“To precipitate, or not to precipitate – that is the question!”

FDA/M-CERSI Physiologically Based Biopharmaceutics Modeling, PBBM Best Scientific Practices to Drive Drug Product Quality: Latest Regulatory and Industry Perspectives

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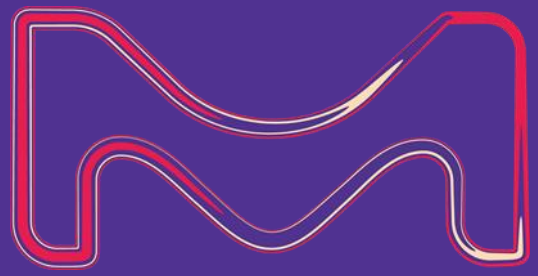


EMD SERONO MilliporeSigma EMD ELECTRONICS

A modern interpretation of Hamlet…

Introduction

Methods to predict precipitation and model it

Conclusions

Predicting drug precipitation: Are we there yet?

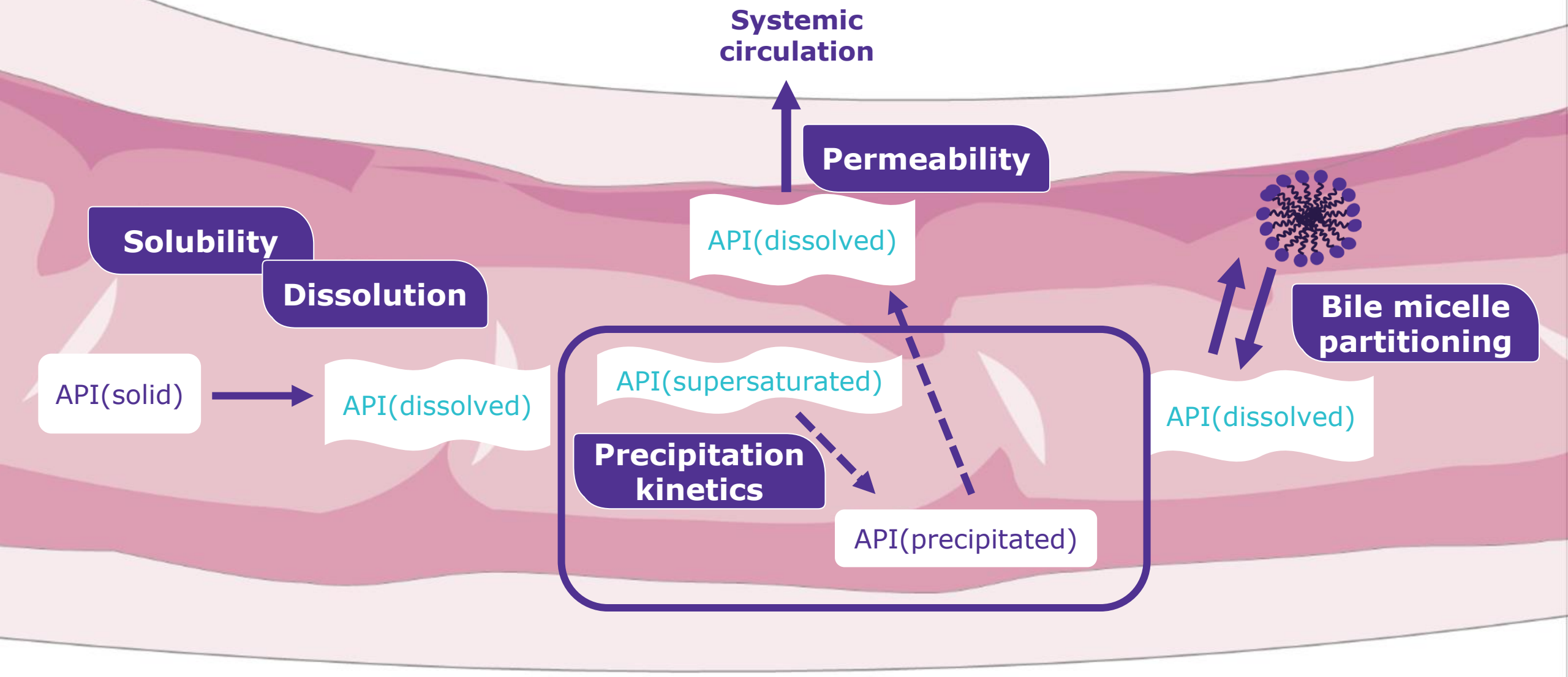
Breakout session

"Best practices for integration of precipitation in PBBM"

