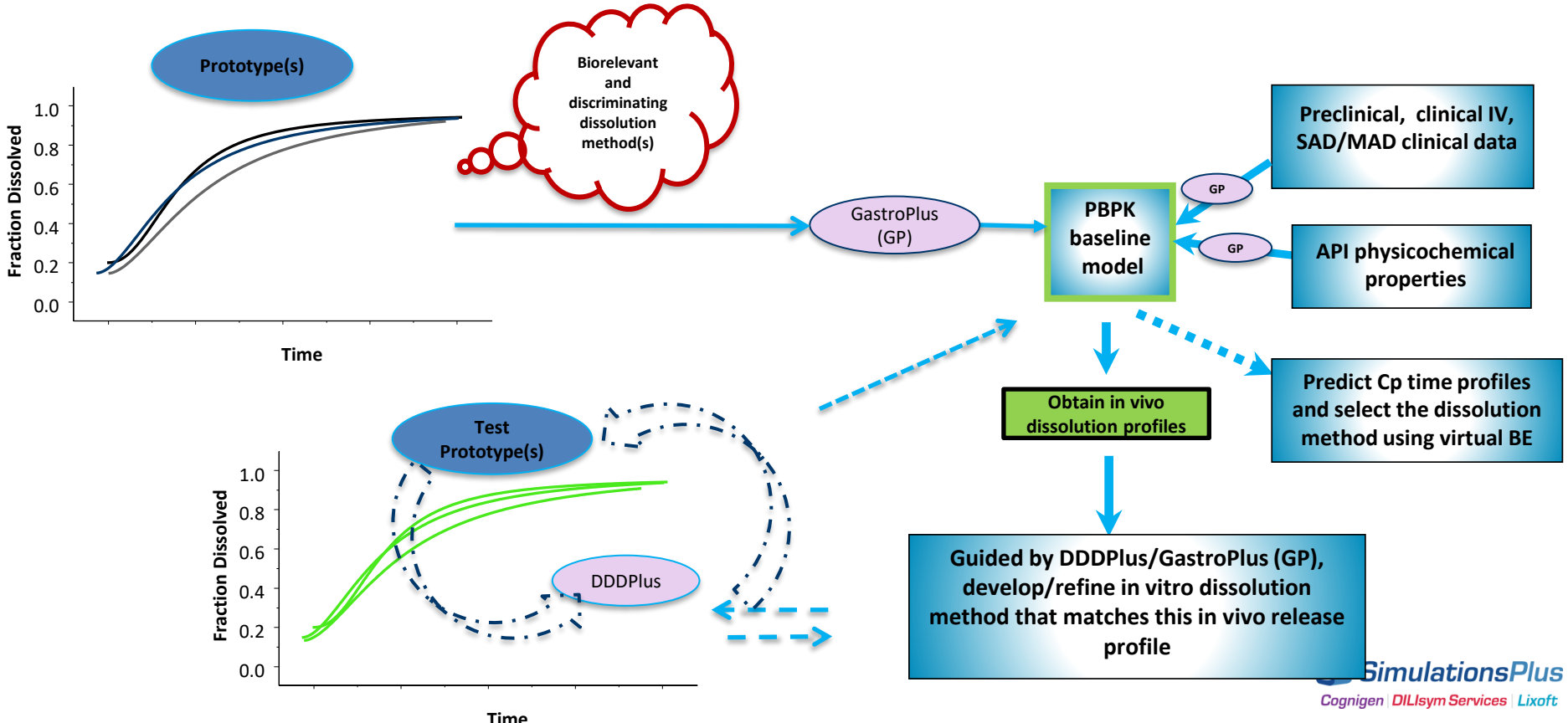
# What Biopharmaceutics Information is Needed for Building Clinical Relevance into RTRT?




