Innovative Medicines Initiative

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Innovative Tools for Oral Biopharmaceutics

FDA Public Workshop on Oral Absorption Modelling and Simulation

Filippos Kesisoglou - 19th May 2016

Overview

- Programme vision, mission and objectives
- Members of the OrBiTo consortium
- OrBiTo Work Packages
  - Aims and deliverables
  - Highlights of progress to date
- Integration of dissolution in PBPK models

OrBiTo Vision Statement

“ Transform our ability to accurately predict the in vivo performance of oral drug products across all stages of drug development ”

OrBiTo Mission Statement

"Through partnership, collaboration and data sharing, we will develop, validate and implement a suite of biopharmaceutics tools applicable throughout the drug development process. By developing our fundamental knowledge of the gastrointestinal environment, we will deliver innovative tools to accurately predict product performance over a range of clinically relevant conditions. The integration of *in vitro* and *in silico* approaches will provide a biopharmaceutics toolkit, validated using clinical data, to accelerate drug development."

Programme objectives

• Define the critical physicochemical, formulation and physiological factors that determine oral drug product performance.

• Develop both experimental and theoretical models which can be used to robustly predict the in vivo performance of formulated drug products.

• Fully leverage industrial knowledge and experience through pooling existing physicochemical, in vitro characterisation, preclinical and clinical data to assess the reliability of currently available prediction methods and to underpin the development of new modelling and simulation tools.

IMI OrBiTo project – innovative tools for oral biopharmaceutics

- IMI funding for the project is €24million over a 5 year period, commencing on October 1st 2012

- OrBiTo consortium comprises 13 EFPIA companies with 14 academic centres and SME companies
  - Managing entity: Uppsala Univ (Hans Lennernäs/Krister Halldin).
  - Scientific coordinators: Astrazeneca (Bertil Abrahamsson) & Pfizer (Mark McAllister)

Project Governance

Steering Committee – All Consortium participants
For annual reviews, approval/removal of participants, approval of resource changes across work packages/project participants

Executive Committee – 14 participants
For operational project leadership, continuous project review, issue resolution, proposal of changes within projects

Regulatory Stakeholder Group

Ethics Advisory Board

Work Package 5
Management and Dissemination (Leaders: UU & AstraZeneca)

Work Package 1
Physico-chemical tools

Leaders:
Public: UCopen
EFPIA: LUB

Work Package 2
In vitro tools

Leaders:
Public: KU Leuven
EFPIA: GSK

Work Package 3
In vivo tools

Leaders:
Public: UMainz
EFPIA: JPNV

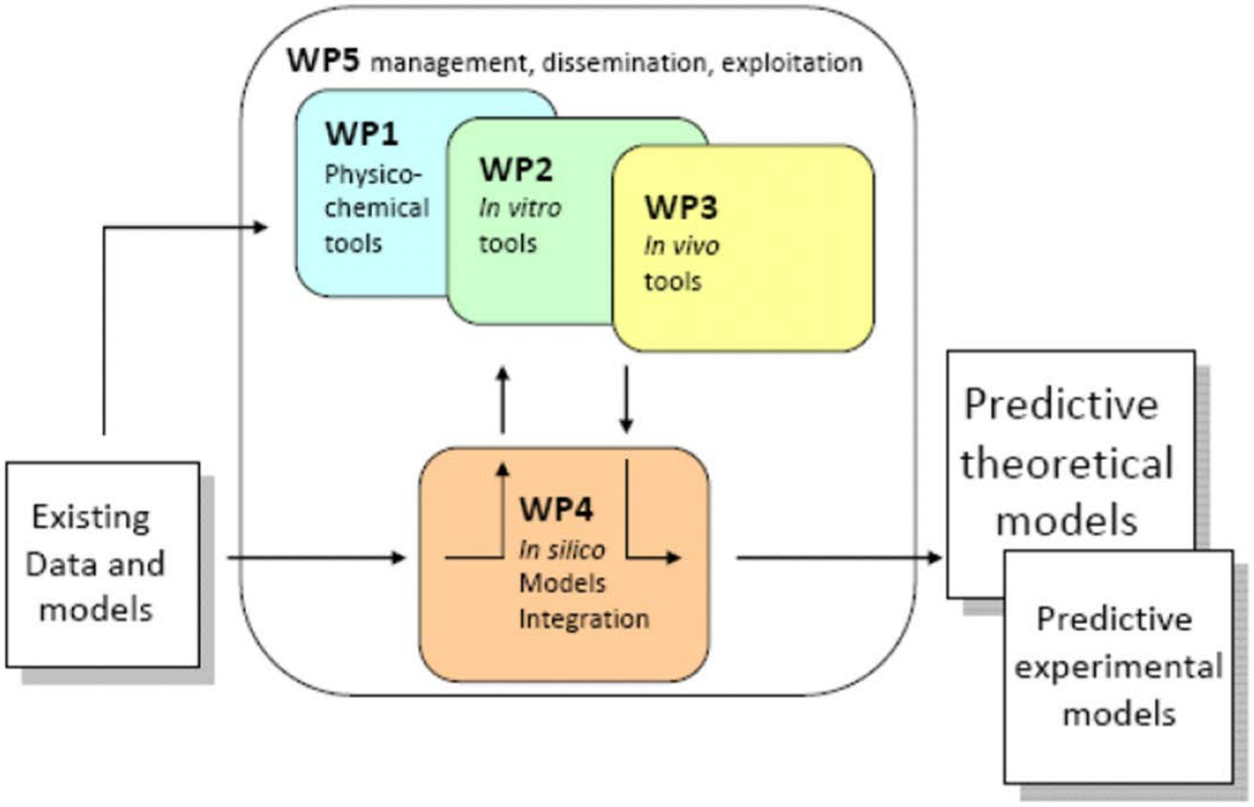
Work Package 4
In silico models & integration