Introduction

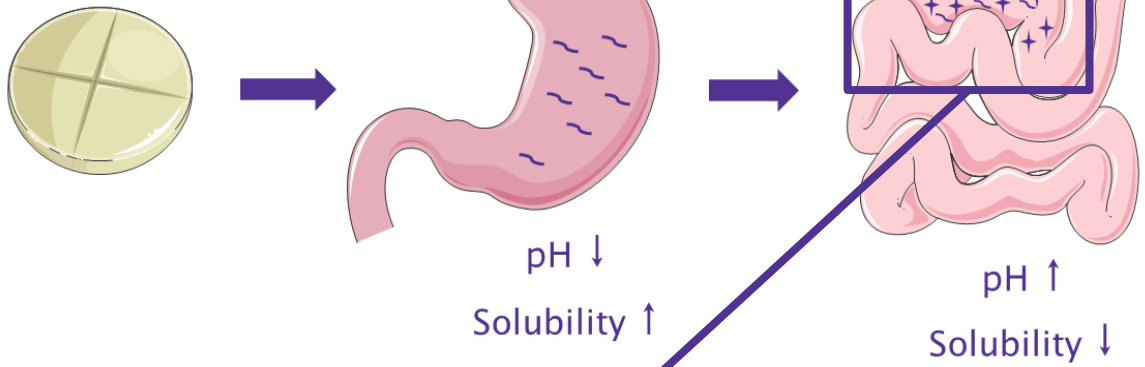
01

Important processes for drug absorption



"Solubility gap" typically driver for drug precipitation

Weakly soluble, basic drug; ASD; etc.



Precipitation can impact oral drug absorption

Rate of absorption (Cmax, tmax)

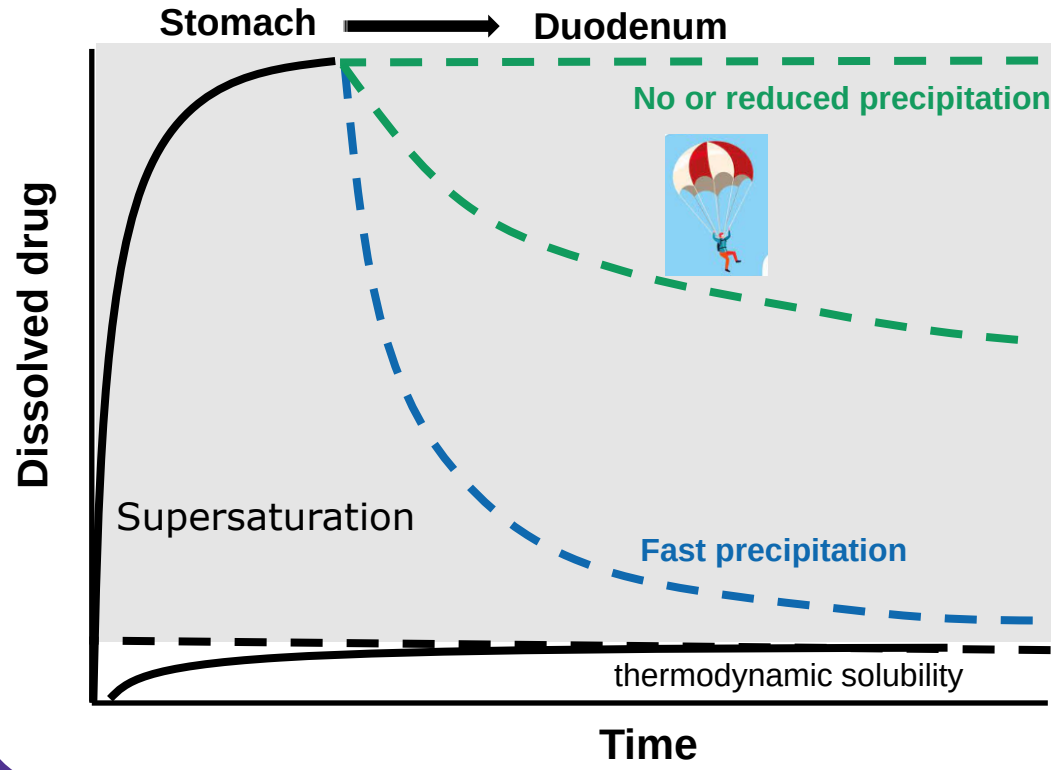
Extent of absorption (AUC)

