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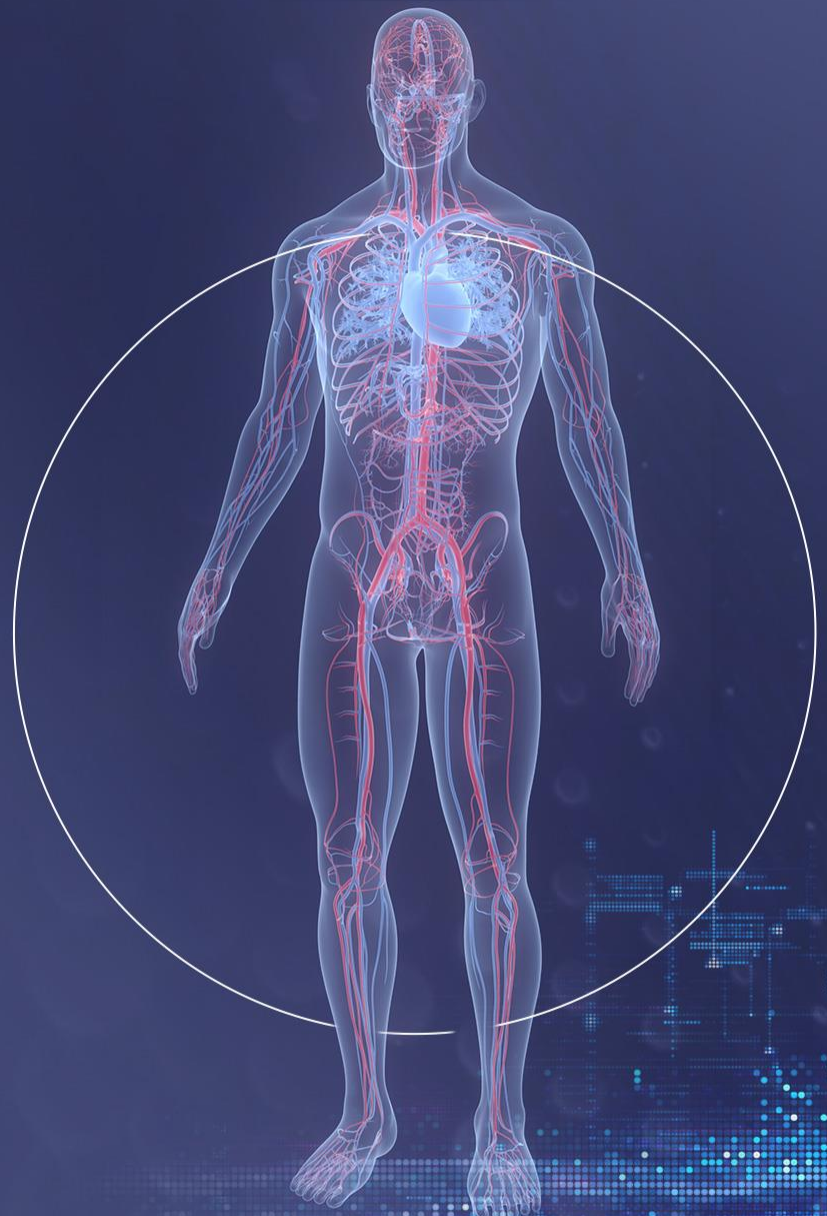
Leveraging OSP for developing dissolution safe space through IVIVC and VBE workflows: a qualification perspective



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Acknowledgments:
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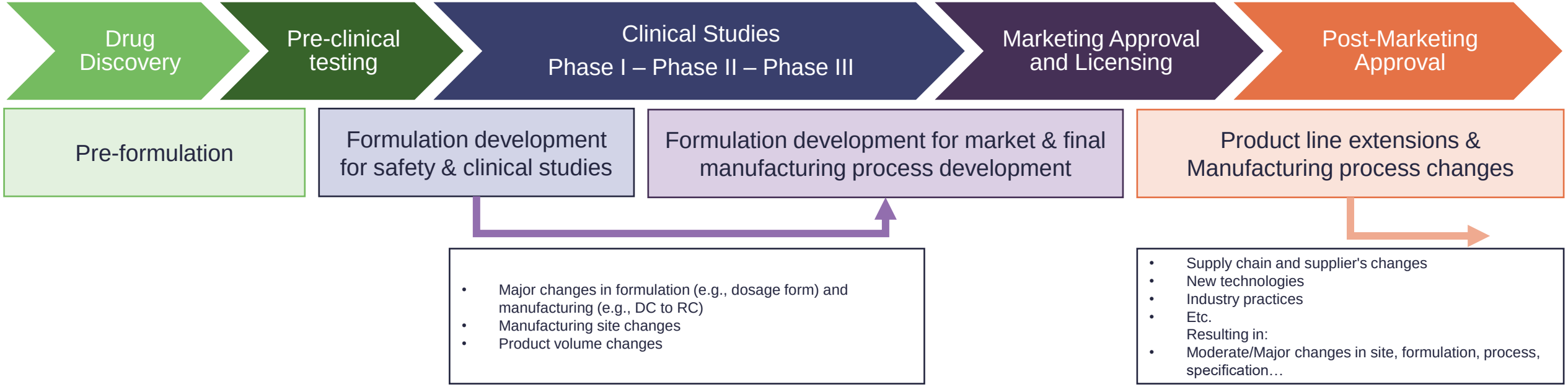
Abdullah Hamadeh

Overview

1. Concepts of dissolution safe space, PBBM-based IVIVC & VBE
2. Current Workflows available
3. Metoprolol case-studies
4. NPOD & CTS algorithms
5. Future-work and Challenges