Leaders:
Public: UNIMan
EFPIA: SARD

OrBiTo Regulatory Stakeholder Board

- Anna Nordmark, MPA, Sweden
- Erika Fredriksson, MPA, Sweden
- Anders Lindahl, MPA, Sweden
- Susan Cole, MHRA, UK
- Henrike Potthast, BfArM, Germany
- Alfredo Garcia, AEMPS, Spain
- Arzu Selen, FDA, US
- Mehul Mehta, FDA, US
- Marilyn Martinez, FDA, US
- Kumiko Sakai-Kato, NIHS, Japan
- Ken-ichi Izutsu, NIHS, Japan

Work packages overview



Work Package 1
Physicochemical tools – Understanding the API

Objectives:

1. Provide a range of in vitro physico-chemical tools and in silico models that can assess the API's key molecular properties important for in vivo performance, including excipient interactions

2. Provide the information gained by use of tools, defined in objective 1, for a subset of the OrBiTo database to establish a Drug Development Decision Tree, expanding the DCS and facilitating drug formulation selection and optimising the dosage form design process

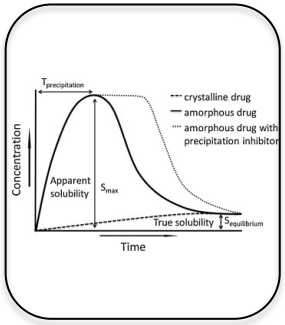
3. Integrate knowledge and results obtained from physico-chemical studies and models in WP1 with "In vitro tools – understanding the formulation" (WP2).

4. Serve as physico-chemical parameter input for integrated modelling and predictive tools developed in WP4 (PBPK modelling).

Workpackage 2: In vitro tools

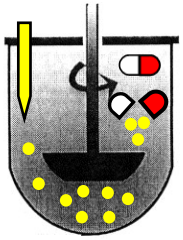
KULeuven, UoA, U-Goethe, UCPH, EMUAG, Umainz, TNO, EFPIA contributors

WP1



- Log P value
- Log D value
- pKa
- Solubilities
- Hydrogen bounding
- Molecular weight
- Supersaturation
- ...

