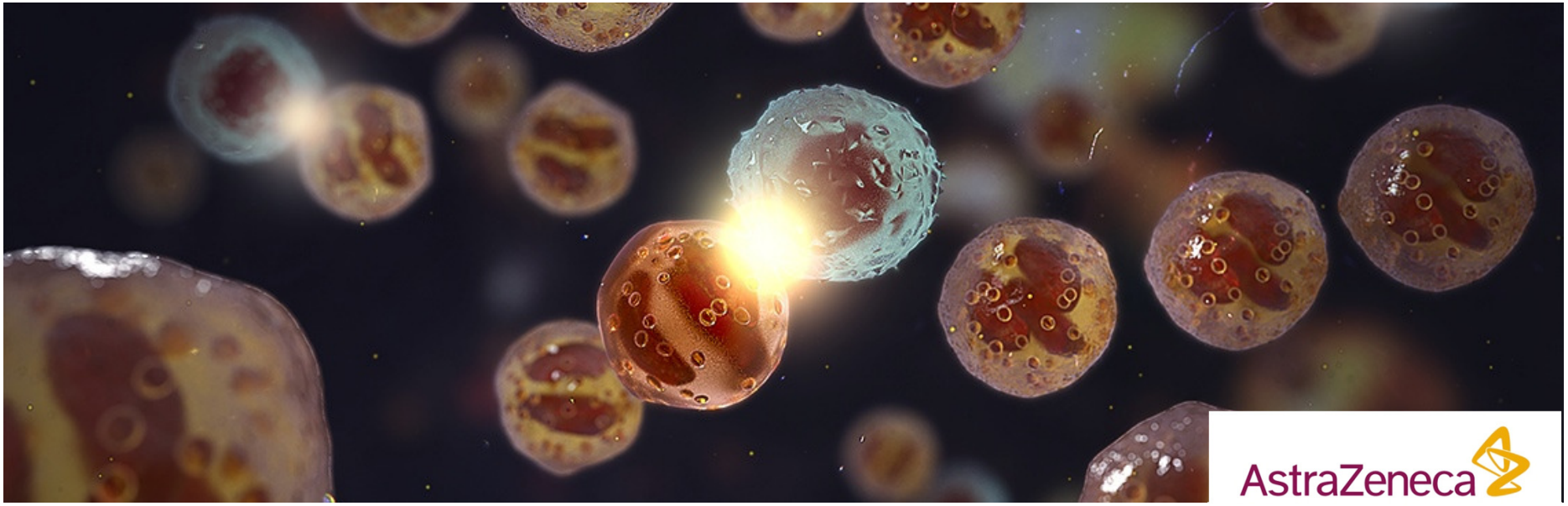
In vivo predictive dissolution (IPD) testing – scientific progress in OrBiTo and enhanced industrial application

Bertil Abrahamsson
PQRI Washington

5 oct 2015



Outline

- Industry situation
- What is OrBiTo?
- Progress highlights from the OrBiTo lab bench
- New opportunities for biowaivers

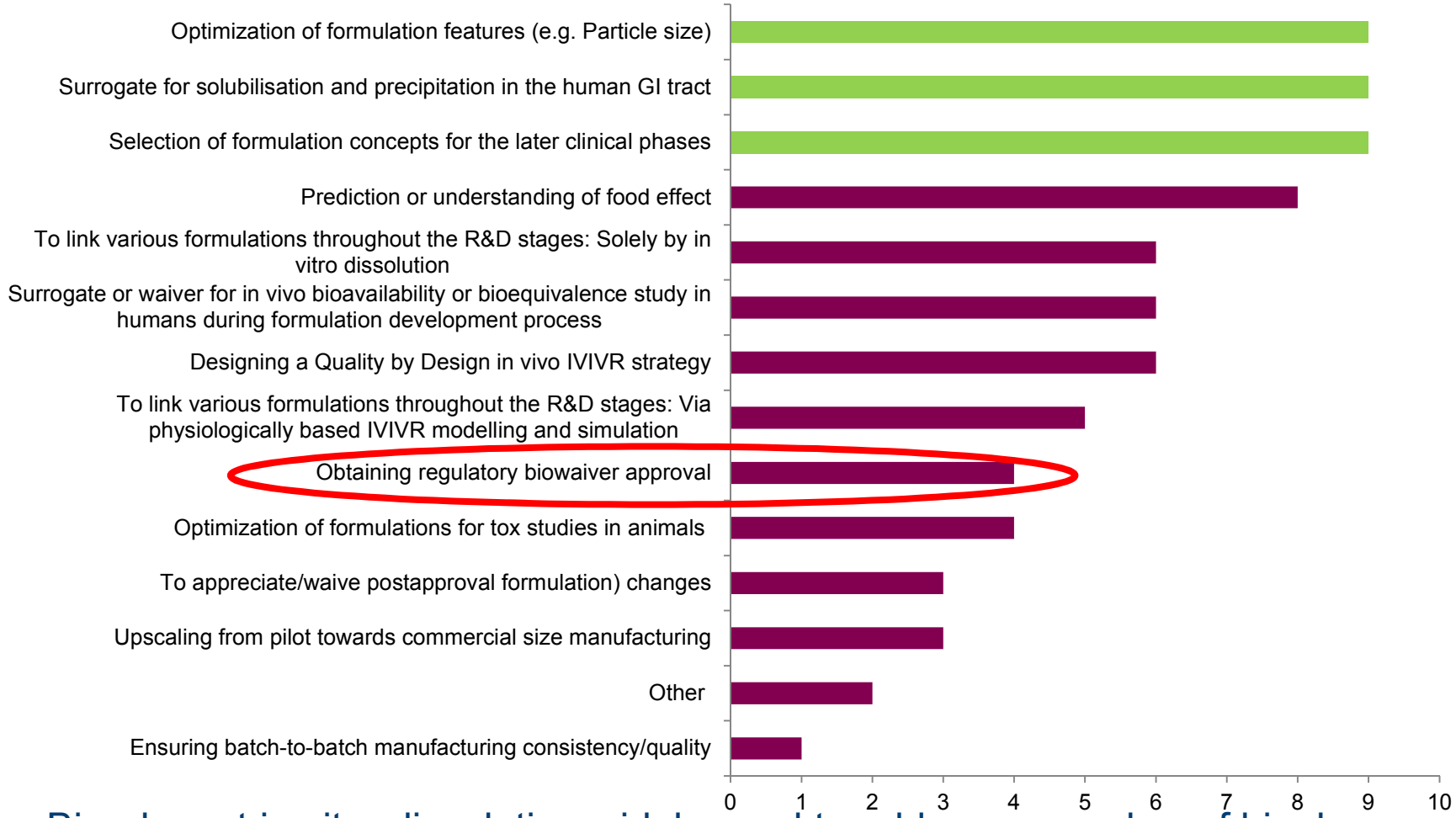
In vivo predictive dissolution (IPD) testing – current situation

- Simulated GI fluids well established as a tool in product development for formulation selection, risk assessment and in vivo predictions
- Science and risk based approaches based on BCS is normal industry practice

BUT

- Validations of IPD approaches generally anectdotal rather than systematic
- Several aspects not well captured by current methods eg;
  - Supersaturation/precipitation/re-dissolution
  - Distal GI fluids
  - GI hydrodynamics
- The interplay between intestinal dissolution and other absorption factors neglected , in vitro dissolution data often used stand alone

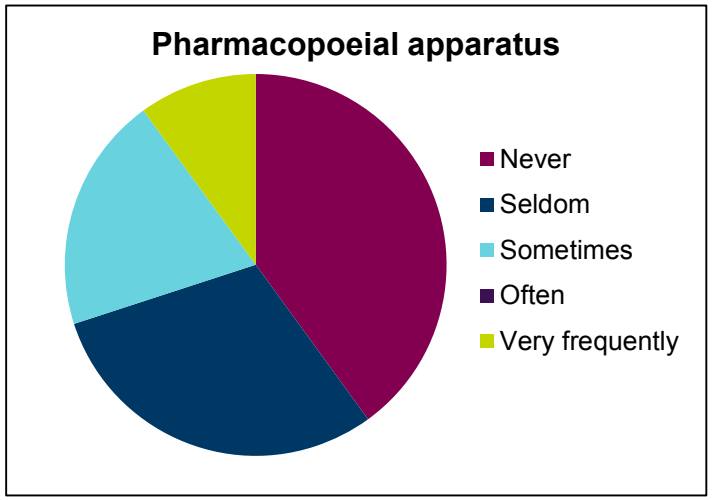
Purposes for biorelevant dissolution testing in product development – industry survey 2015