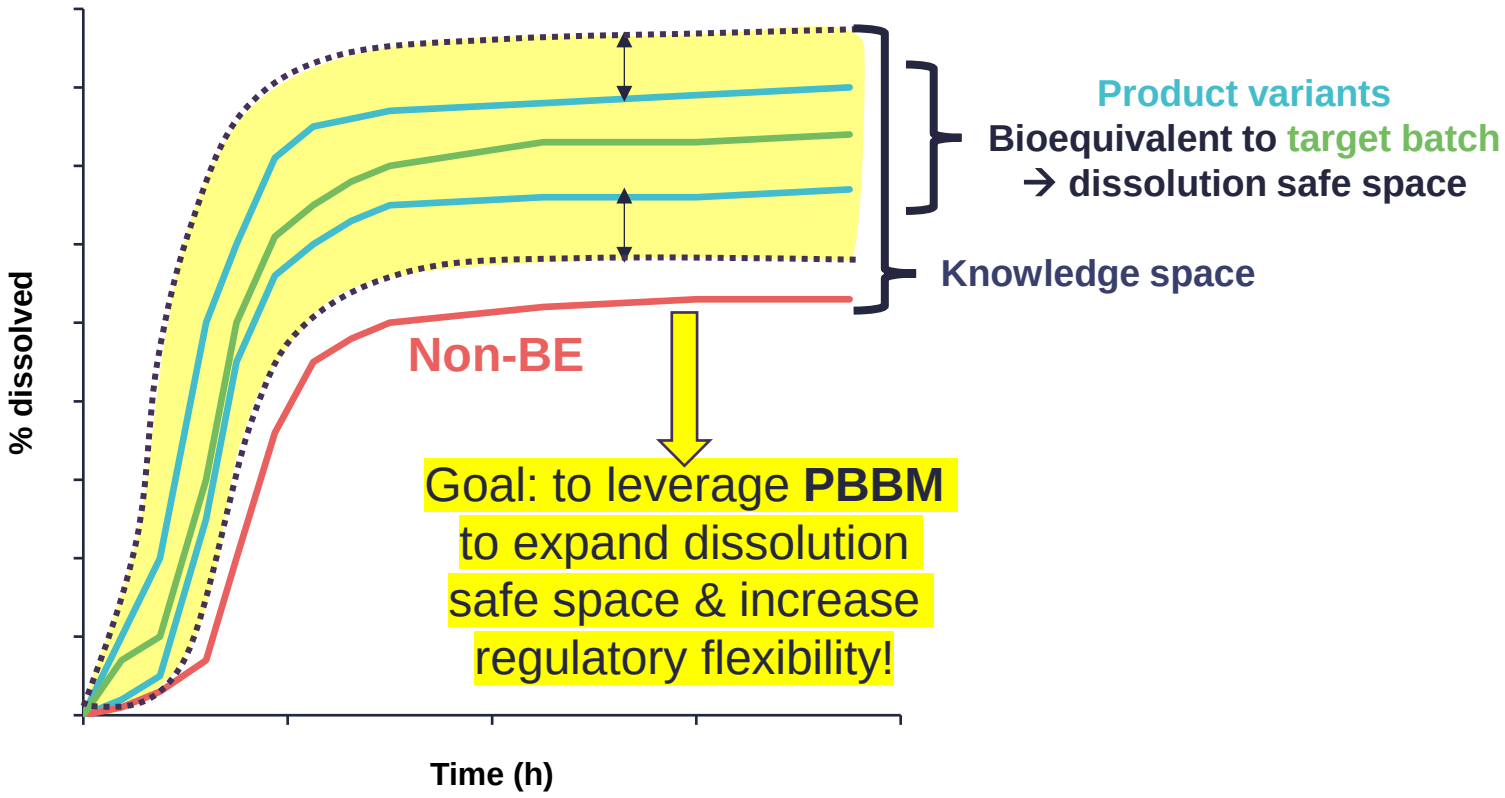
Why is dissolution safe space such an important PBBM application?



- Drug development is a long and complex process
- Changes to the formulation/manufacturing **are common**
- There is a **need to evaluate the impact of these changes on drug product quality and risk to patients** (level of risk will depend on the nature of the change (minor/moderate/major), development phase, level of biopharmaceutical risk, and risk mitigation strategies…)
- **Dissolution safe space** offers the opportunity to **link dissolution and *in vivo* performance** → of **patient-centric drug development** & **increased regulatory flexibility**

Finding dissolution safe space

- **Dissolution safe space** = **Dissolution boundaries** from which **drug product variants are equivalent**
- **Knowledge space** = ***in vivo*** + ***in vitro*** data used to build a safe space (can/should include non-BE batch)
- **Product variants are** created by varying relevant drug product quality attributes (CQA's)]



Initial experiments in vitro define CPPs and CMAs (CQAs) Influence on Dissolution

↓

Plan Experiments to understand (e.g., DoE) the relationship of CQAs with dissolution

↓

rBAs and BE trials can support defining bioequivalence safe space between chosen variants