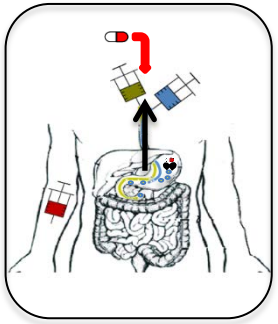
Simple, one-compartimental models

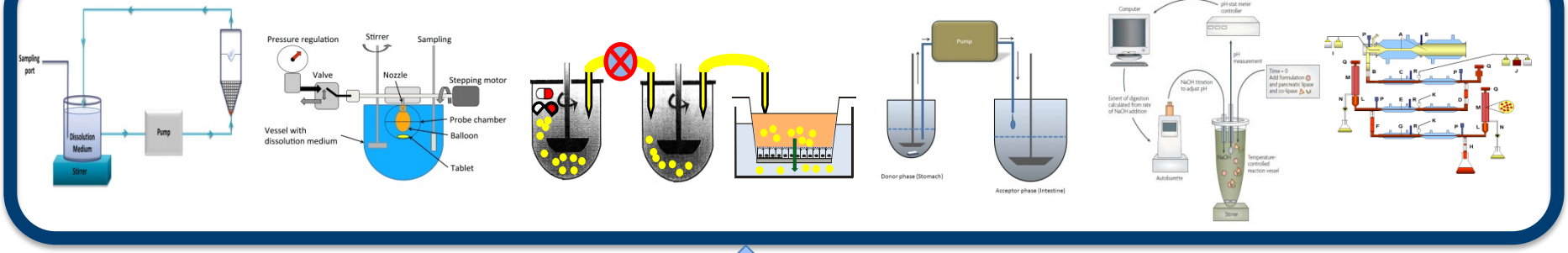


Optimizing models by applying knowledge of the gastrointestinal environment:

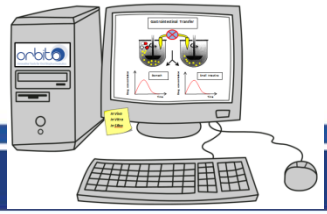
- Hydrodynamics
- Gastric/ intestinal fluids
- Gastrointestinal transit
- Drug absorption
- ...

WP3





WP4



Innovative Tools for Oral Biopharmaceutics

Workpackage 2: In vitro tools

KULeuven, UoA, U-Goethe, UCPH, EMUAG, Umainz, TNO, EFPIA contributors

GOALS:

1. **Optimize/develop *in-vitro* tools for formulation evaluation with maximum ability for prediction of oral absorption in humans (**by integrating knowledge on *in-vivo* drug and formulation behaviour)
2. **Develop a decision tree to select most appropriate *in-vitro* tool(s)**
3. **Provide relevant input data on formulation behaviour for PBPK modelling (WP4)**

Task 2.1 - Analysing the current status, gaps and requirements for in-vivo predictive in-vitro evaluation of orally administered dosage forms

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Review

In vitro models for the prediction of *in vivo* performance of oral dosage forms

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WP3 In Vivo Tools: Scope, Vision and Mission

1. Providing approaches and data to better understand the in vivo systems and systems biology impacting drug formulation behaviour and drug absorption.

2. Improving mechanistic in vivo tools for better in vivo animal-in vivo human translation and in vitro –in vivo relationships.

3. Assessing drug dissolution and drug supersaturation and precipitation in vivo.

4. Aid in altering and validating in silico and in vitro methodologies to increase bio relevance.

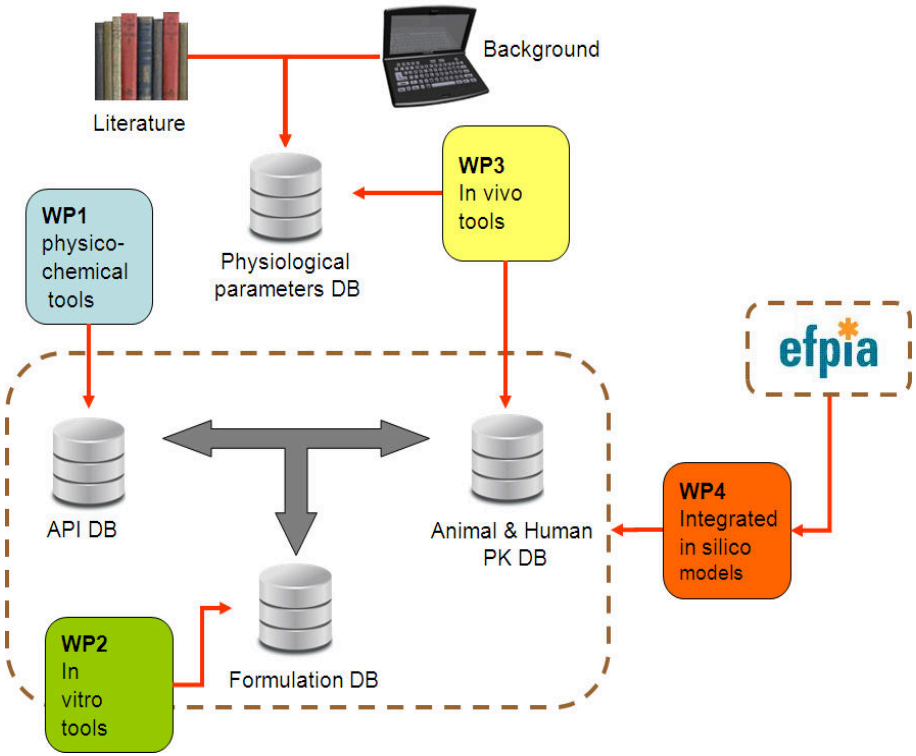
WP3 In Vivo Tools: Scope, Vision and Mission