*References: Adapted from J. Lee et. Al. Public workshop summary report on FY2021 Generic Drug Regulatory Initiatives. 2020 CPT. 110 (5)*

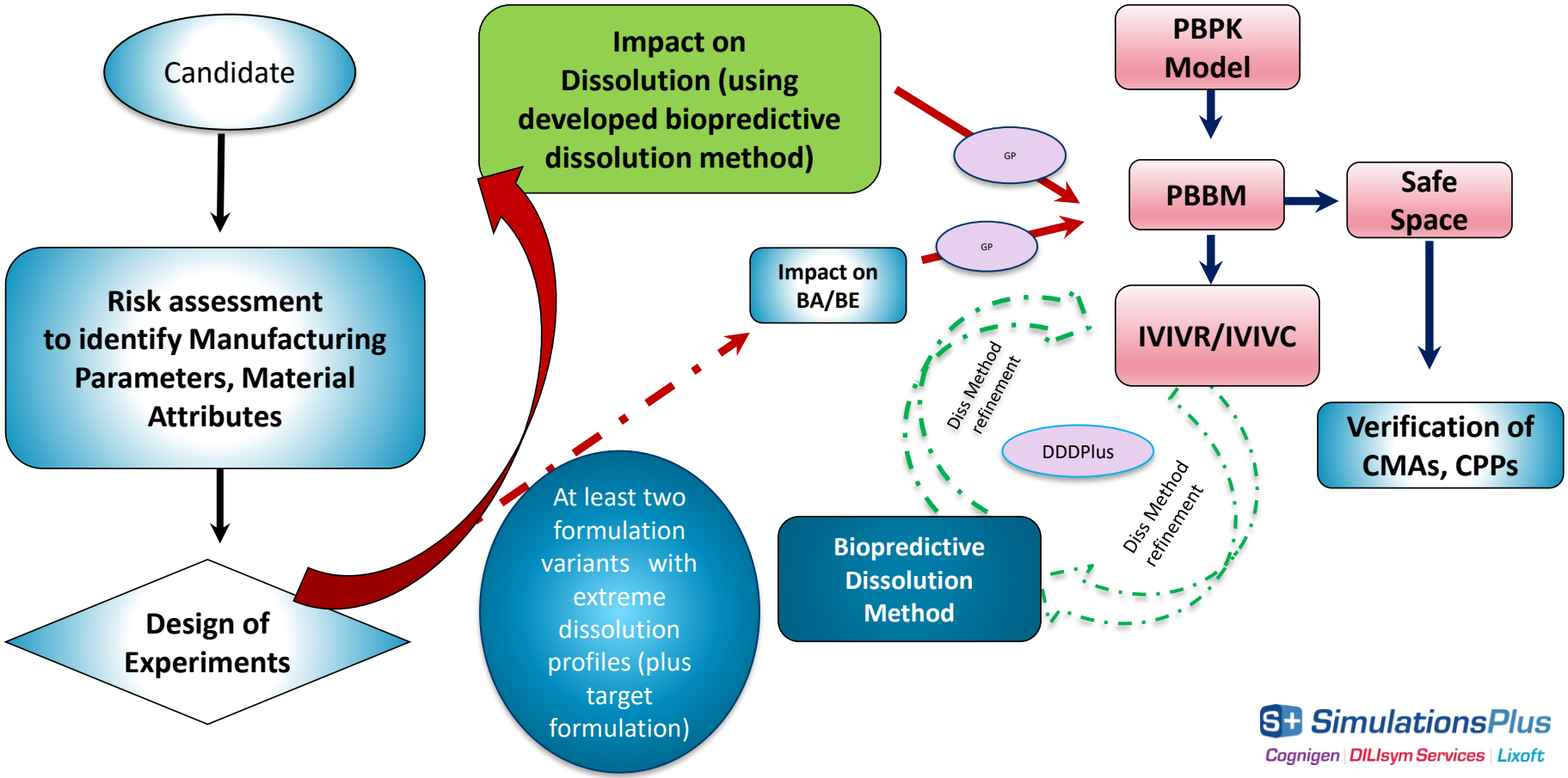
# *Potential Path for Building Clinical Relevance into RTRT via the Development of FPDM that is biopredictive: The Use of PBBM*