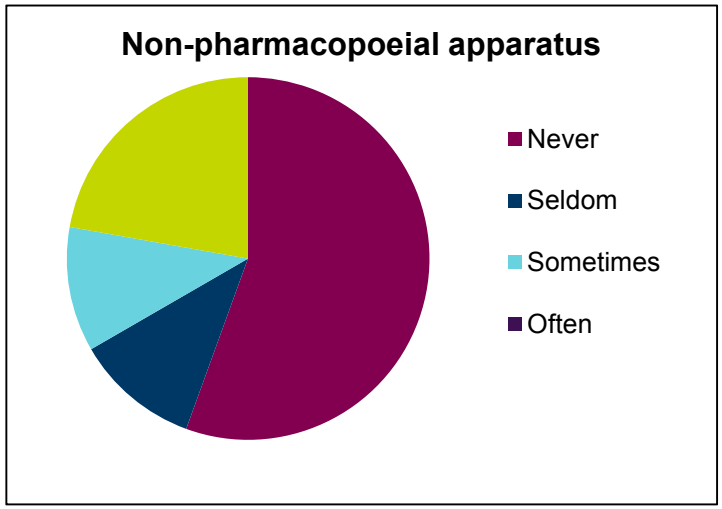


- Biorelevant in vitro dissolution widely used to address a number of biopharm issues
- Most often performed for formulation selection and optimisation

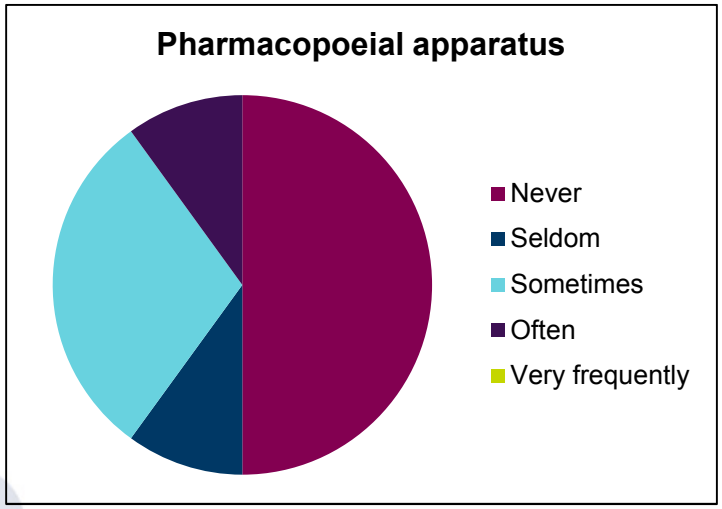
How often is this data submitted as part of regulatory scientific interactions?

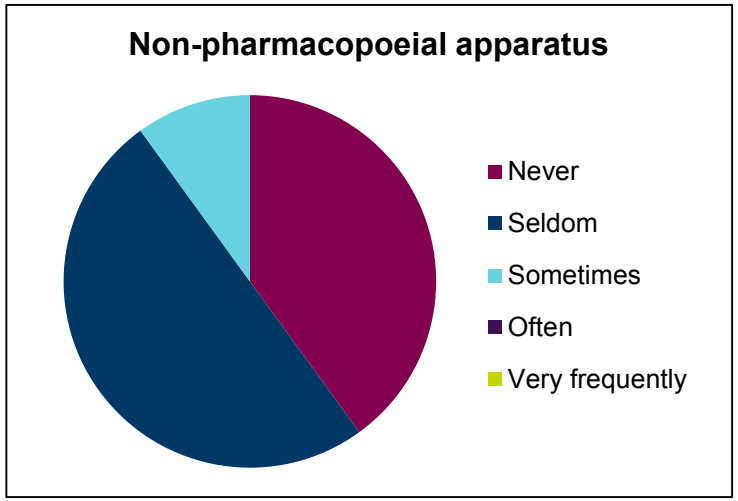
In early regulatory interactions (IND, IND updates)





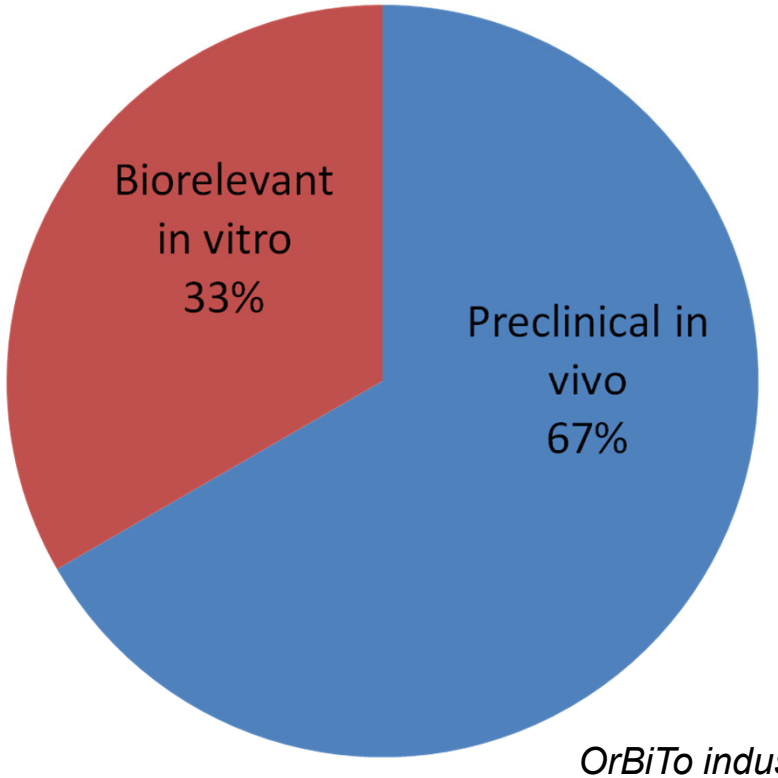
In MAA/ NDA





Industry survey- animal study or IPD?

Question: If you had to predict the relative human in-vivo performance of two very different IR formulations of the same poorly soluble drug, what prediction would you trust most?



OrBiTo industry partners survey 2014

Industrial problem statement

⇒Extensive use of animal testing in formulation selection

⇒ Iterative human BA/BE studies in development

⇒ Limited options (BCS I and III) for biowaivers

⇒ Quality critera based on pivotal batches rather than clinical performance

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."

OrBiTo is a
Research consortium between EU and european
Industry (EFPIA) within the Innovative Medicines Initiative (IMI)

The OrBiTo Consortium

EFPIA Partners

• **Abbvie**	*Germany*
• **Bayer Pharma AG**	*Germany*
• **Boehringer-Ingelheim**	*Germany*
• **GlaxoSmithKline R&D**	*UK*
• **J&J**	*Belgium*
• **Lundbeck**	*Denmark*
• **Merck**	*UK*
• **Novartis**	*Switzerland*
• **Orion Pharma**	*Finland*
• **Pfizer**	*UK*
• **Sanofi-Aventis**	*France*
• **AstraZeneca**	*Sweden*

Academic Partners

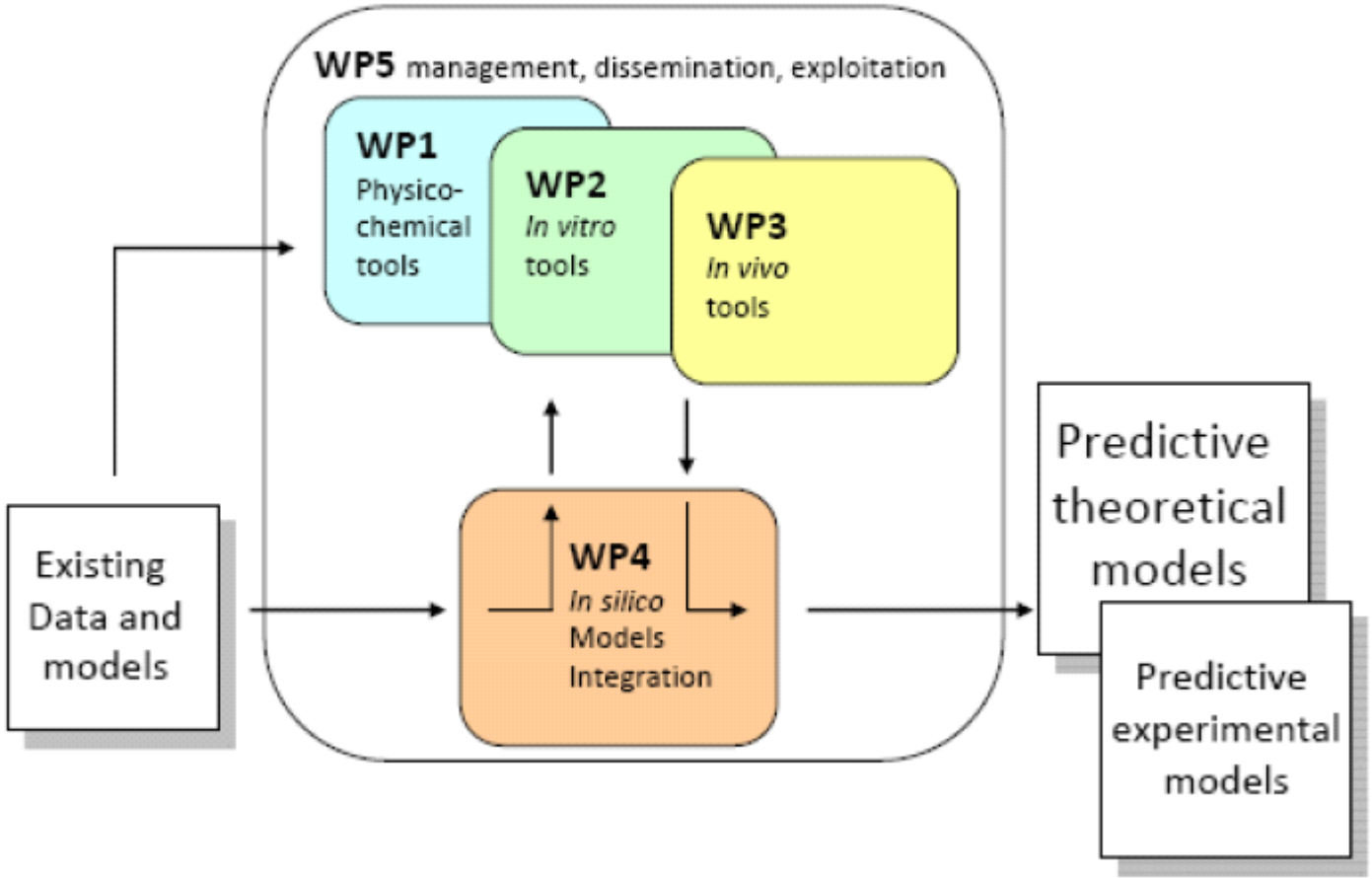
- **Uppsala University** *(Hans Lennernäs)*
- **Universiteit Leuven** *(Patrick Augustijns)*
- **University Mainz** *(Peter Langguth)*
- **Manchester University** *(Amin Rostami)*
- **University of Athens** *(Christos Reppas)*
- **Goethe University** *(Jennifer Dressman)*
- **Greifswald Univ.** *(Werner Weitshies)*
- **Copenhagen Univ.** *(Anette Müllertz)*
- **Strathclyde Univ.** *(Clive Wilson)*