Understanding and leveraging knowledge and data for validation of drug substances and formulations in vitro (WP 1 and 2) and in silico (WP 4)

- ***The Gastrointestinal System***
  - **the pattern of fluid availability and distribution**
  - **the influence of hydrodynamic and mechanical stresses on dosage form behaviour**
- ***Intestinal fluid composition and dissolution media:***
  - **the composition and properties of GI fluids from animals and man under a variety of states including nutritional state, age and collection method.**
  - **GI fluid architecture using non-invasive techniques visualizing the formulation in vivo including g-scintigraphy, magnetic marker monitoring (MMM), magnetic resonance imaging (MRI).**
- ***In Vivo Dosage Form Behaviour* in animals and human to better understand in vivo dissolution, absorption and transit properties of drug substances and dosage forms on several fronts including:**
  - **dosing of suspensions and deconvolution of the resulting plasma level**
  - **dosing drug product and assessing gastric aspirates for dissolved drug**
  - **assessing API and drug product for their tendency to generate supersaturated drug solution in vivo**
  - **imaging of in vivo disintegration (camera-in-pill, MRI)**
  - **imaging intestinal dosage form transit**

Work Package 4: In-silico tools

- Refinement of integrative *in silico* tools (enhanced physiological database, new model algorithms and new *in vitro* inputs in connection with WPs 1-3
- Development of framework for API formulation type selection and identification of biowaiver (in vitro BE) opportunities based on predictive models
- Dissemination and propagation of information related to model based drug development concerning oral absorption



Workpackage 4: In silico tools

Abbvie, AstraZeneca, Bayer, BMS, GSK, Janssen, MPA, MSD, OP, Pfizer, SARD, Sim, SPlus, UGoethe, UMainz, UNIMAN, UU

- T4.1 OrBiTo database architecture + plug ins+ web platform
- T4.2, T4.3, T4.4 EFPIA phase 0 data collection and upload
- T4.8 Setting up model quality indicators

Database creation and quality indicators

Initial gap analysis (blinded PK data)

- T4.10 : Ideal systems biology description and physico-chemical inputs to PBPK tools, cross –comparison of tools
- T4.6 : Gap analysis on missing data → feed back to EFPIA
- T4.9 : Initial gap analysis (blinded bottom-up anticipation of human PK)→ indentification of gaps to be filled

- T4.7 regular updates of the database with EFPIA data
- T4.5 Population of database with RIVM or ICRP data
- T4.14 Novel models for super-saturation and precipitation
- T4.15 Integration of release performance for enhanced formulations
- T4.16 Changes to PBPK model physiology
- T4.17 New algorithms for passive and active permeability
- T4.18 Setting up a lymphatic absorption route
- T4.19 calculation of dynamic bile salt concentration in the lumen of the intestine

Making changes to PBPK tools

- T4.10 Prediction errors of tools in the framework of the rDCS
- T4.11 Selection of internal optimization and validation compounds for rDCS. Impact of enhanced formulations on classification

Refined DCS

Testing various improvements/inputs

- T4.13 Integration of release data for ER products in PBPK (IVIVe) + comparison with IVIVc
- T4.20 Testing of various improvement options for in silico models
- T4.21 Develop a predictive model for negative FE of BCS class III compounds
- T4.22 Use of refined in silico tools to suggest extension for biowaivers

Highlights of progress to date

- Reviews summarising state of the art for API characterization approaches, *in vitro and in vivo* oral bioavailability tools and systems biology, a gap analysis of in-silico commercial biomodelling software have been completed and accepted for publication in an OrBiTo themed special issue of European Journal for Pharmaceutical Sciences (doi: 10.1016/j.ejps.2013.10.012)

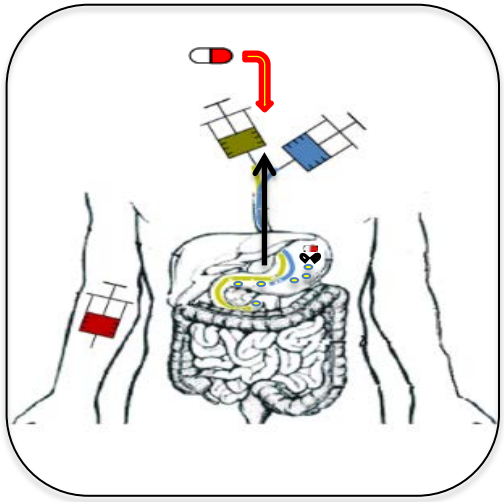
- Database established compiling physicochemical and preclinical and clinical ADME/PK data
  - 90 EFPIA compounds, 594 formulations, 492 PK studies, 1580 study arms, 25764 datapoints !