# Development of a Fit-for-Purpose Biopredictive Dissolution Method: Early Phases of Product Development



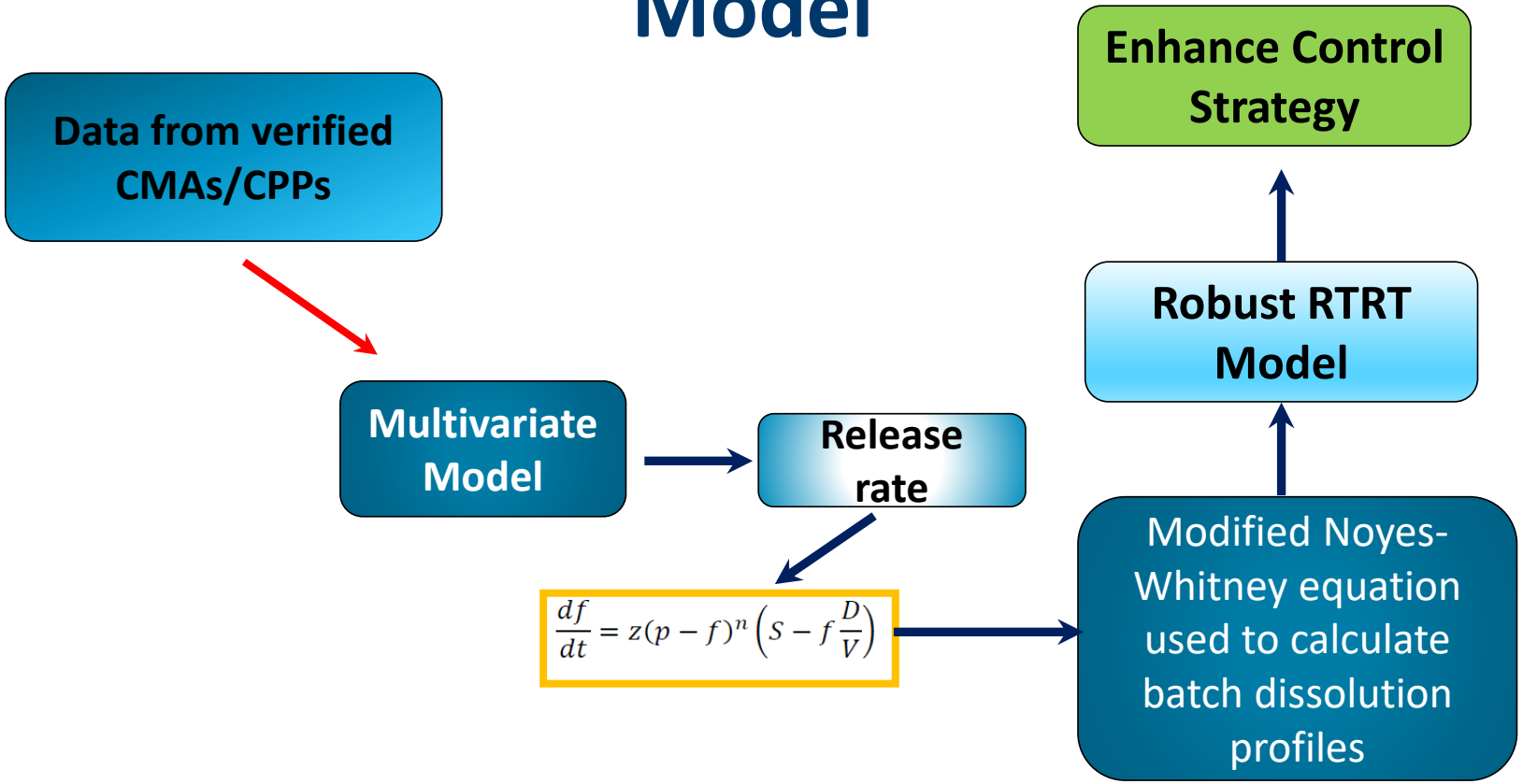

SimulationsPlus
Cognigen | DILIsym Services | Lixoft

# Development of a Safe Space to Confirm the Criticality of Quality Attributes




SimulationsPlus
Cognigen | DILIsym Services | Lixoft