Simcyp - TNO - Sirius Analytical - Simulations Plus
Medical Products Agency Sweden

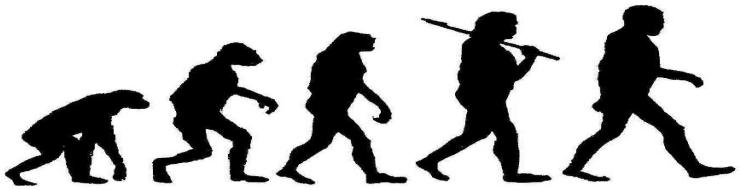
5 year project with 25 million Euro budget (half EU funding, half industry in-kind)

orbito
Innovative Tools for Oral Biopharmaceutics

Work package overview



Key areas in OrBiTo



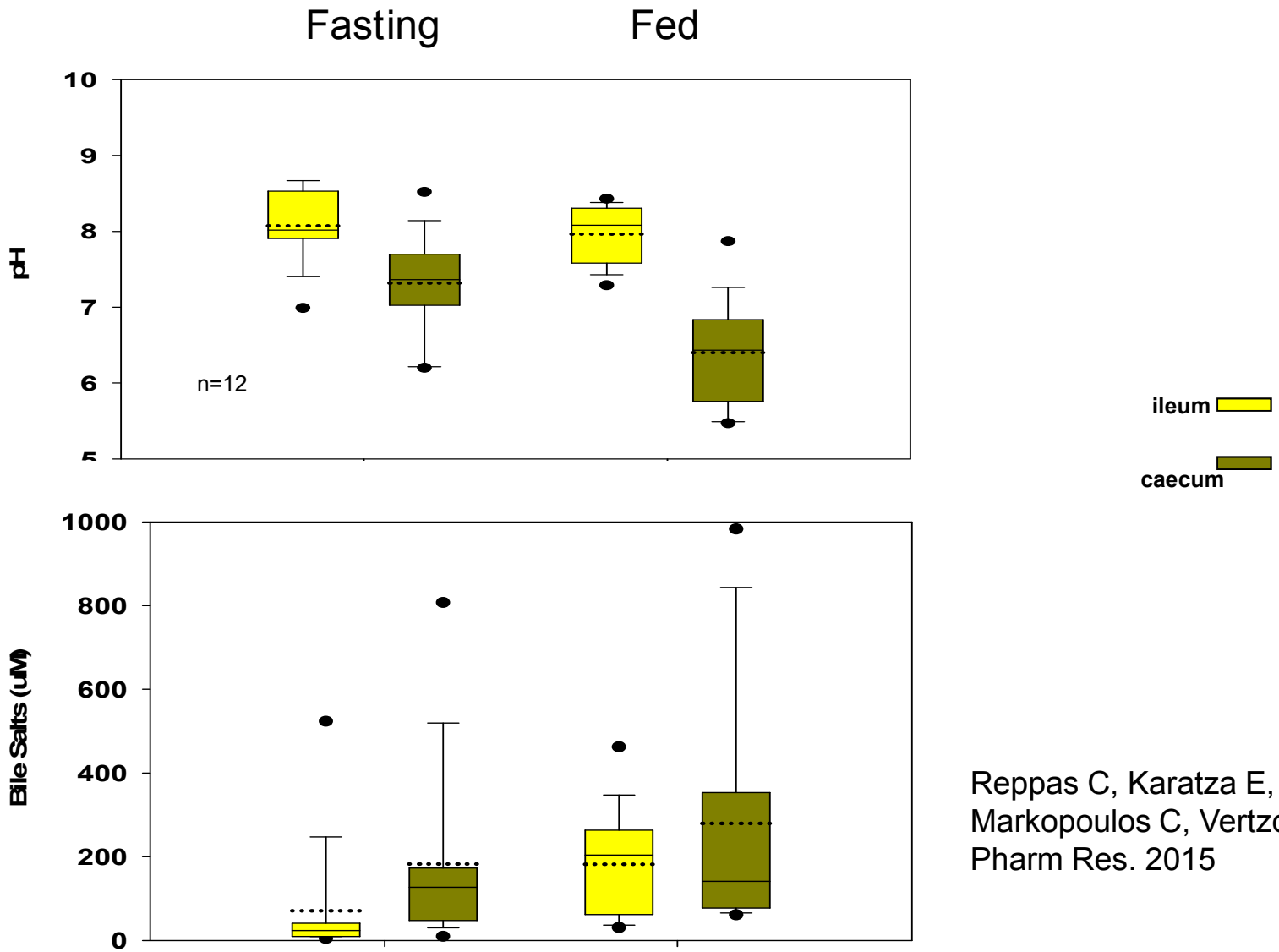
I. **Improve IPD methods and increase confidence in usage** by

- Enhance in vivo understanding
- Increase in vivo relevance by refining method design and settings
- Extensive validation to find ”domains” where predictions can be trusted
- Propose test strategies going from simple to advanced as needed

II. **Combine IPD with improved PKPB for absorption predictions**

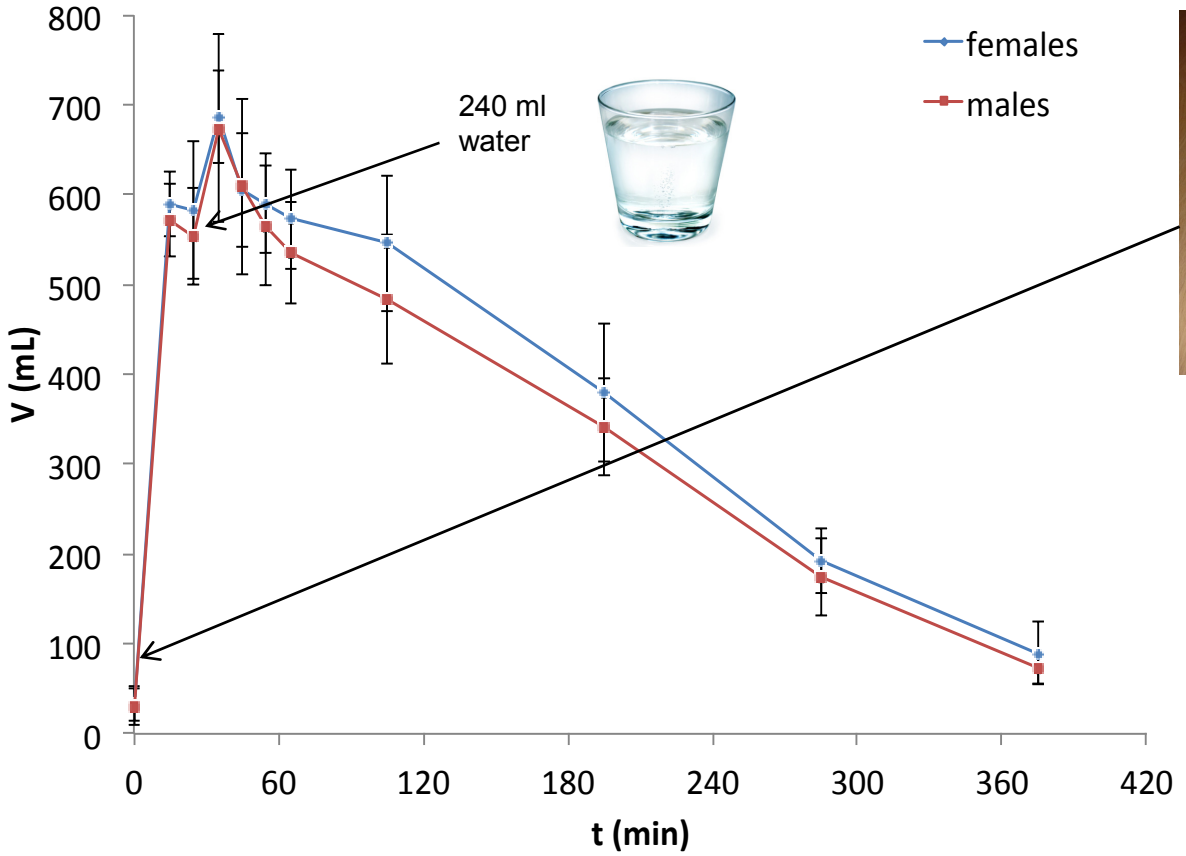
- Develop approaches for ”intelligent”integration of product in vitro dissolution data into PBPK
- Improve PBPPK algorithms, physiological settings, input data