Highlights of progress to date

- Developed a standardized protocol for sampling and analyzing human gastric and intestinal fluids (both upper and lower intestine)
- Identified composition and major components of human intestinal fluid, based on literature review and data from OrBiTo partners. This dataset was used to develop a set of simulated gastric and intestinal fasted state media using a DoE approach.
- Completed a human clinical study of a non-absorbable compound (Gabrorol®) with or without various co-medications (Imodium® and Motilium®), in fed or fasted conditions to allow for the assessment of transit using in vivo gastrointestinal sampling techniques
- Developed and validated a novel MRI method for assessing GI water content based on volumetry rather than water signal determination
- Development of a predictive mathematical model for the negative food effect of BCS class III compounds in solid drug formulations

Integrating dissolution profiles into PBPK models

In vitro



In vivo

Challenges:

- *in vitro* conditions differ from *in vivo*
- *in vivo* dissolution/release profiles are challenging to determine.

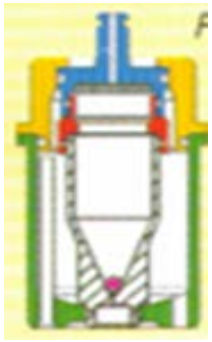
Why Are We Interested in Incorporating Dissolution in PBPK?

- For the majority of the formulated products (not API powder), dissolution modeling based on API properties does not agree with observed dissolution data
- Allow for more mechanistic modeling of dissolution regardless of dissolution media
  - Eg. account for differences in pH, volumes, surfactants (bile salts, etc).
- Facilitate development of “biopredictive” dissolution method

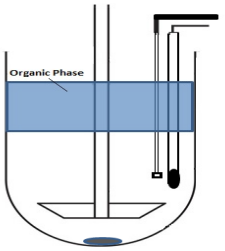
Various Solubility/Dissolution Experiments/Apparatuses

Solubility

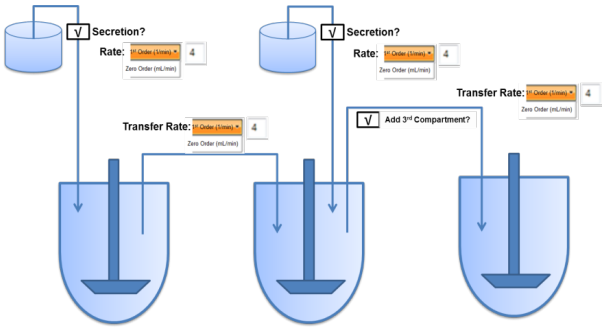
USP II



USP IV?

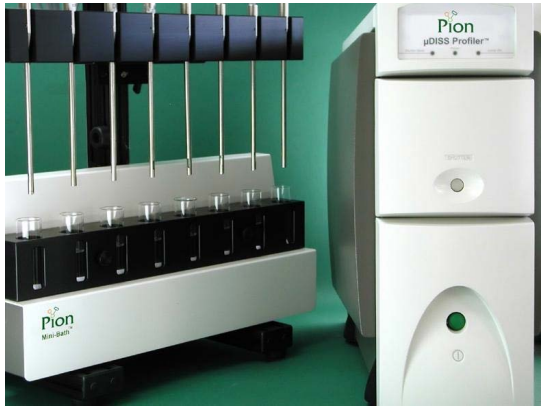


2-Phase/Serial Dilution



Transfer Experiments

Sirius T3



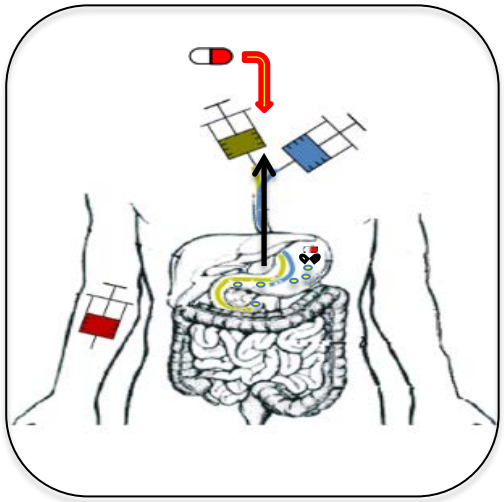
Pion µDISS Profiler

Mechanistic Dissolution Modeling

"Deconvolute" *in vitro* data

$$DR(t) = S * N \frac{D_{eff}}{h_{eff}(t)} 4\pi a(t)\left(a(t) + h_{eff}(t)\right)\left(C_{surface} - C_{bulk}(t)\right)$$