Lack of dose-linearity

Variability

Precipitation leads to reduction of free energy

Precipitation rates; spring and parachute



Methodology to predict precipitation and model it

02

General workflow

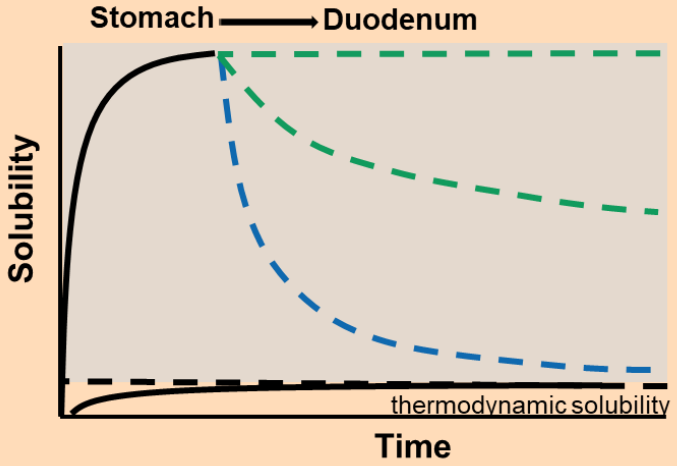
In vitro characterization of precipitation behavior

- Simulated gastrointestinal transit
- For **"bottom-up"** predictions

In vivo characterization of precipitation behavior

- Preclinical species or humans
- Directly: Gastrointestinal sampling
- Indirectly: Single ascending dose PK and/or different formulations
- For **"top-down"** predictions

Deducing precipitation kinetics



Precipitation rate?

Extend of supersaturation?

Nucleation rate?

Particle growth?

Implement into PBBM to predict oral drug absorption

Examples:

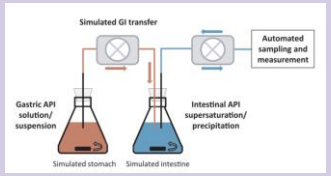
Model validation

In vitro assays

- For drug substance
- Investigation of compound-specific precipitation kinetics
- Early formulation screenings

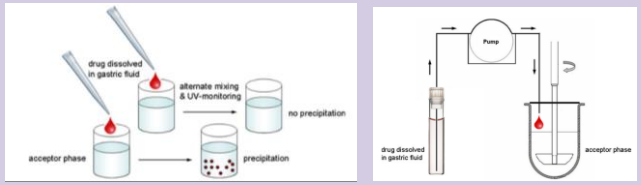
- For drug product
- Investigate performance of formulation and impact of excipients

'Small scale' assays



Mini transfer model

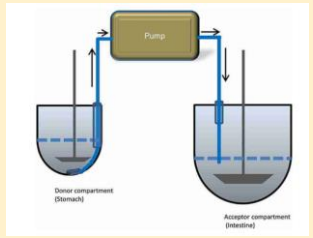
Jede et al. (2019), DOI: 10.1016/j.ijpharm.2018.12.013



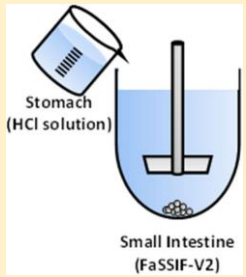
Based on 96-well plate and mini-

10

'Large scale' assays



Transfer model (based on

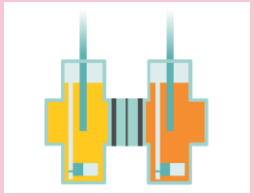


Dumping model

Kambayashi et al. (2016), DOI: 10.1016/j.ejpb.2016.03.020

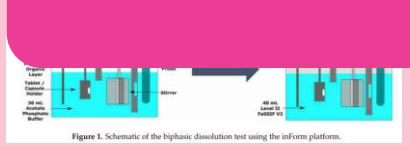
So many models (and even more) – which one to use?

Is there a gold standard?



MicroFLUX from Pion

https://pion-inc.com/scientific-instruments/in-vivo-predictive-tools/absorption/microflux

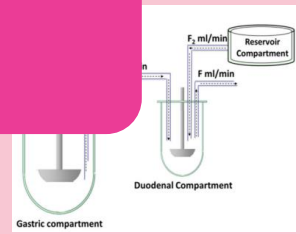


Inform from Pion

O'Dwyer et al. (2020), DOI: 10.3390/pharmaceutics12030272

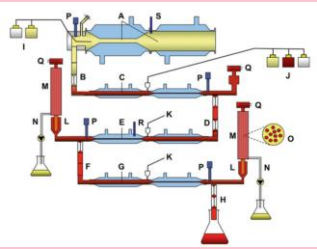
Dissolution-transfer-partitioning system