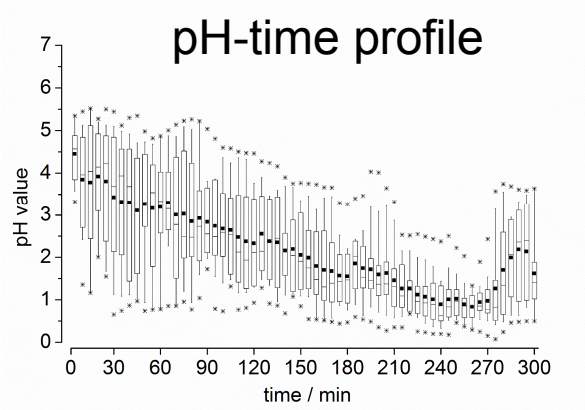
Characterisation of intestinal fluids from terminal ileum & caecum in healthy volunteers (n 12)



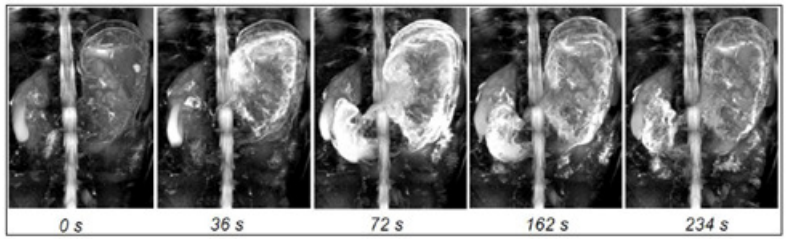
Reppas C, Karatza E, Goumas C, Markopoulos C, Vertzoni M. Pharm Res. 2015

Gastric volumes in healthy volunteers after FDA breakfast





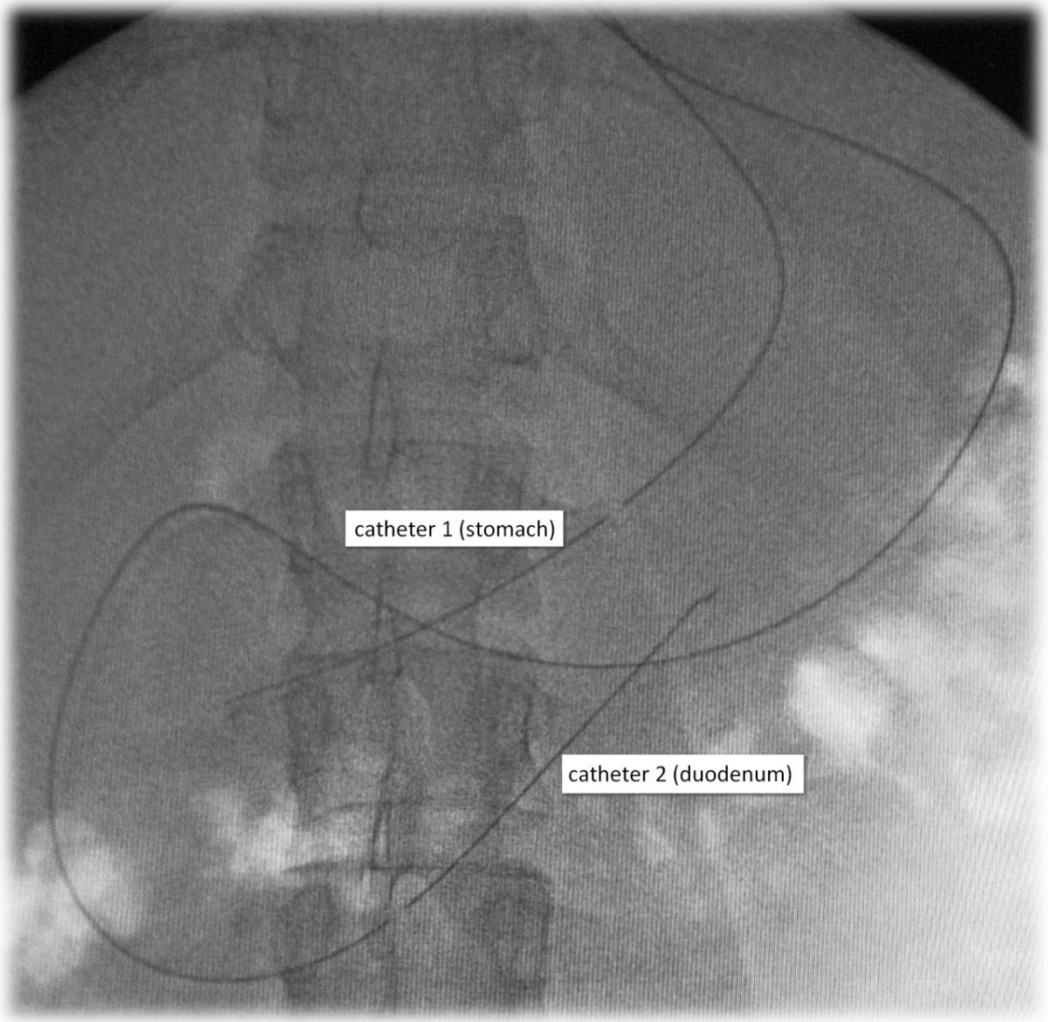
MRI images



Koziolek M, Grimm M, Garbacz G, Kühn JP, Weitschies W. Mol Pharm. 2014

Intraluminal drug sampling in humans

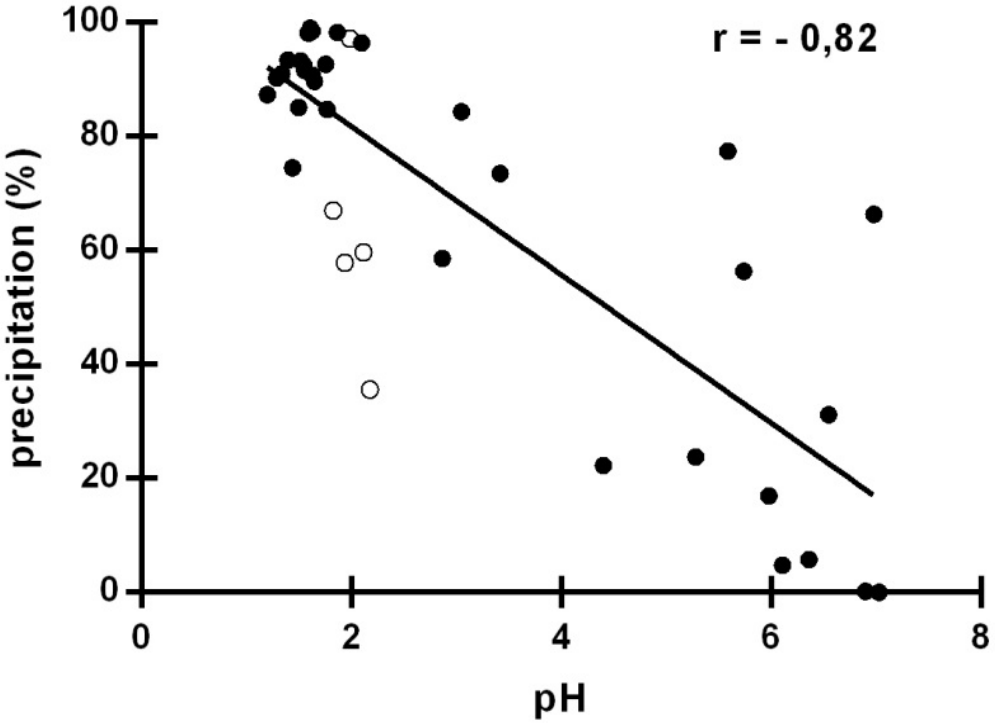
KU LEUVEN



- Posaconazole: intestinal supersaturation/precipitation
- Diclofenac: gastric supersaturation/precipitation
- Itraconazole: gastric and intestinal supersaturation/precipitation