To separate *in vitro* **system data** (e.g. rpm, buffer, pH, [BS], *etc*) from **API/formulation data** (e.g. S_0, pKa, PSD, SR, PRC, *etc*)



"Re-convolute" ***in vivo*** system data and API/formulation data using PBPK modelling

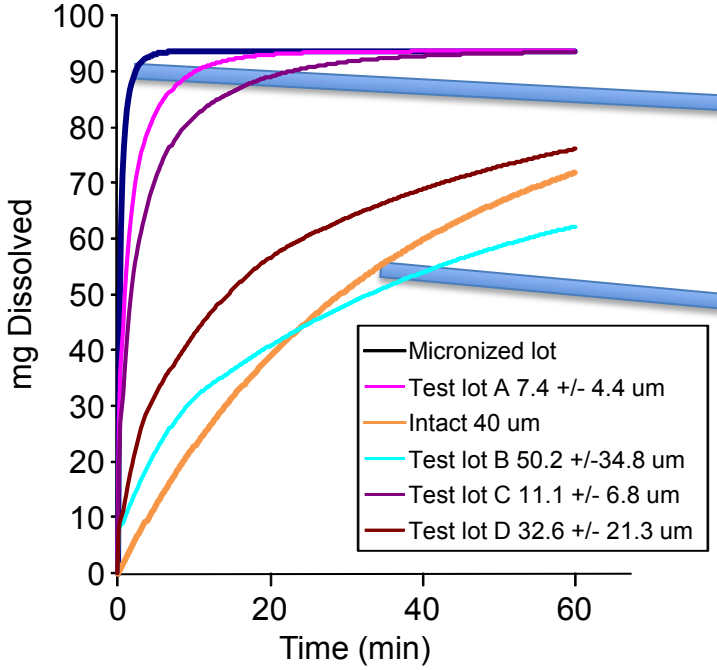
Predict – Learn – Confirm

Case Study – Dissolution Simulation of API

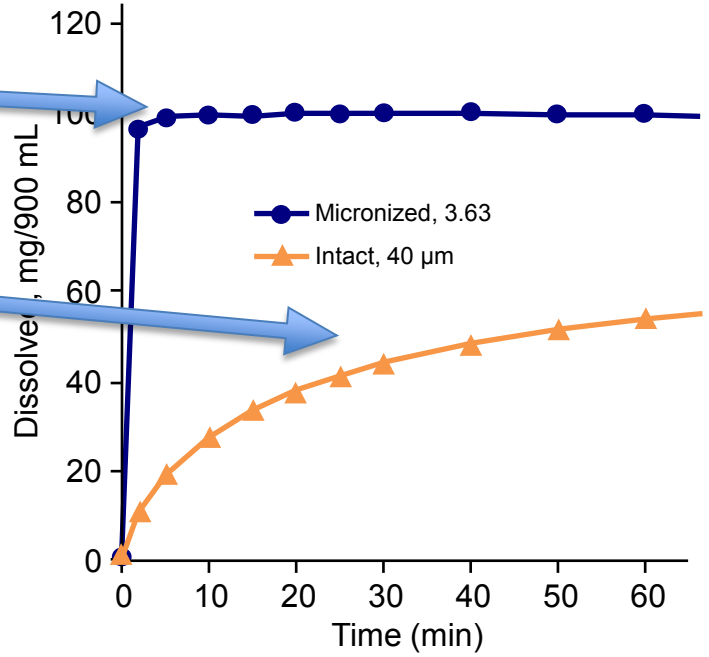
Nernst-Brunner/Noyes-Whitney equation

$$\frac{dX}{dt} = \frac{3 \cdot D \cdot X_0^{1/3} X_s^{2/3}}{h \rho r_0} \left(C_s - \frac{Xd}{V} \right)$$