# Development of a Robust RTRT Dissolution Model



# Case Study

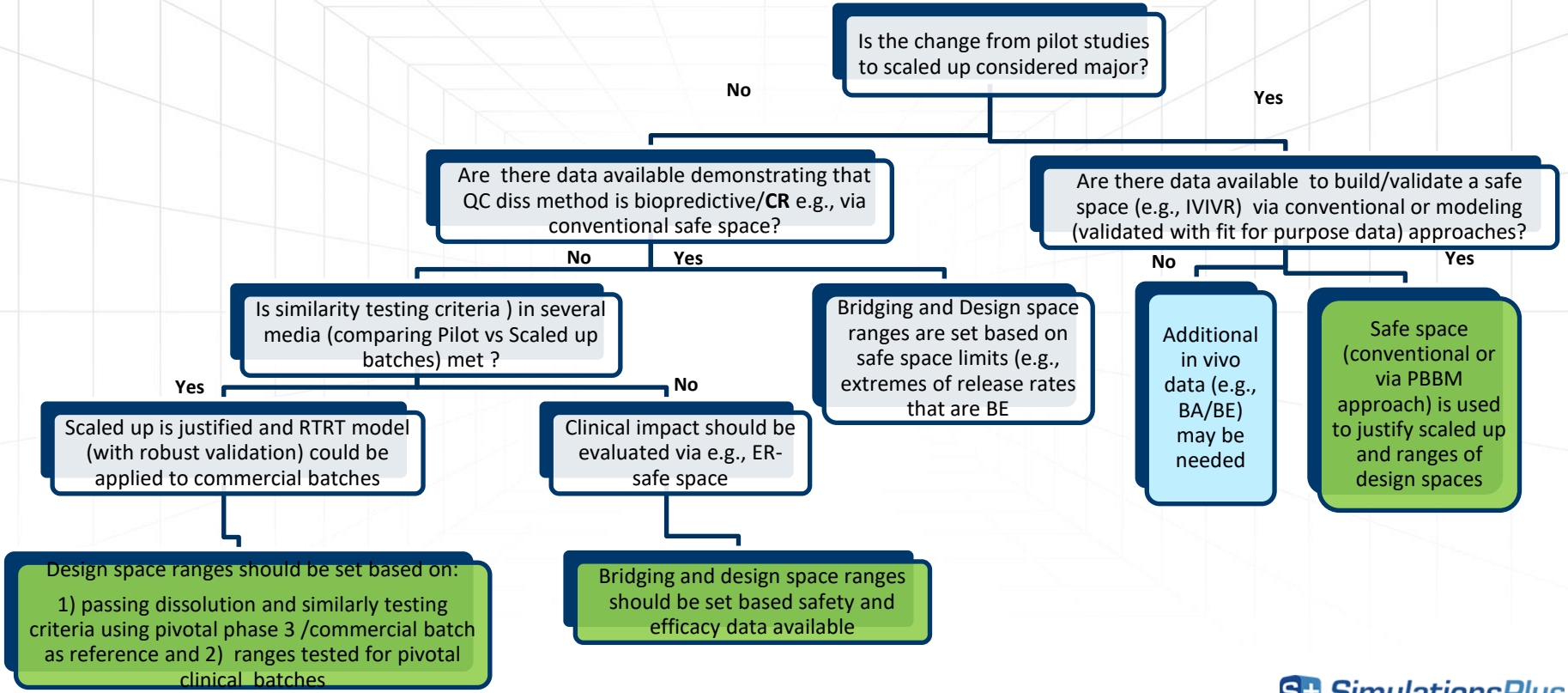
# Biopharmaceutics Risk Assessment Implementation: Building Clinical Relevance into RTRT Dissolution Model via Conventional Approach

# Case Study: Safe Space Establishment Using Conventional Approaches

**Purpose:** Build a safe space/clinical relevance to justify the bridging between pilot DoE to Scaled up for RTRT implementation