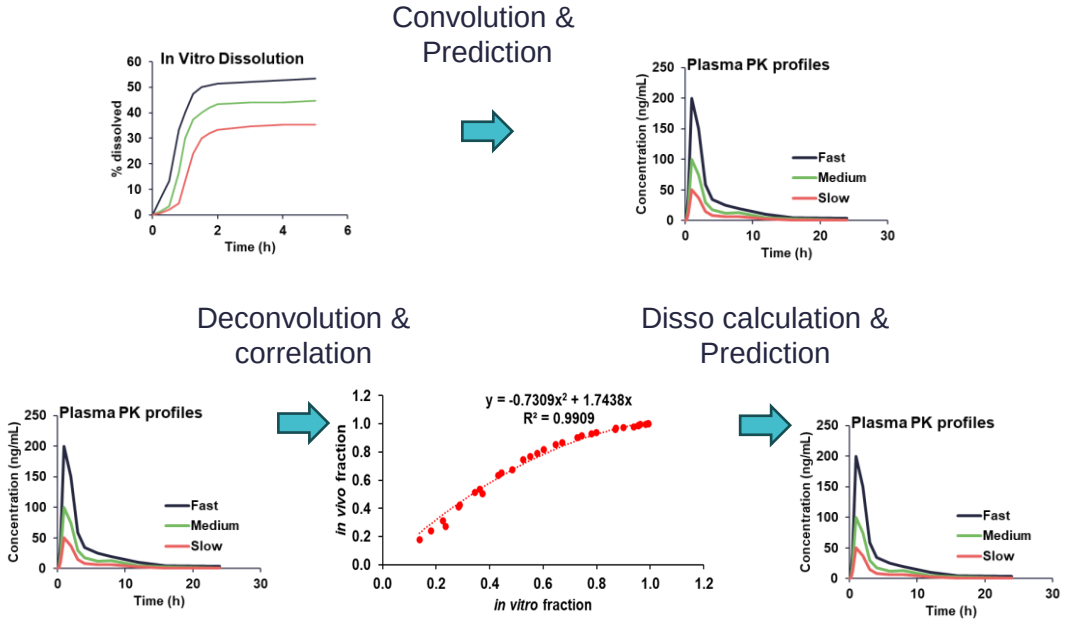
↓

PBBM (IVIVC/R + VBE) = 'wider' dissolution specifications (i.e., regulatory flexibility)

Suarez-Sharp, S, et al. AAPS J. 2018 Aug 27;20(6):93. doi: 10.1208/s12248-018-0252-3.
Mitra A, et al. J Pharm Sci. 2021 Feb;110(2):594-609. doi: 10.1016/j.xphs.2020.10.059.
Pepin XJH, et al. J Pharm Sci. 2021 Feb;110(2):567-583. doi: 10.1016/j.xphs.2020.09.021

IVIVC approaches: Traditional vs PBPK

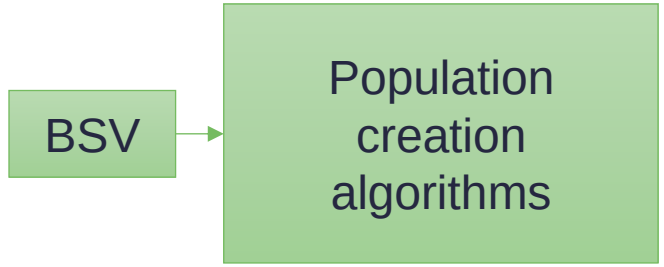
- **One-step IVIVC** (based on convolution/differential equations i.e., using plasma concentrations directly e.g., 1:1 relationship PBPK) **or Two-step IVIVC** (after deconvolution in comparison to reference formulation, the most common, can also be used with PBPK)
- **Traditional deconvolution methods** e.g., Numerical, Wagner Nelson, Loo-Riegelman
- Several assumptions are made, including 1-2-3 compartmental drug distribution, 1st order absorption, no saturation of processes, terminal Cp points do not contribute to absorption
- All of these methods estimate ***in vivo* Bioavailability** (extent of drug appearing in systemic circulation i.e. drug in central compartment *vs* time profile) and **cannot differentiate prior steps** such as dissolution profile in lumen, absorption profile in enterocytes, and bioavailability
- **PBPK-based-IVIVC**
  - PBPK models allow differentiation between key processes before the drug reaching the systemic circulation:



Dissolution → Permeation → Gut Metabolism → Liver Metabolism → Reaching systemic circulation

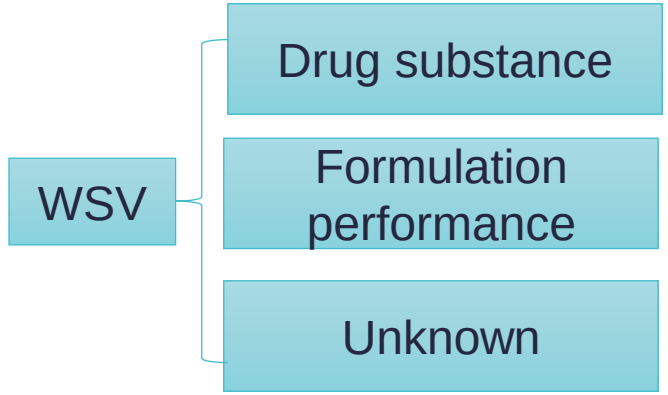
Virtual Bioequivalence (vBE)

- **Virtual Bioequivalence is a tool that can be used for both Generic and Innovator companies can use:**
  - Extrapolating formulation performance between special populations
  - Risk/assessment of dosing schedules Fasted/fed and absorption DDI
  - Assessing the risk of formulation changes
  - Setting clinically relevant dissolution specifications e.g., finding dissolution safe-space



- **One of the biggest challenges of VBE is the need to ensure accurate capture of population variability:**
  - The **inter-individual variability (IIV)** or **between-subject variability (BSV)** represents the variability in a certain parameter measured between different subjects.
  - The **intra-subject variability (ISV)** or **within-subject variability (WSV)** refers to variations observed within the same subject over multiple measurements or conditions. In other words, it's the variability seen when the same individual is measured or tested repeatedly

    Known also as Intra-occasion **variability (IOV) in cross-over studies** is an integral part of ISV and represents the variability in a certain parameter measured in the same subject on separate occasions.