Jede et al. (2023), DOI: 10.3390/pharmaceutics15041069



BioGIT

Kourentas et al. (2018), DOI: 10.1208/s12248-018-0231-8



TIM Model

Minekus (2015), Springer Open

Assays accounting for absorption

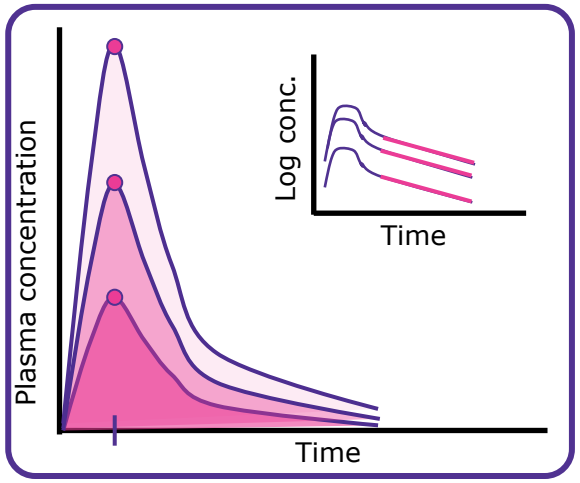
- Drug disappearance (absorption) is incorporated, *e.g.*, by membranes, organic layer, or dilution

And many more...

Deduce from *in vivo* data

! Exclude confounding factors (non-linearities in clearance; time-dependent effects; etc.) → Clinical data ideally from single ascending dose PK, or formulation study (*e.g.*, non-precipitating solution *vs.* tablet)

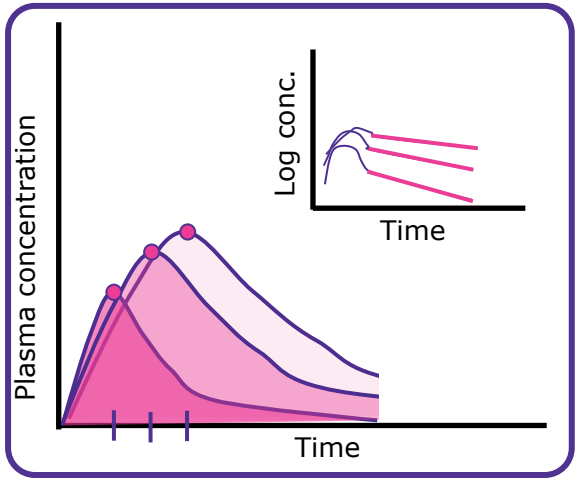
Impact of precipitation on PK: No



- Linear PK (AUC, Cmax)
- Tmax not shifted (very much)
- Linear elimination phase (no flip-flop kinetics)

Adjust PBBM as part of model building: Increase precipitation time; decrease precipitation rate constant; adjust MNG parameters.
Verify with independent PK data set.
Re-dissolution of precipitate: Not relevant (lack of precipitation *vs.* fast re-dissolution *in vivo* hard to distinguish, parameter-identifiability likely not relevant)

Impact of precipitation on PK : Yes



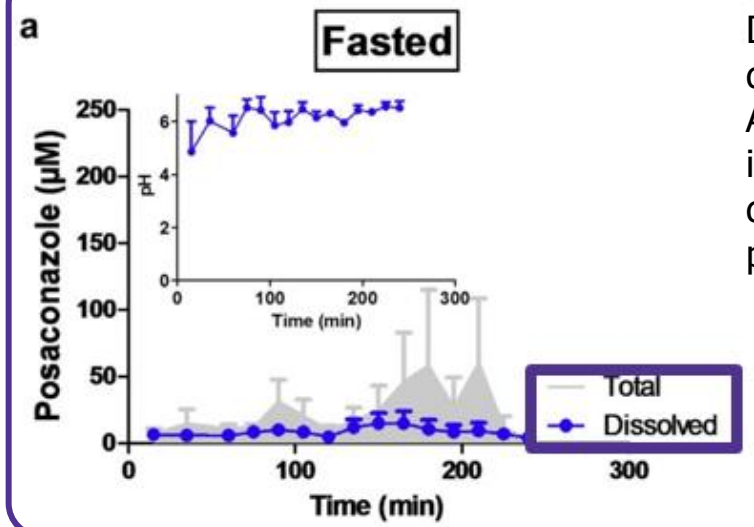
- Non-linear PK (AUC, Cmax)
- Tmax likely shifted
- Eventually flip-flop kinetics (ka > ke)
- Caveat: Interplay solubility, supersaturation, precipitation (parameter identifyability)

Adjust PBBM as part of model building: Fit precipitation parameters to match observed non-linearity.
Verify with independent PK data set.
Re-dissolution of precipitate: Does it occur? Kinetics? How to deal with?

Investigation of luminal precipitation; re-dissolution

In vivo techniques for investigating luminal precipitation

Duodenal sampling in healthy volunteers (*e.g.*, cinnarizine, gefitinib, ketoconazole, posaconazole, etc.)