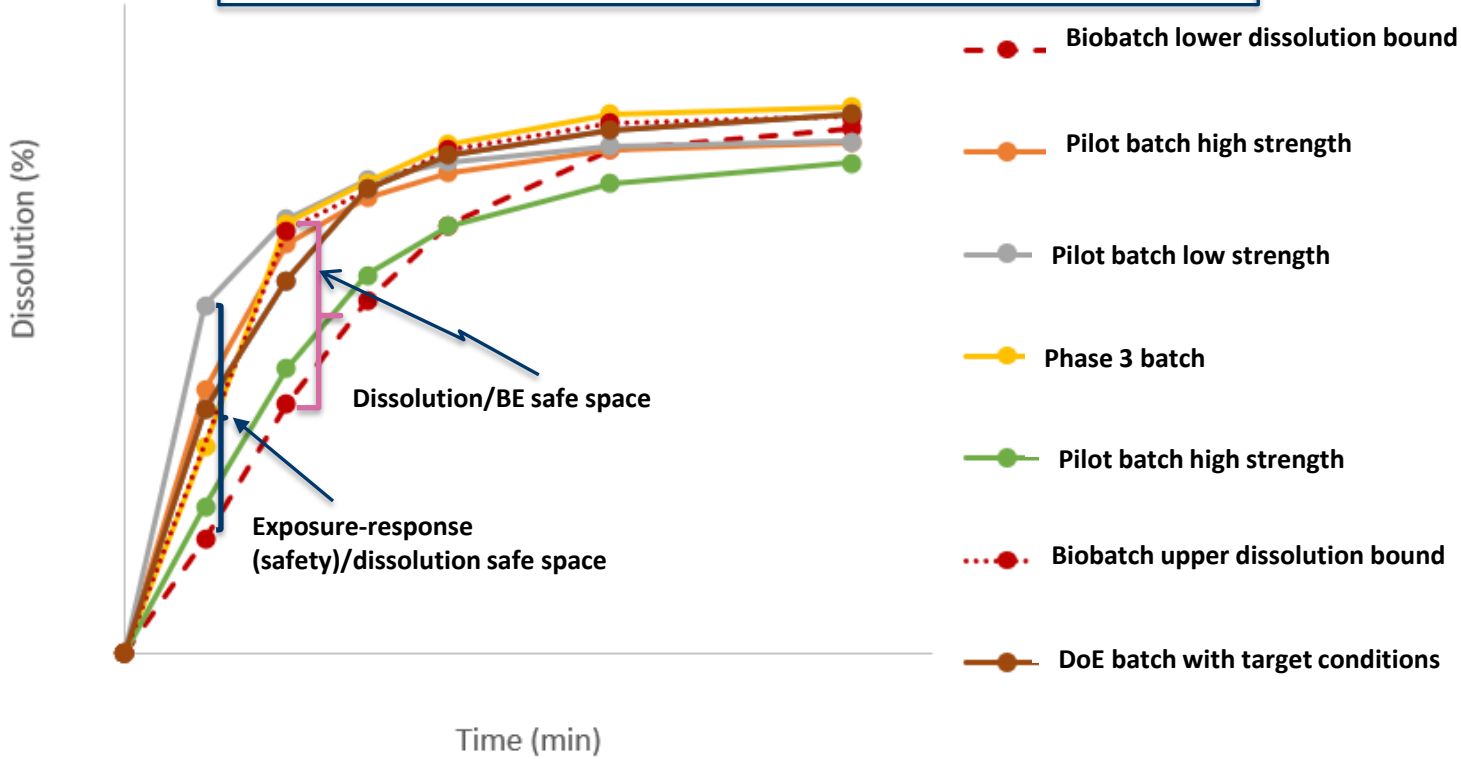
- Immediate release tablet/low solubility API, approved by regulatory agency based on batch manufacturing process
- A CMC Supplement was submitted which included RTRT dissolution model
  - In lab dissolution method contains surfactant
- DoE studies for RTRT purpose were conducted using pilot batches for compression and granulation
  - to quantify the relationship between process conditions and CQAs
- Discriminative dissolution method was used as endpoint in DoE studies
- The RTRT dissolution model was challenged with batches out of proposed specifications

# Pilot RTRT to Scaled up Bridging: Biopharmaceutics Risk Assessment Strategy



# Building Clinical Relevance into RTRT Using Conventional Approaches

**Dissolution profiles of batches tested in pilot DoE and batches representative of Ph3 and pivotal BA/BE study**



# Take Home Message

- Biopharmaceutics risk assessment is critical to determine the need for building clinical relevance into RTRT

- The use of  a clinically relevant/biopredictive dissolution method in DoE studies for low solubility IR drug products and MR drug products is warranted for building a robust RTRT dissolution model

- The use of PBBM/PBPK- dissolution safe space via DDD Plus/GastroPlus is a feasible approach to streamline the development of clinically relevant/biopredictive dissolution methods and thus, a robust control strategy
  - When dissolution/BE safe space is not sufficient to justify a CMC change, exposure-response data may be used to expand the dimensions of the dissolution/BE safe space, and thus, gain regulatory flexibility