Challenges in performing Virtual Bioequivalence

Incorporation of WSV/IOV

Option 1 – Mechanistic Propagation

Variability is propagated through system parameters throughout the simulations

Advantages:

- 👍 Mechanistic propagation through GI system variability → key for poorly soluble compounds

Disadvantages:

- 👎 Can potentially cause inflated variability and 90% CI
- 👎 Current understanding of sources of WSV is still limited
- 👎 Mechanistic dissolution model needed, which are not as useful for MR/Complex formulations (e.g., bio-enabling)

Option 2 – Empirical Post-hoc Propagation

Variability based on prior knowledge such as previous replicated clinical studies (e.g., through bootstrap and linear mixed effect models)

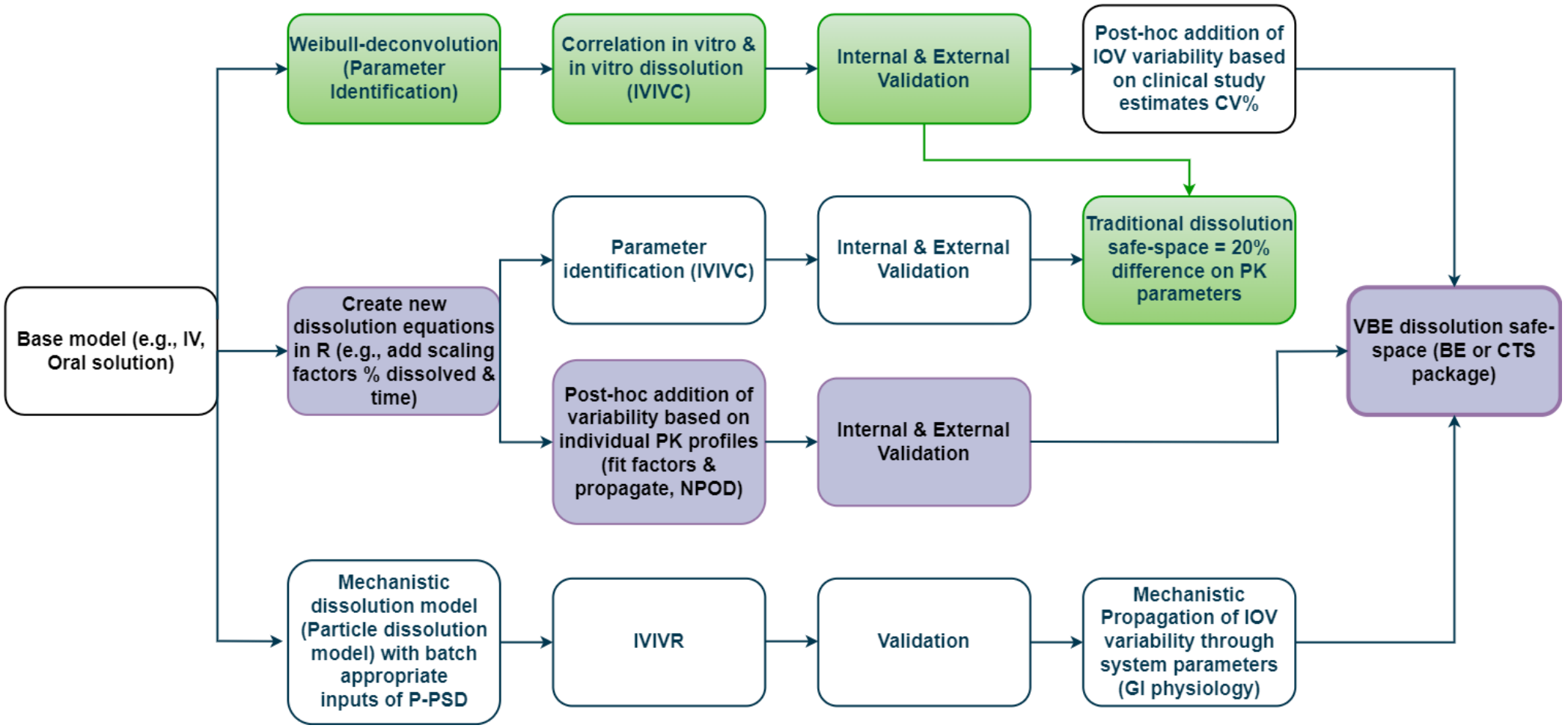
Advantages:

- 👍 Pragmatic

Disadvantages:

- 👎 Lacks mechanistic understanding
- 👎 Requires ‘training’ based on *in vivo* data
- 👎 WSV based on previous knowledge and not formulation-specific

Workflows outlined to establish dissolution safe-space



Metoprolol - datasets

- BCS class 1 drug (highly soluble, highly permeable)
- Short elimination half-life

- **Formulations:**
  - 3 selected prototypes of metoprolol tartrate extended-release formulations containing HPMC as a release rate-controlling excipient
  - designed to release metoprolol at 3 different rates and will be referred to as slow, medium, and fast formulations

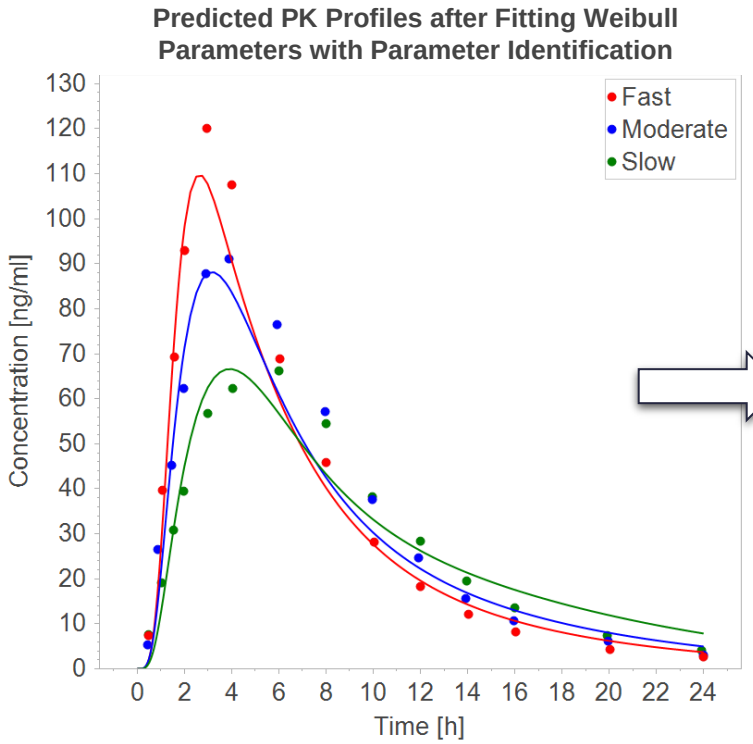
- **In vitro Dissolution data:**
  - USP I apparatus, pH 6.8, at 150 rpm (selected based on previous work)