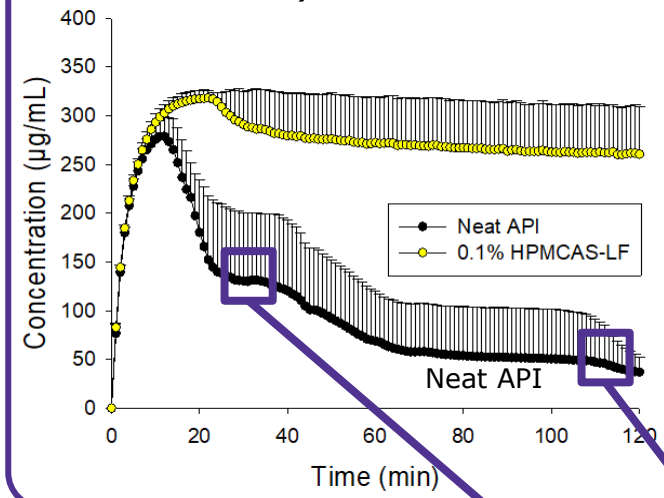
Dissolved drug < total API, indicating drug precipitation

Integration into PBBM should be feasible

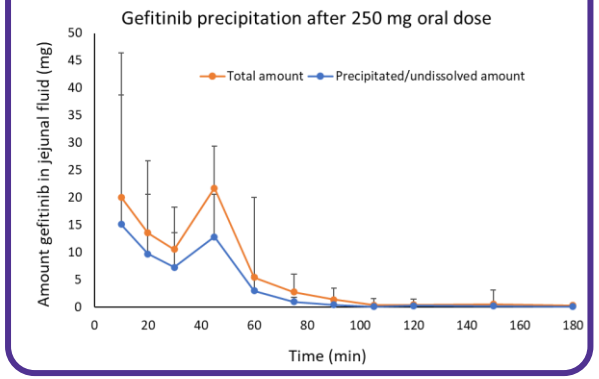
Highest evidence, but no standard technique. Availability of CROs (*in vivo* sampling systems)?

Solid state of precipitate; re-dissolution

Gefitinib precipitation (small-scale transfer model)



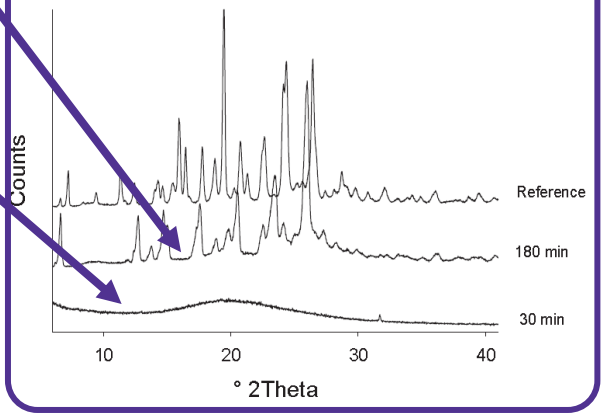
Gefitinib precipitation *in vivo*



Amorphous precipitation with subsequent (slow) re-crystallization confirmed. Solubility amorphous *vs.* crystalline drug? Impact on absorption?

Whenever possible, characterize solid state of precipitated API and adopt PBBM.

XRPD of gefitinib precipitate



Hens et al. (2016) J Pharm Sci 105; 2904-2912

Jede et al. (2019) International Journal of Pharmaceutics 565; 458–471
Bergmann et al. (2007) International Journal of Pharmaceutics 341; 134-142

Software tools to predict drug precipitation

1. First order precipitation model

- Factors: Critical supersaturation ratio, Precipitation rate consta
  (+ optional secondary precipitation rate consta

2. Advanced precipitation models

- Nucleation model (based on classical nucleation theory)
- Growth model (based on diffusion layer model)

- Modelling of experimental data with SIVA toolkit

1. First order precipitation model

- Mean precipitation time

- Modelling of experimental data with DDDPlus

Mechanistic (nucleation and growth) *vs.* descriptive (precipitation rate):

Which one to use? Gold standard?