Input: Solubility, PSD, dissolution volume



In silico predicted dissolution profiles based on API PSD

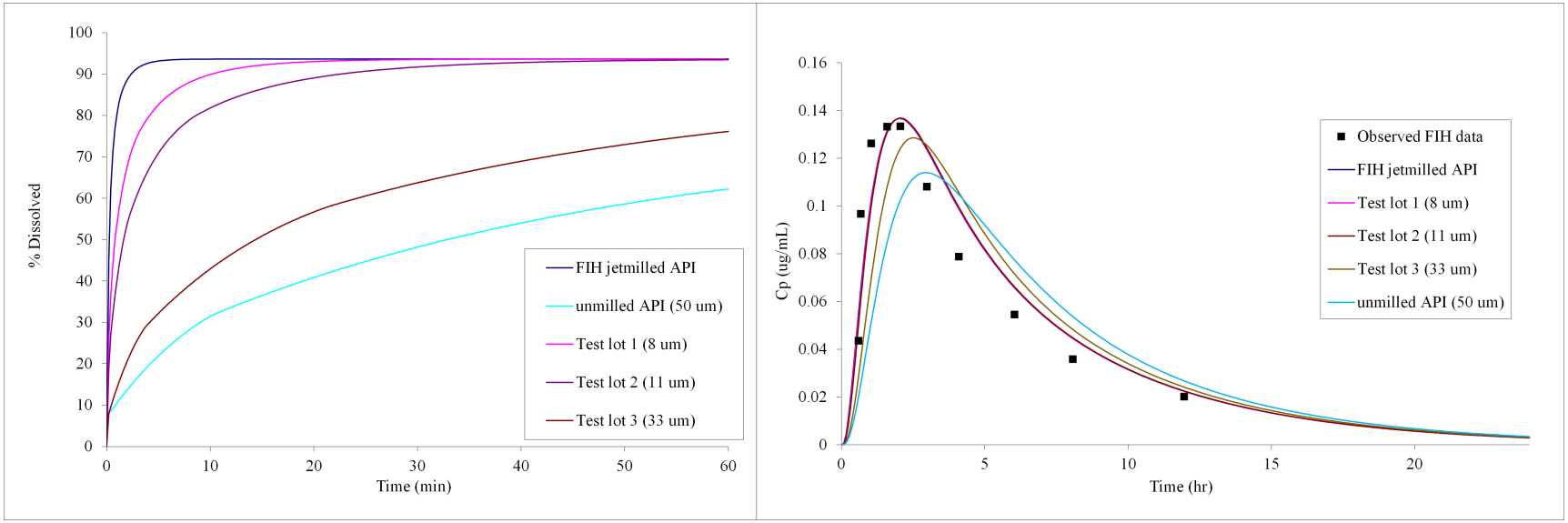


Observed dissolution profiles for dispersed API powder

Good agreement between in silico and experimental dissolution profiles

(generally expected for dissolution of API powder)

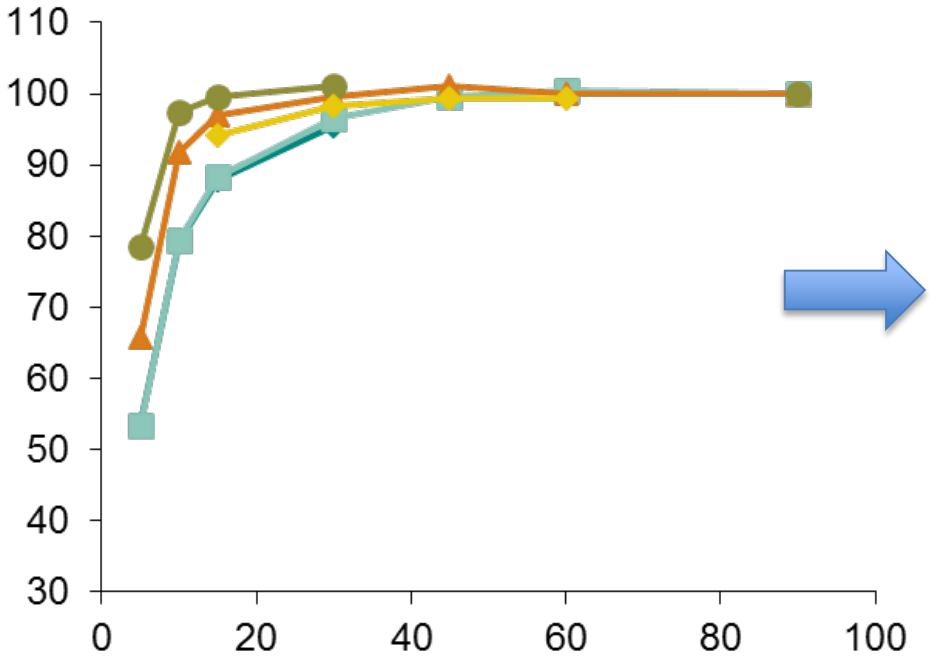
Case Study – API PSD simulation in PBPK model