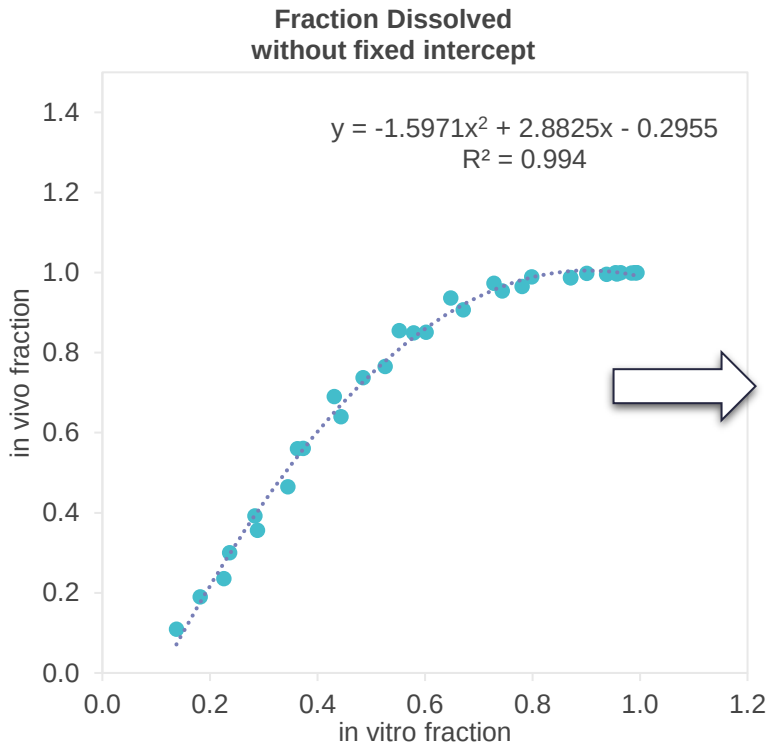
- **In vivo PK data:**
  - 50 mg of Oral solution of metoprolol tartrate → used to develop the base PBPK model (distribution/ elimination and permeability through Parameter identification)
  - Three 100 mg tablet formulations containing metoprolol tartrate of different release rates

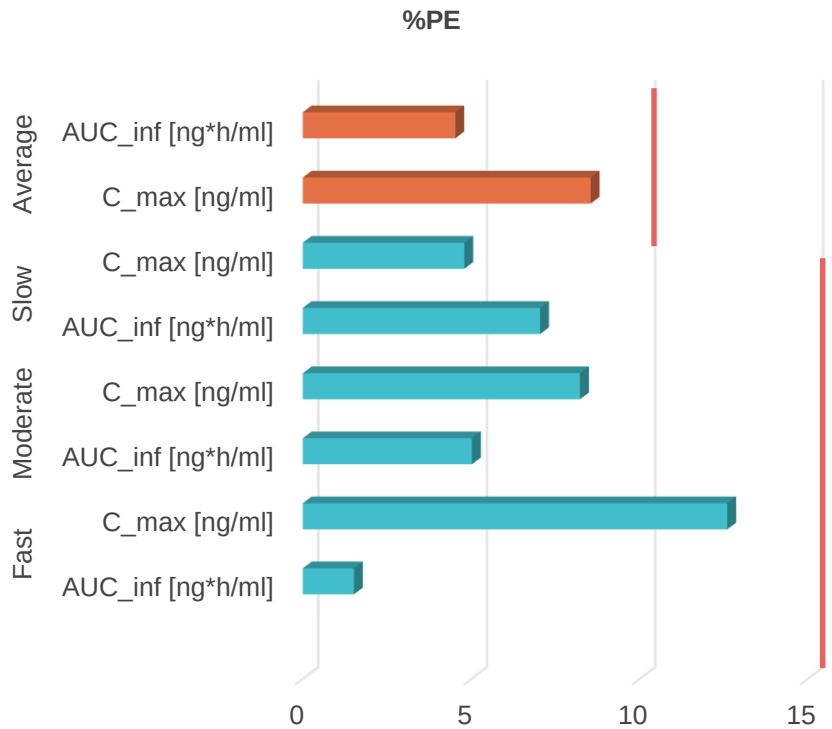
Eddington, ND., et al. *Pharm Res* 15.3 (1998)

Weibull-mechanistic IVIVC development & validation

Work in progress







- Fitting of the Weibull dissolution parameters is not straightforward
- Including the Weighing scheme appears to improve fitting reliability
- Although T_{max} is not an IVIVC validation criterion, it can be observed that T_{max} is not well predicted for all formulations