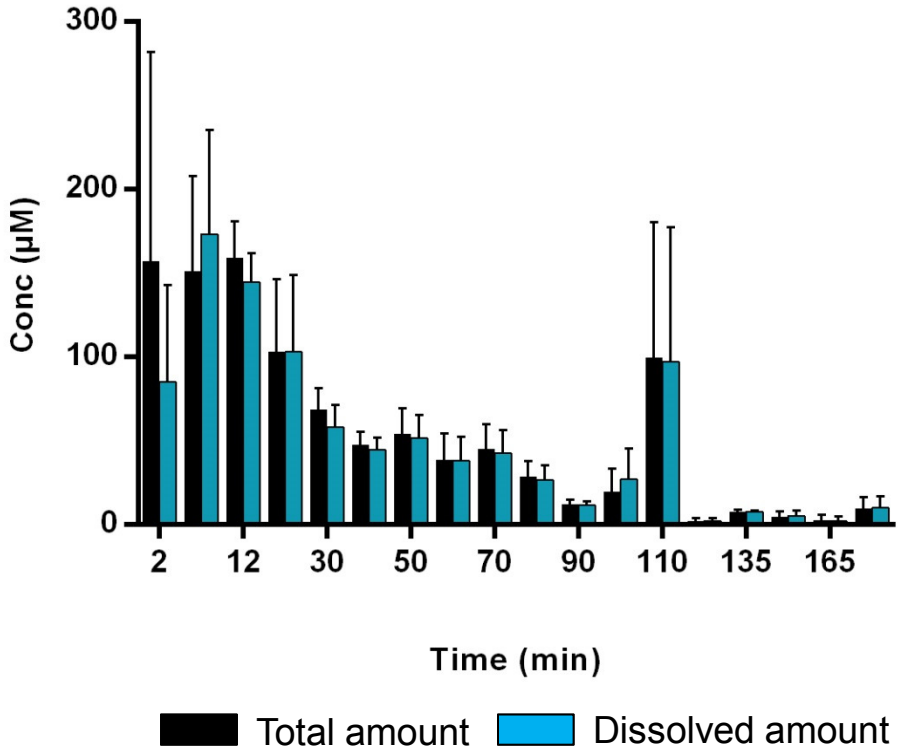
Gastric precipitation of diclofenac

Adminstration of diclofenak as water solution



Van Abeele J, Brouwers J, Mattheus R, Tack J, Augustijns P.J Pharm Sci. 2015

Redissolution of gastric precipitate in intestine

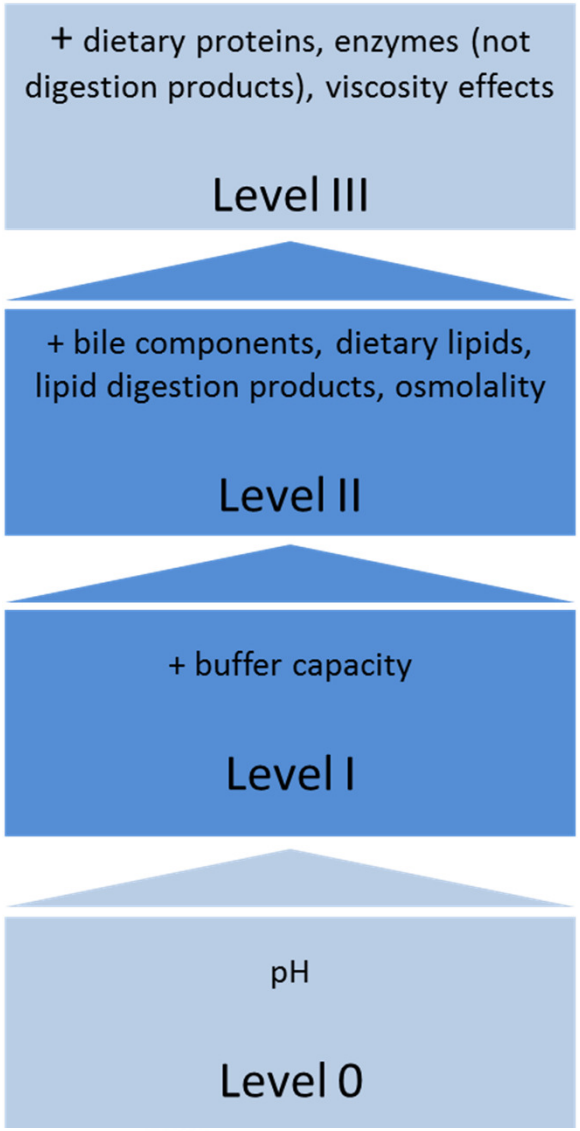


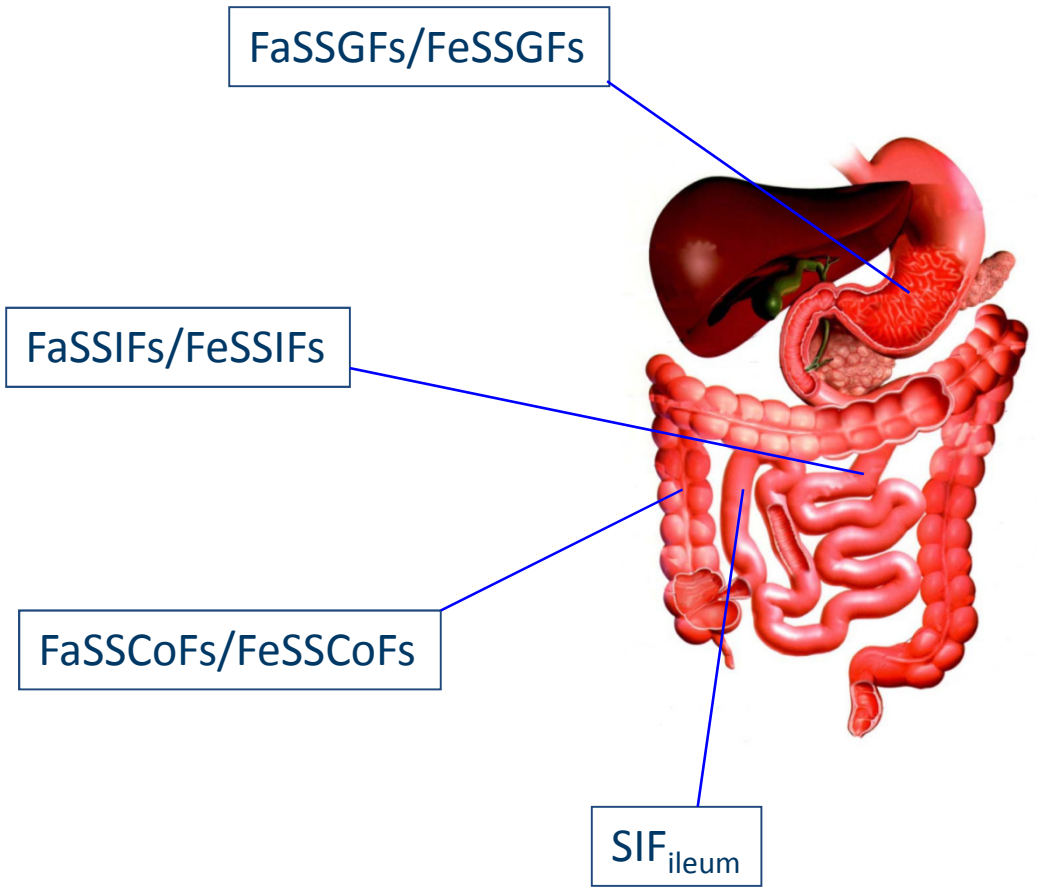
All diclofenac in solution in the duodenum (5 out of 5 volunteers)

Suggests rapid redissolution of gastric precipitate

Van Abeele J, Brouwers J, Mattheus R, Tack J, Augustijns P.J Pharm Sci. 2015

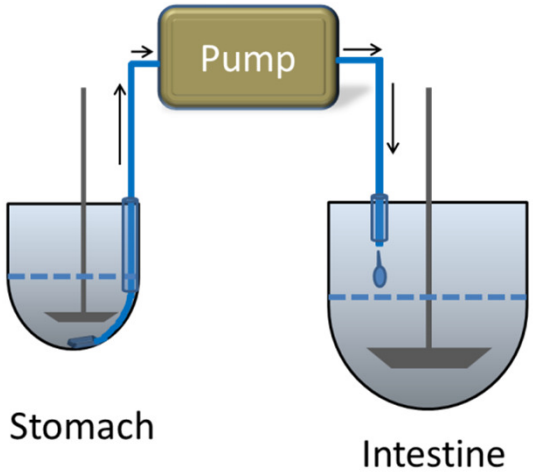
Levels of simulation of luminal composition – going from simple to complex