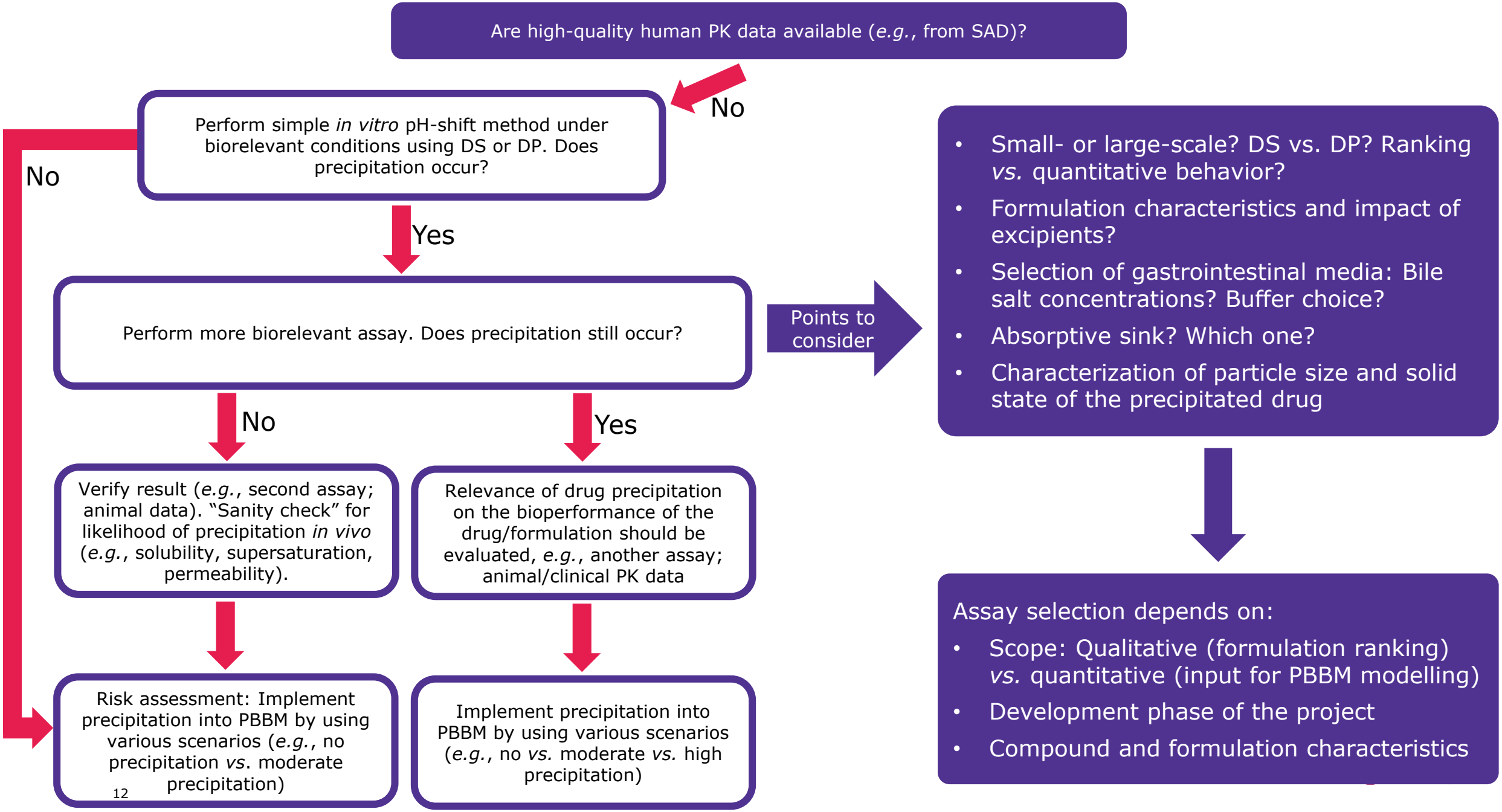
1. Mechanistic precipitation model

- Nucleation model (Mullin, empirical power law kinetics)
- Crystal growth model (population balance-based model, molar flux balance on particle surface)

- Customization possible
- Modelling of experimental data in gPROMS software

Proposal for assay selection and workflow design

Adopted and refined from Wagner et al. (2021), DOI: 10.1208/s12248-021-00601-0.