- 2nd order Polynomial equation was used to build the IVIVC

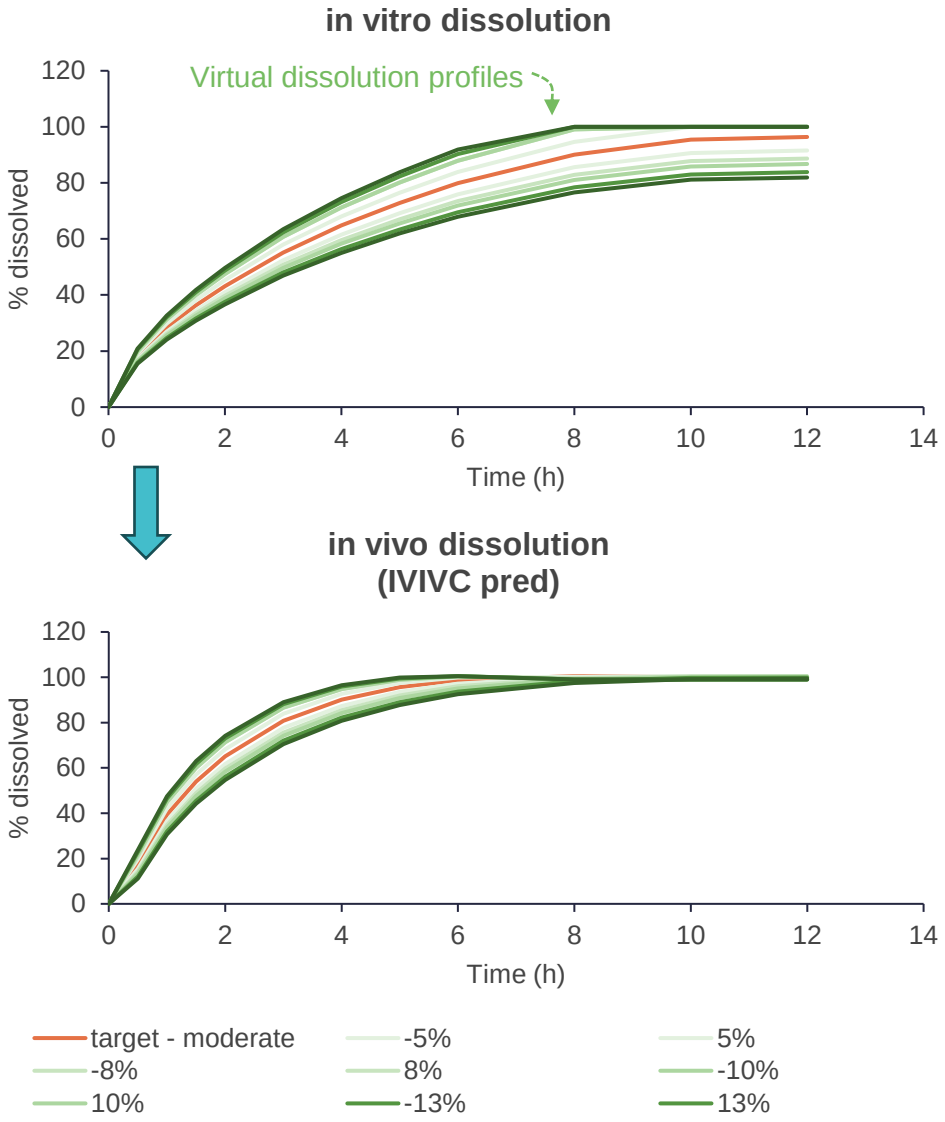
Internal Validation Criteria is met:

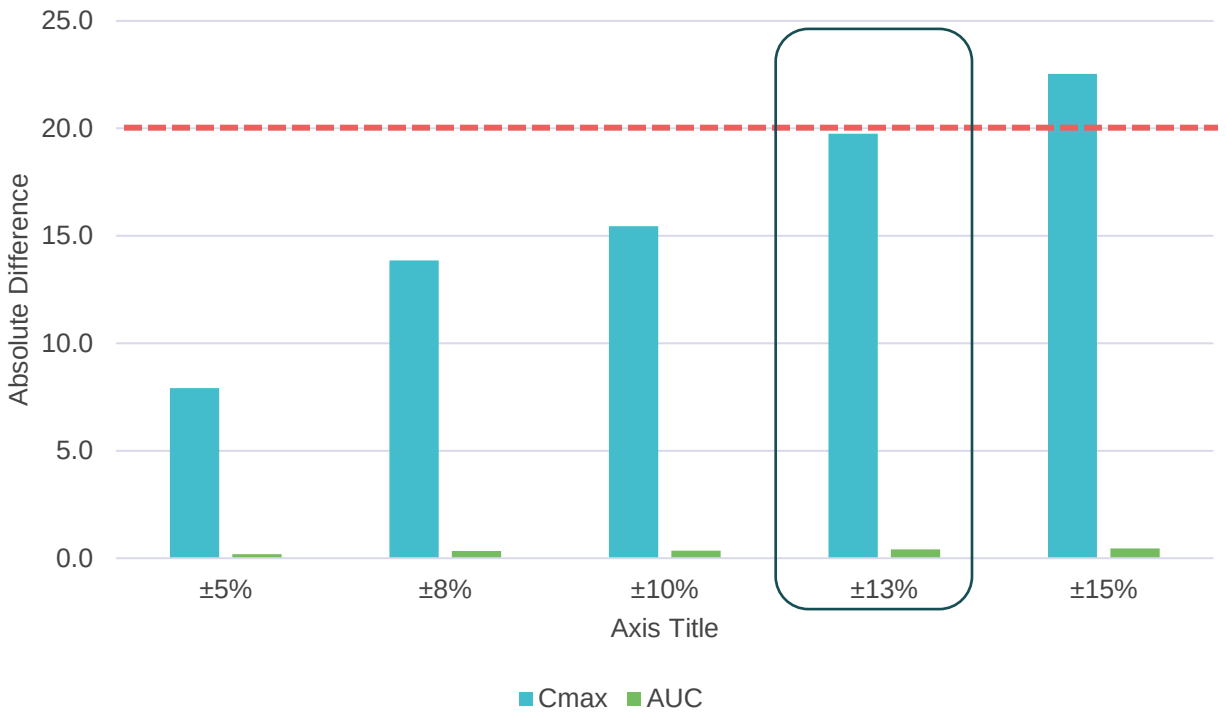
- ✓ 15% Cmax and AUC individual formulations
- ✓ 10% Cmax and AUC Abs Average