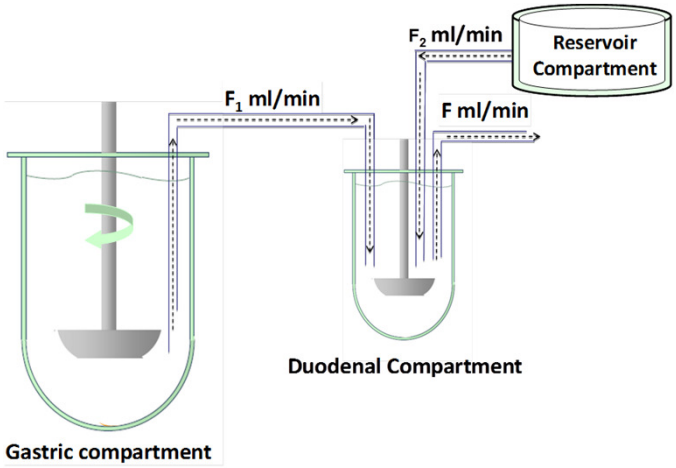


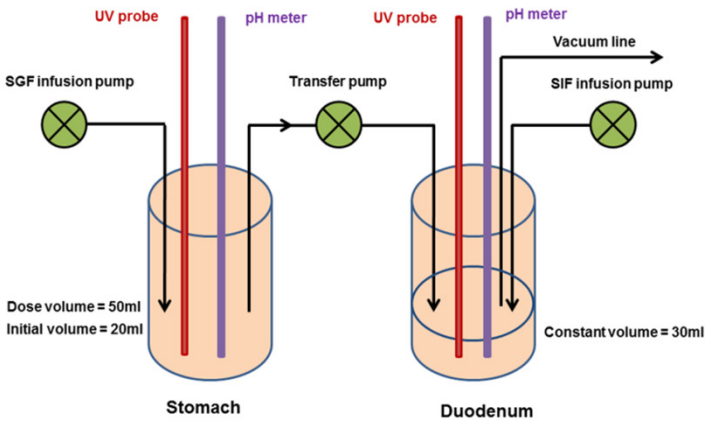


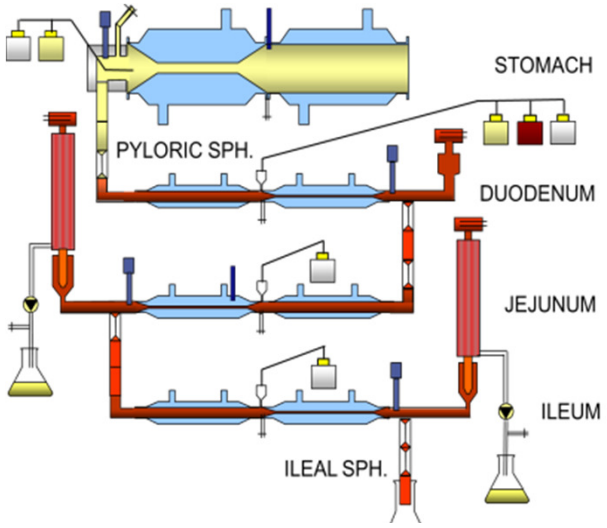
Markopoulos, Andreas et al. EJPB 93: 173-182(2015)
Khadra et al. EJPS 67:65-75 (2015)

In vitro methodologies for simulating GI transfer and predicting supersaturation, precipitation and concentrations in upper intestinal









Transfer model setup - UoAthens

M. Symillides
M. Vertzoni
C. Markopoulos
A. Kourentas

It is based on previous models (Psachoulias et al. 2012; Dimopoulou et al. 2015)

Shown to be useful in reproducing luminal concentrations of 2 weak bases and provide luminal data for additional 3 weak bases which are in line with previously collected plasma data

Why develop new?

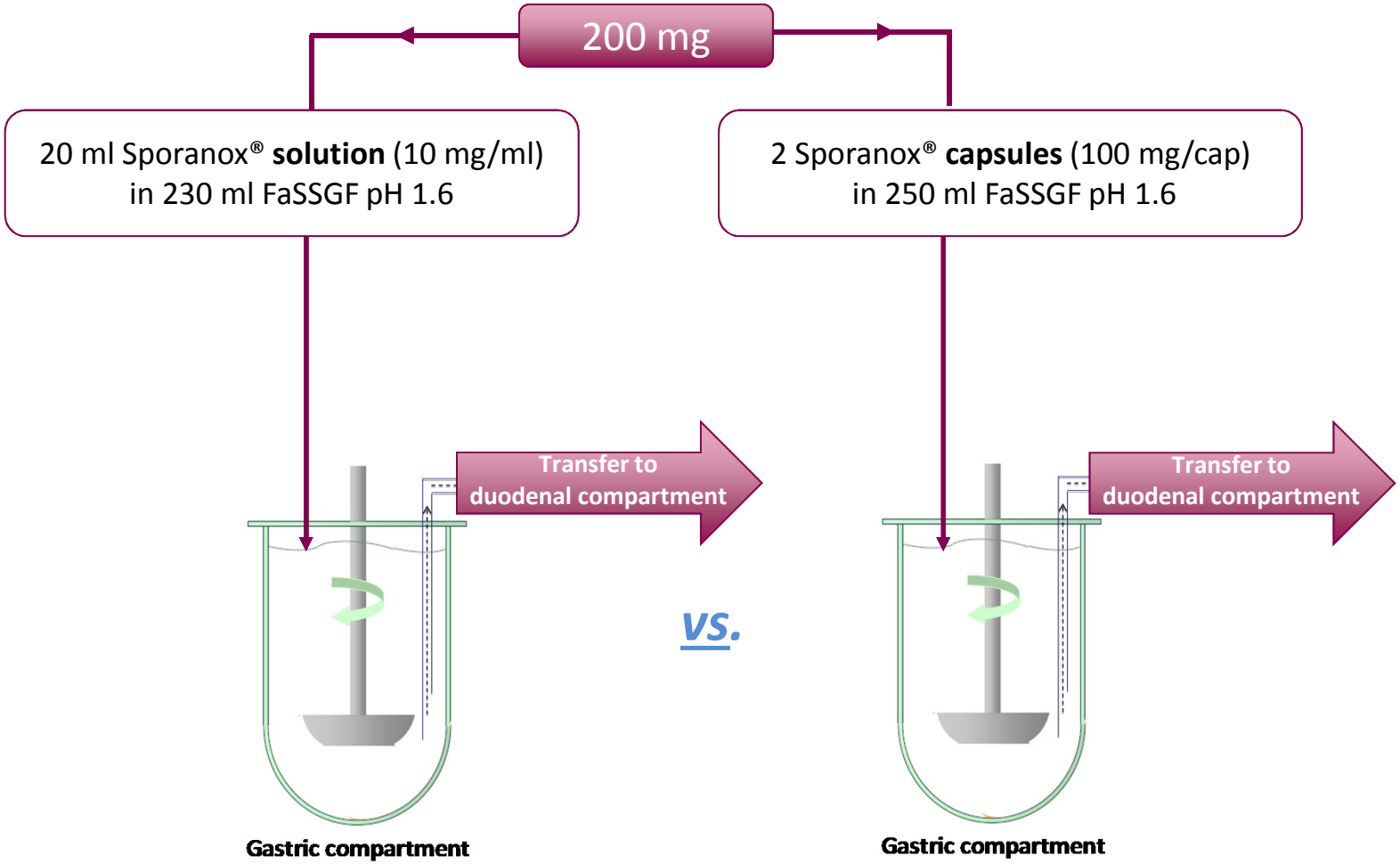
- In vitro conditions are based on volume of duodenal contents and input/output duodenal rates estimated, after modelling luminal data
- In vitro methodology complies with the continuous gastrointestinal transfer process in vivo
- Required equipment that is commercially available

How the new model is being evaluated?