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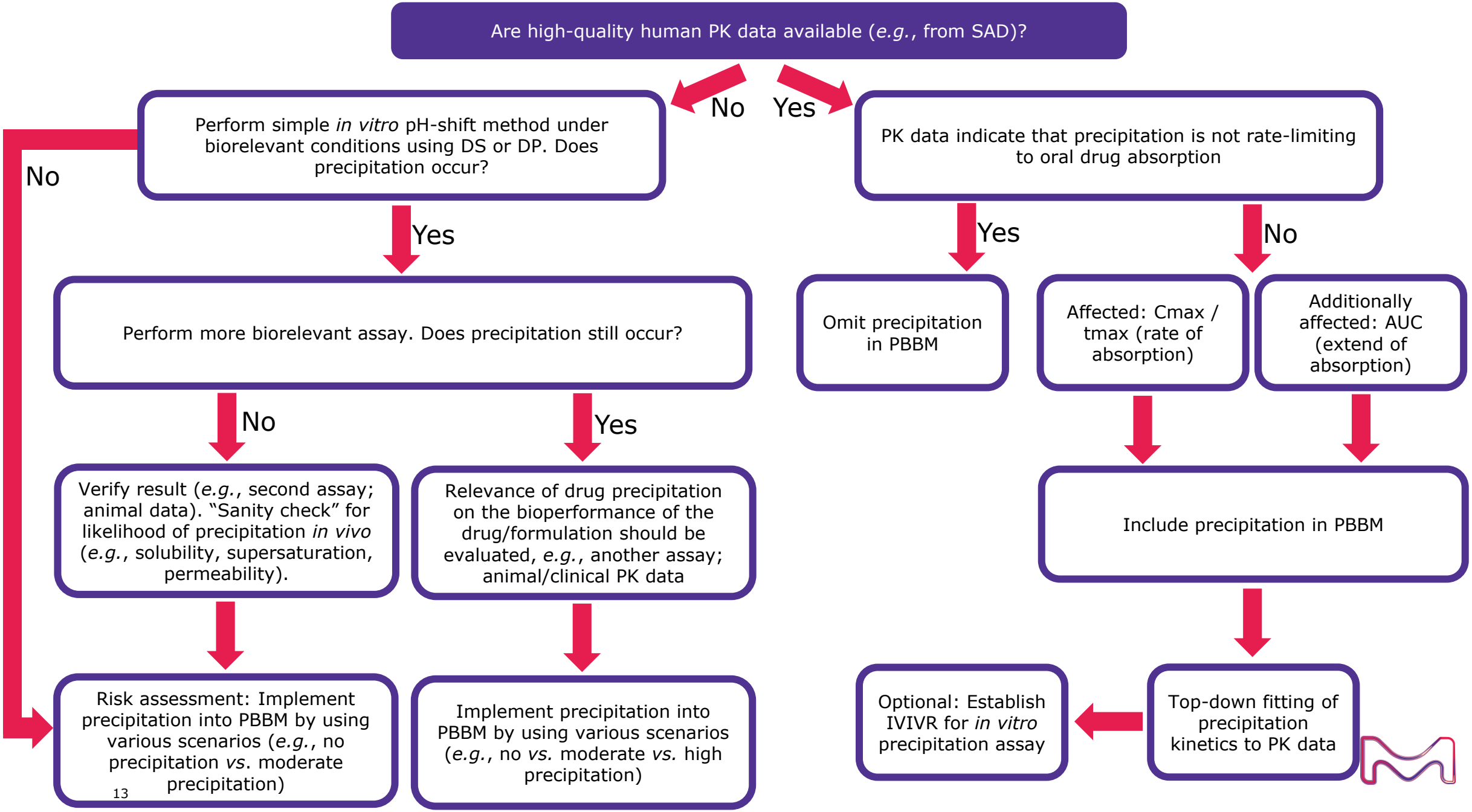

Conclusions: Are we there yet?

03

In an ideal scenario…

Absorption

- Trans- and paracellular permeability
- Transporters
- Molecular mobility (mucosa; micelles)
- …

Physiology

- Emptying rates (particle size dependent; "Magenstraße")
- Hydrodynamics
- Site-dependent bile concentrations; micellar structure
- (Free) liquid volumes, water pockets
- Pressure events
- …

Solubility, dissolution, supersaturation

- Bile-dependent solubility (solubilization ratio)
- Effect of micelles on precipitation kinetics
- Common ion effects
- Effect of food / digestion components
- Particle size / morphology
- Degree of supersaturation (weak bases; supersaturating formulations)
- …

Precipitation and re-dissolution

- Nucleation and growth
- Effect of mucosa on precipitation
- Solid state
- Re-dissolution
- …

We have a thorough understanding of the system physiology and how it impacts drug solubility / super-saturation / dissolution / absorption – also in hard-to-access regions of the GIT

+

We understand our drug / formulation properties via *in vitro* or *in silico* techniques

+

Our state-of-the-art PBBM is capable of integrating all relevant factors (integrative tool for "connecting the loose ends")

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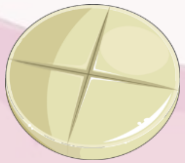
https://smart.servier.com/

… and where we currently are. Is there need for improvement?

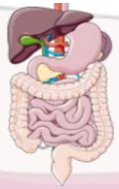


Drug and formulation attributes

- One single biopredictive tool *vs.* simulation of individual steps
- Predictivity of *in vitro* tools (solubility, supersaturation, permeability / "absorption") for drug precipitation
- Nucleation and growth parameters for drug substance / formulation
- Impact of buffer species and excipients on solubility and supersaturation
- Prediction of regional solubility (impact of bile, bile partitioning)
- Solid state and re-dissolution

Biorelevant ≠ biopredictive

Standardization *vs.* case-by case



Physiology (system parameters)

- Hydrodynamics and transit rates (incl. "Magenstraße")
- Fluid volumes (stomach, small intestine, colon) and distribution thereof (fluid pockets)
- Local bile salt concentrations in SI, micellar structure
- Impact of mucus on precipitation (molecular mobility)
- Translation of *in vitro* to *in vivo* permeability (incl. transporter effects; large molecules)

Still many unknowns. Would "filling the gaps" increase predictive performance?