Eddington, ND., et al. *Pharm Res* 15.3 (1998)
FDA, IVIVC guidance, 1997

Setting Dissolution safe-space according to FDA Guidance

Work in progress





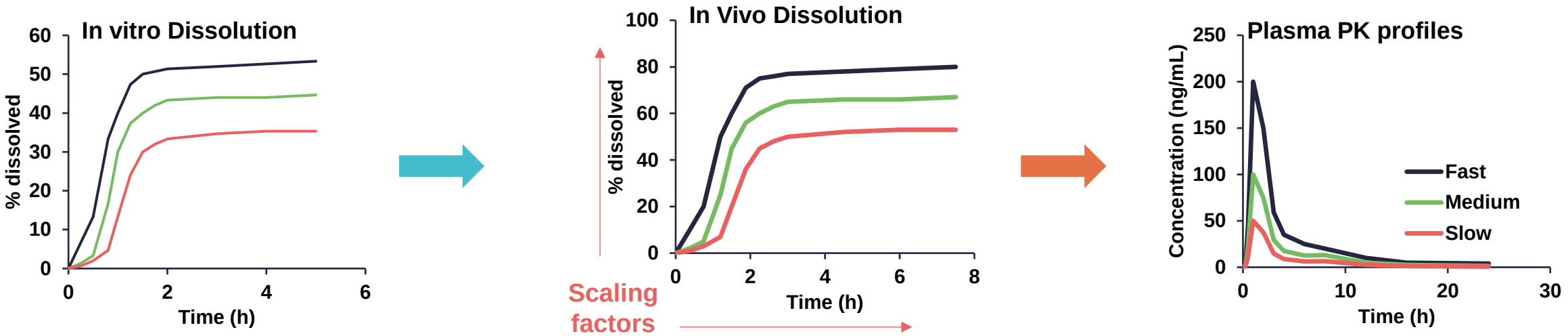
$$Absolute\ difference = \frac{PK\ parameter\ upper\ profile - PK\ Parameter\ lower\ profile}{PK\ Parameter\ upper\ profile} * 100$$

FDA, IVIVC guidance, 1997

Scaling factors-IVIVC development & validation

Work in progress

Dissolution equations can be modified, and scaling factors can be introduced in MoBi to establish an IVIVC/R



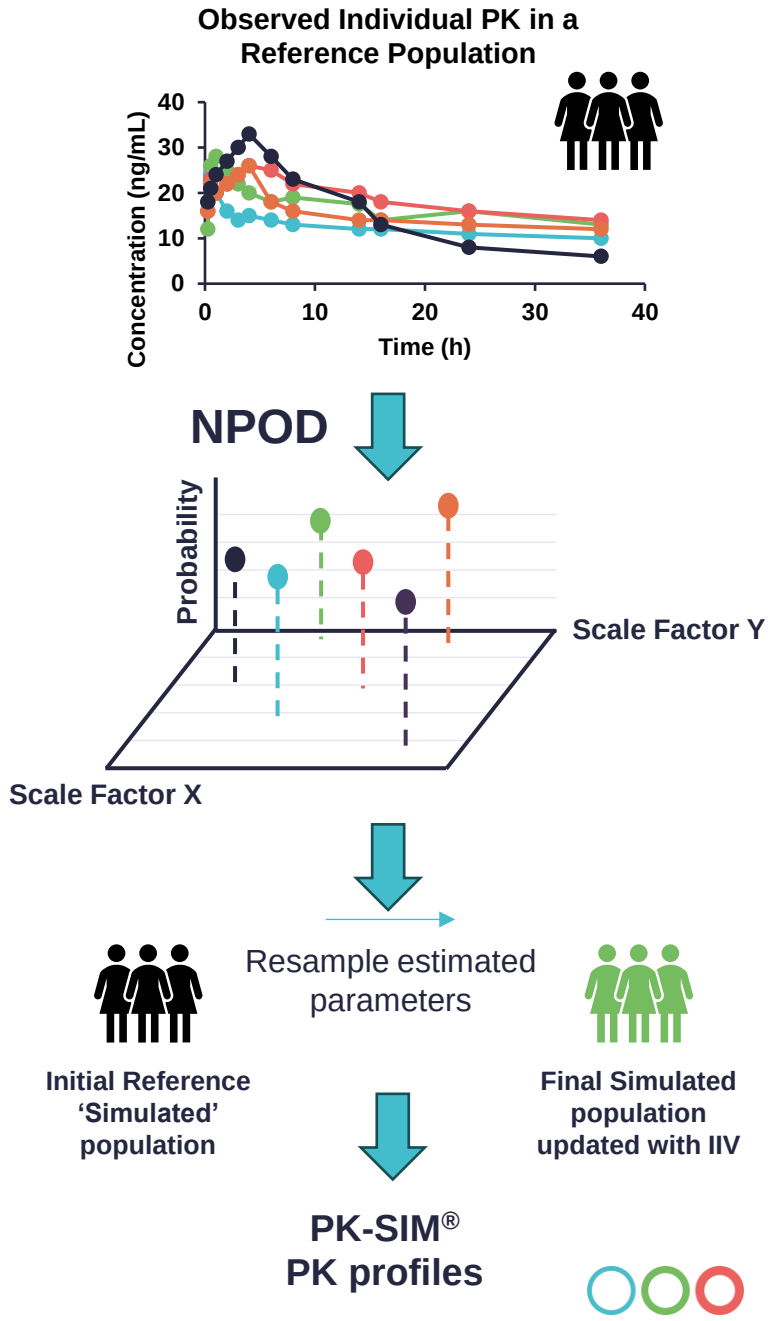
PK-SIM® → Add formulation in vitro dissolution → MoBi® → Scaled dissolution profile → Simulate Plasma PK Profiles