- Direct comparison of *in vitro* with luminal data
- Investigate the importance of degree of simulation of gastric and duodenal composition

Itraconazole (Dose: 200 mg) solution *vs* capsule

M. Symillides
M. Vertzoni
C. Markopoulos
A. Kourentas



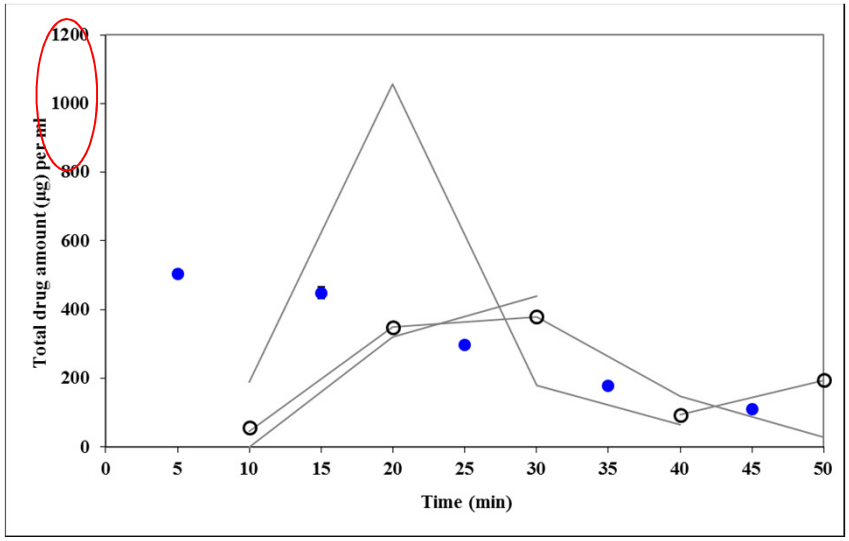
Itraconazole

Dose: 200 mg

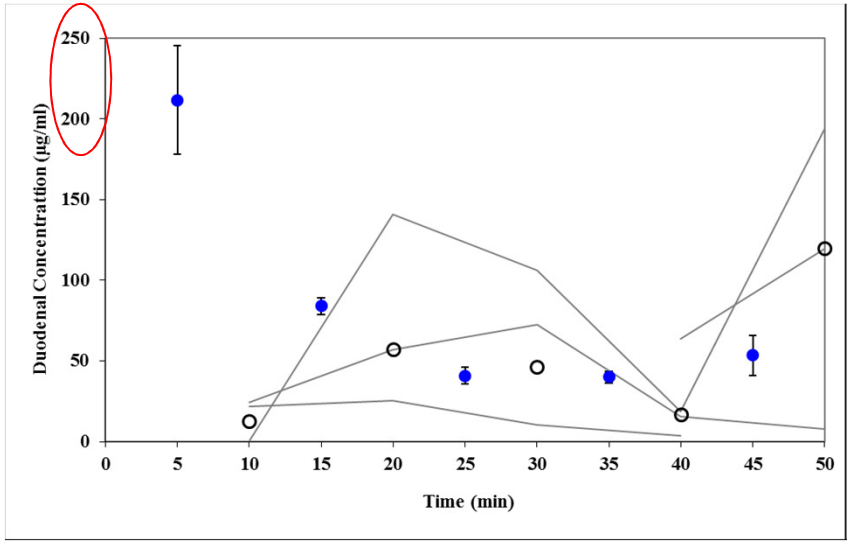
Sporanox® **Solution** 10 mg/ml

M. Symillides
M. Vertzoni
C. Markopoulos
A. Kourentas

Duodenal Total drug amount (solid and dissolved, µg) per ml



Duodenal Concentration (µg/ml)



Individual luminal data

Median luminal data

Mean±SD *in vitro* data

Satisfactory prediction of concentratrions/precipitation during the first hour post-dosing

Luminal data have been provided by KU Leuven

Systematic validation of existing and novel model systems using selected formulations with human PK data provided by industry partners
(Task 2.13)

Defining standardised testing protocols

WP3 input, pilot studies, industry input

Model reproducibility

Do we get similar results when the same model using the same conditions on the same formulation is run at different sites?

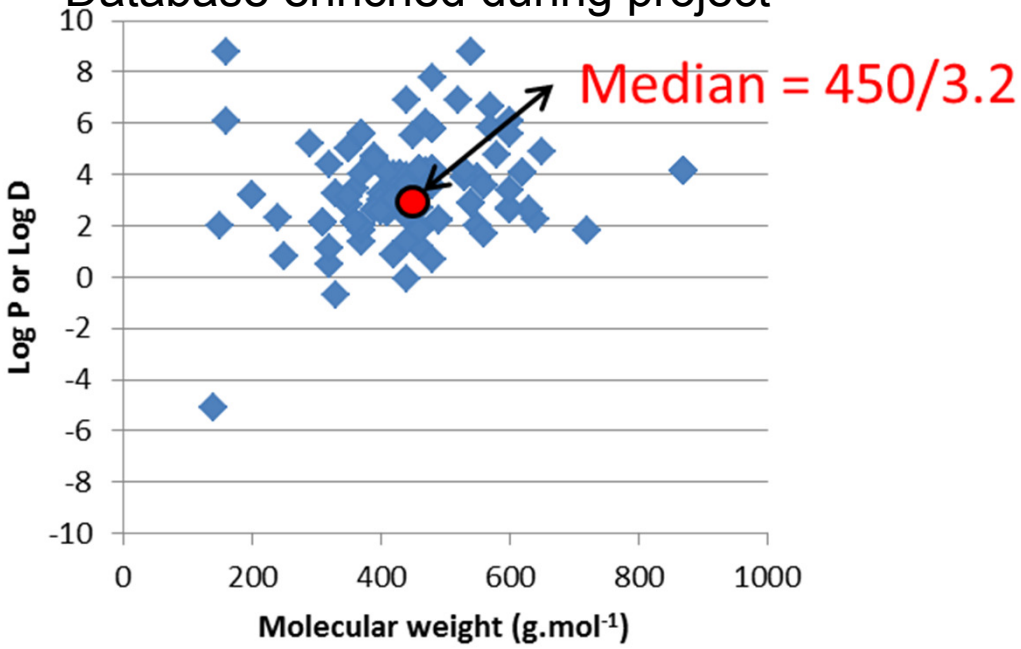
Test performance versus human data

How accurately does each model predict relative in-vivo perfor
a set of 3-6 suitable comparison examples?

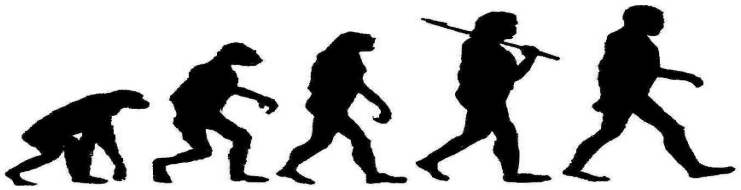
no correlation,
rank order,
quantitative when combined with PBPK,
directly quantitative

OrBiTo database

- A novel database with historical PK data for modern drugs from industry partners
- About 90 compounds and 600 formulations
- Also include biopharm drug&product characteristics and study design information
- Database enriched during project



Key areas



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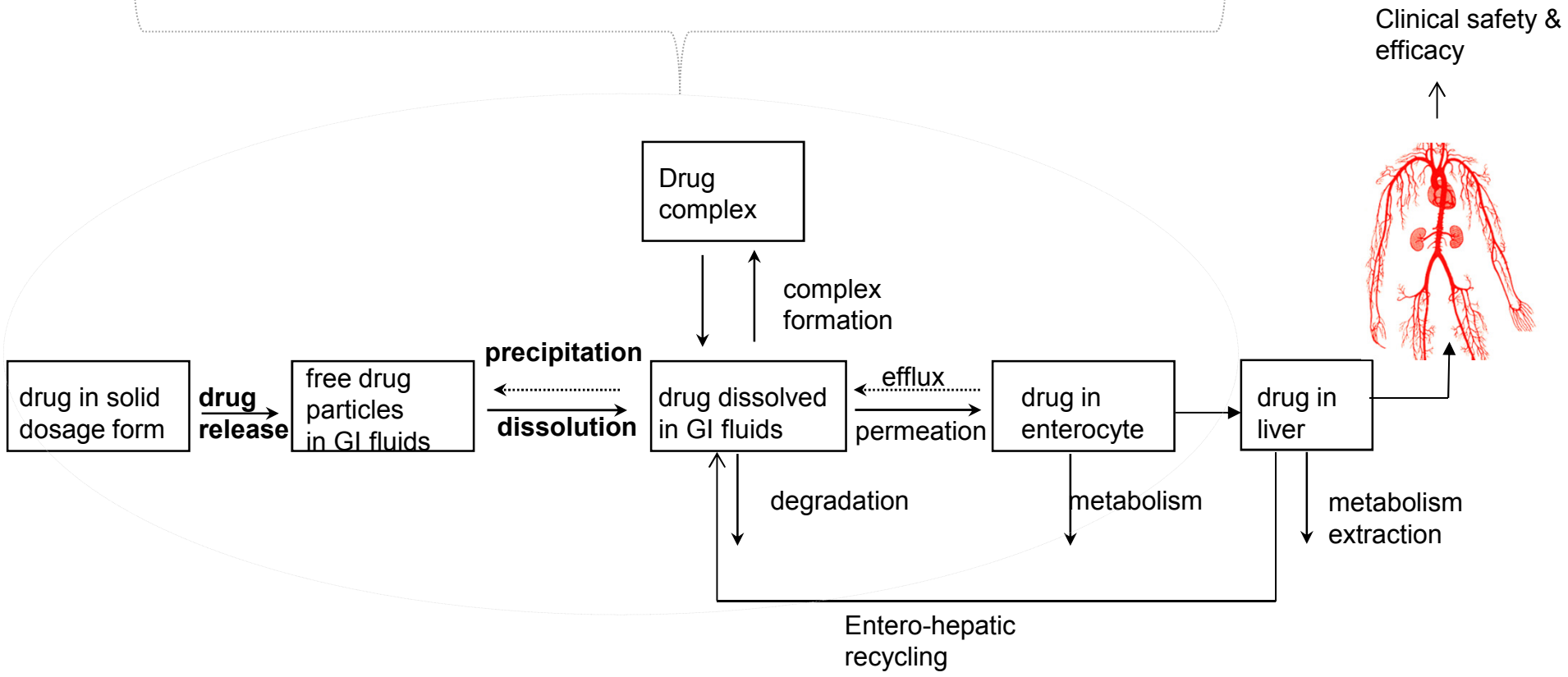
II. Combine IPD and PKPB for absorption predictions