PBBM capabilities and modeling approaches

- Are our PBBM "state-of-the-art"? *E.g.*, simulation of nucleation and growth; common ion effects; "correct" physiology; etc.

PBBM need some improvement. Best practices in PBBM workflow desirable (standardize as much as possible)

Which degree of uncertainty is acceptable? → 100% *vs.* 70%, 80%, 90% solution? Fit for purpose? What is good enough? → Breakout session ☺

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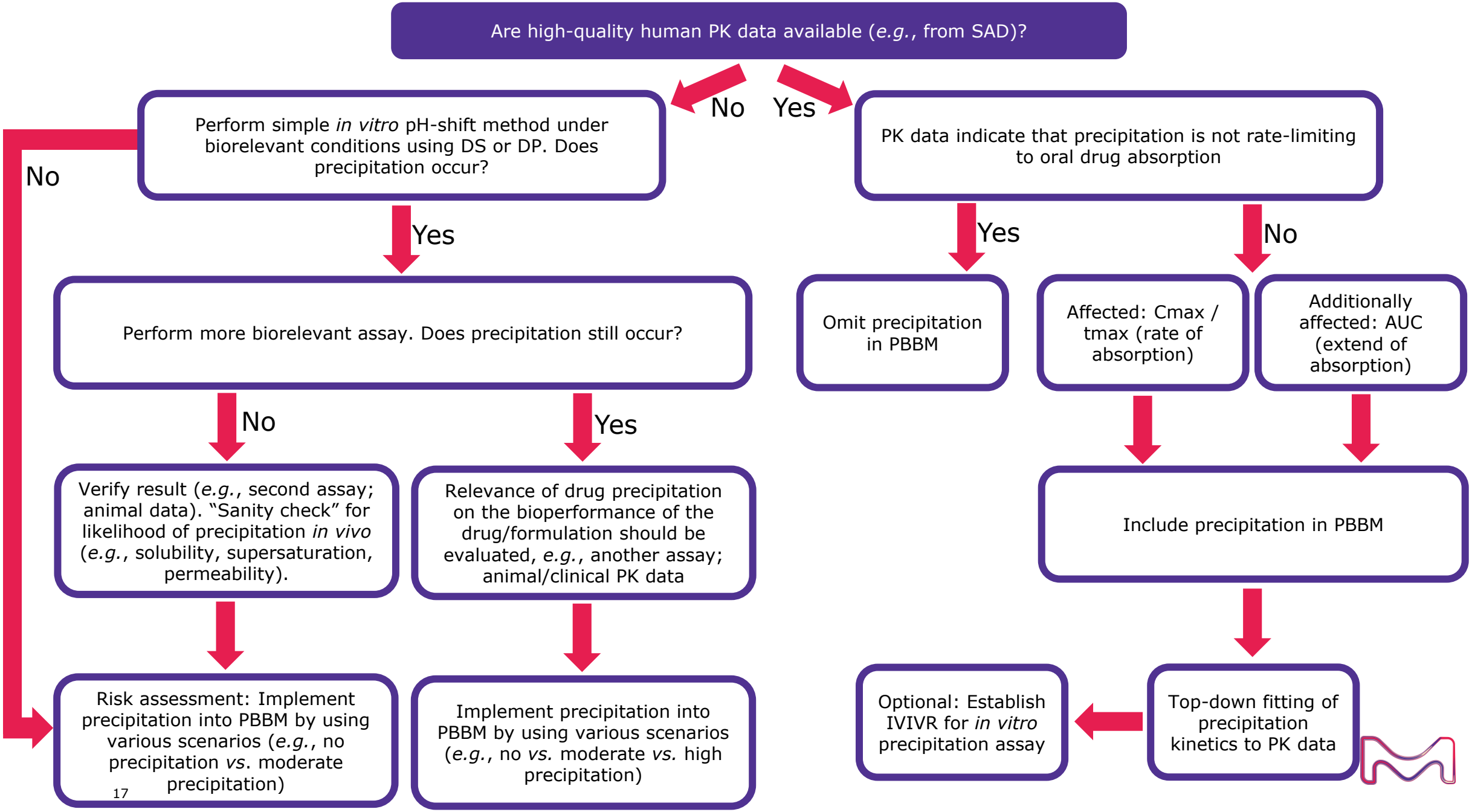

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