Conclusion based on API PSD based modeling: Unmilled API potentially lower Cmax and slightly lower AUC

Case Study – Formulation Dissolution in PBPK model

Observed Dissolution Profiles for Formulated API

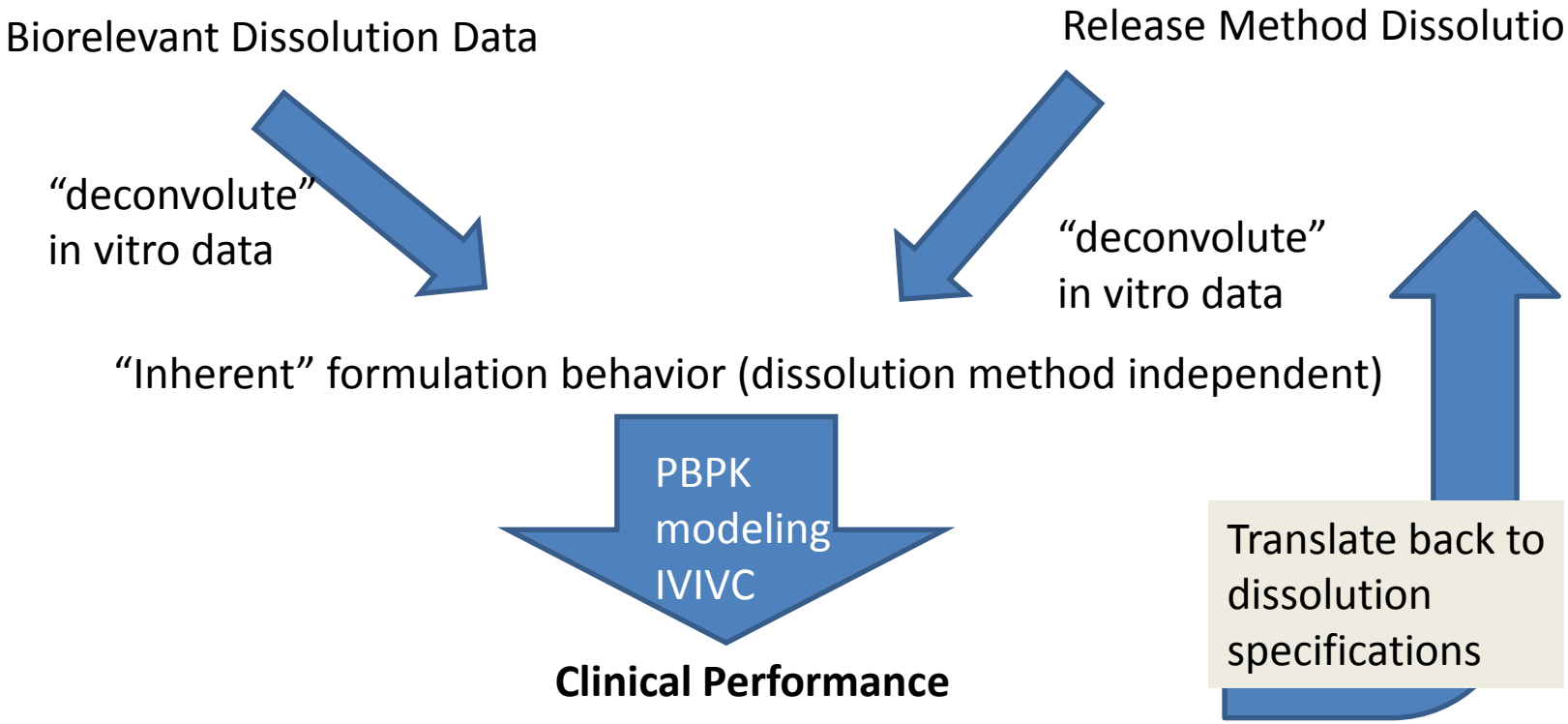


No significant PK impact expected

"Relaxed" requirements on API PSD

Increasing Impact: Towards a “Biopredictive” method

There is an increased emphasis on development of “clinically relevant specifications”. Incorporation of Dissolution in PBPK models may further facilitate the connection of dissolution and Clinical performance.



Acknowledgements

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- Many OrBiTo contributors!

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