At this stage decide how to estimate scaling factors e.g. NPOD

NPOD R framework

Work in progress

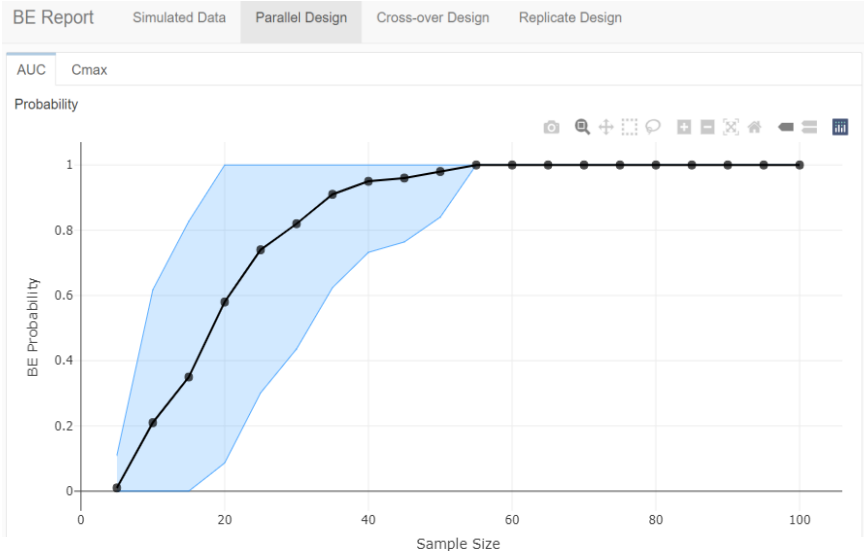
- After creating IVIVC with scaling factors in MoBI® these can be **estimated by NPOD**
- Other **sensitive** and **critical parameters,** such as permeability, clearance, etc., **can be estimated**.
- **NPOD algorithm** will fit a distribution to **individual PK data** to capture **Inter-Individual Variability (IIV)**
- **Outcome:** Posterior distribution (support points and respective weights)
- Support points can be used to **create a 'new' population with associated variability in estimated factors**
- **Plasma concentration-time profiles can be generated** for the updated virtual population in **PK-SIM® and it can be immediately linked to VBE framework (will be discussed in the next slide).**



Acknowledgments
US FDA grant U01FD006549: Virtual bioequivalence (VBE) workflow
Packaged can be found in:
Laboratory of Applied Pharmacokinetics and Bioinformatics (github.com)
Contacts for more info: Michael Neely, Abdullah Hamadeh

CTS – Clinical Trial Simulator

- CTS under development
- **Aim:** sample from the population and calculate BE statistics
- **Input:** Simulated Plasma Concentration profiles between reference and test formulation
- Outputs are the **BE probability of success** for different test sample sizes



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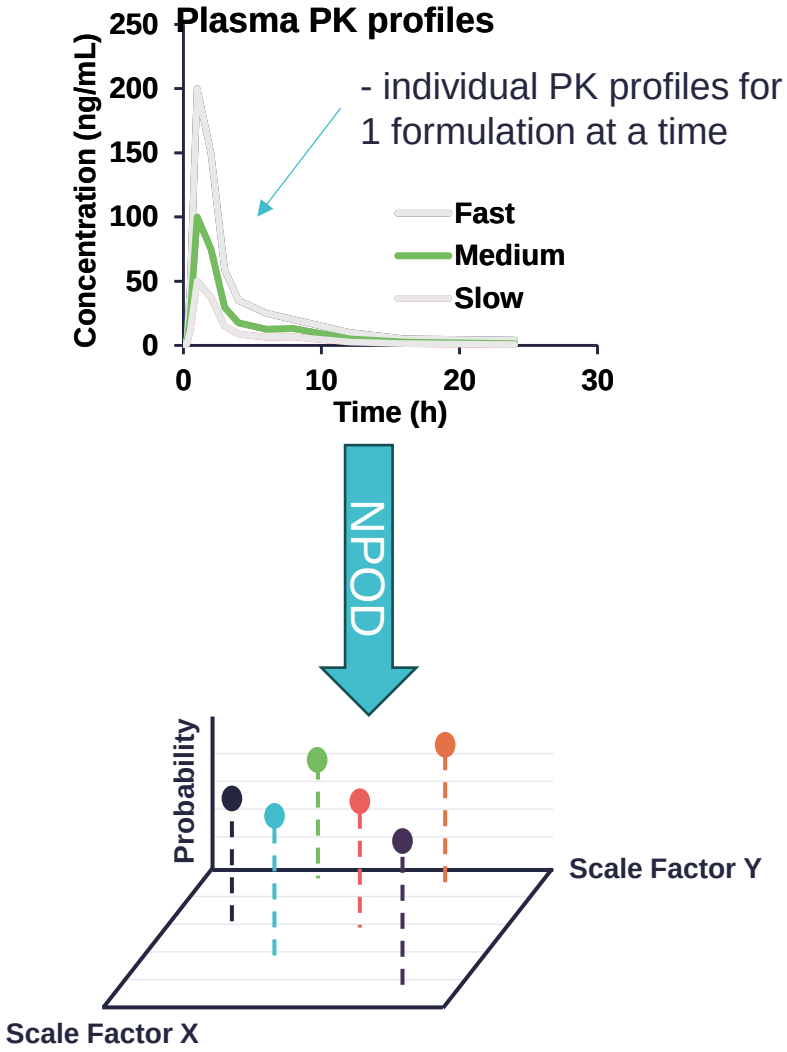
Application of NPOD to learn scaling factors

Work In Progress



What we are currently exploring:

Option 1

1. Use NPOD independently for all simulations and combine the distributions OR extend code to support multiple simulations
2. Internal Validation and if needed External Validation
3. Use the combined support points for CTS afterward.

Option 2

1. Fit the starting point with mean PK data for all formulations in MoBi®
2. Internal Validation and if needed External Validation
3. Apply NPOD to the 'target' formulation to learn the distribution
4. Use distribution to generate a population for CTS.

Achievements, Challenges and Future work

ACHIEVEMENTS

Outlined workflows for dissolution safe-space establishment

Successful development of 1st case-study

Initiated 2nd case-study with NPOD and CTS

GOAL

Establish qualification examples for the outlined workflows

CHALLENGES & FUTURE WORK

The VBE field is still evolving

Data access is a challenge for some of these workflows, engage with us if you are interested!!!

Technical: further code development /testing needed