- Develop approaches for ”intelligent”integration of product in vitro dissolution data into PBPK
- Improve PBPPK algorithms, physiological settings, input data quality and user expertise

Predicting drug absorption

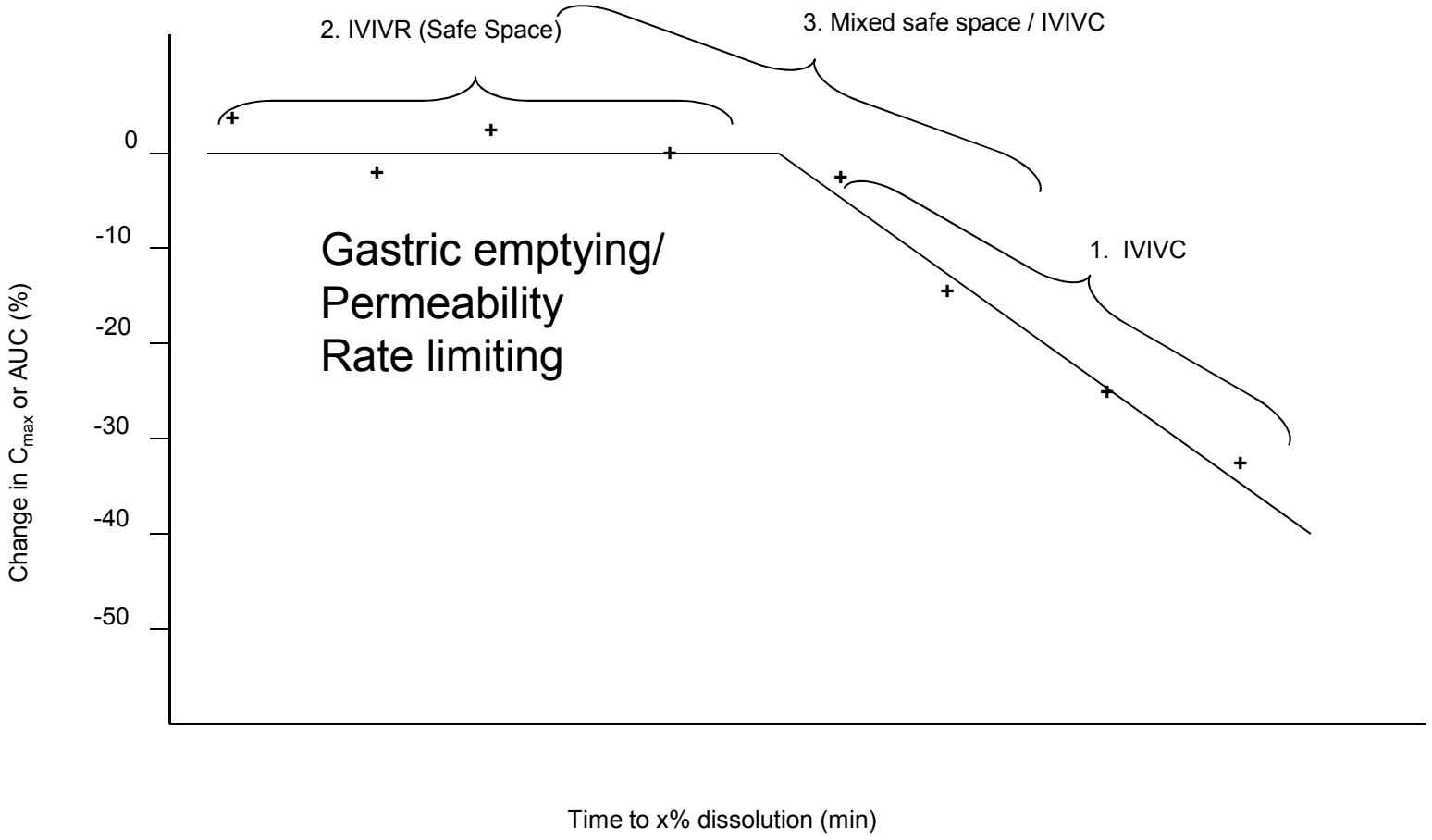
stomach ➡ duodenum ➡ jejunum ➡ ileum ➡ colon



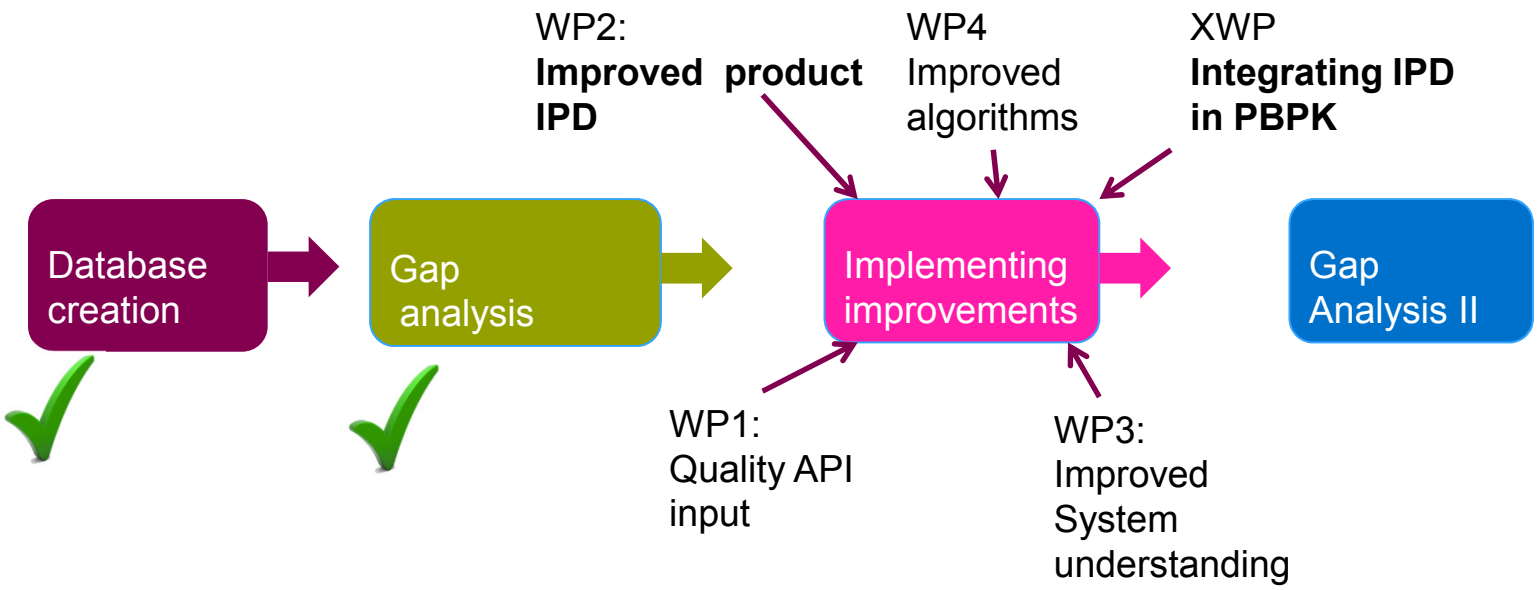
The effect of dissolution on absorption is modulated in an intricate manner by all other factors!

Innovative Medicines Initiative

Example relationship between dissolution and absorption

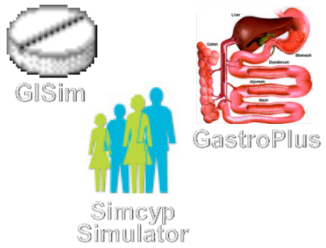


OrBiTo PBPK roadmap



PBPK gap analysis

T4.9 : “Bottom-up” anticipation of human PK
• Use of in vitro an in vivo preclinical information
• Actual PK profiles are blinded



- 43 APIs chosen for simulation task,
  - Over 165 Human Studies
  - Over 600 Human Study Arms
- Human Study Arms modelled
  - In 3 different softwares
  - by 15 different groups
- Modelled with overlap
  - 1 API chosen to be modelled by all groups
  - 9 additional to be modelled by 4 groups
  - Remaining APIs modelled by 1 group per software

T4.9 – Preliminary analysis

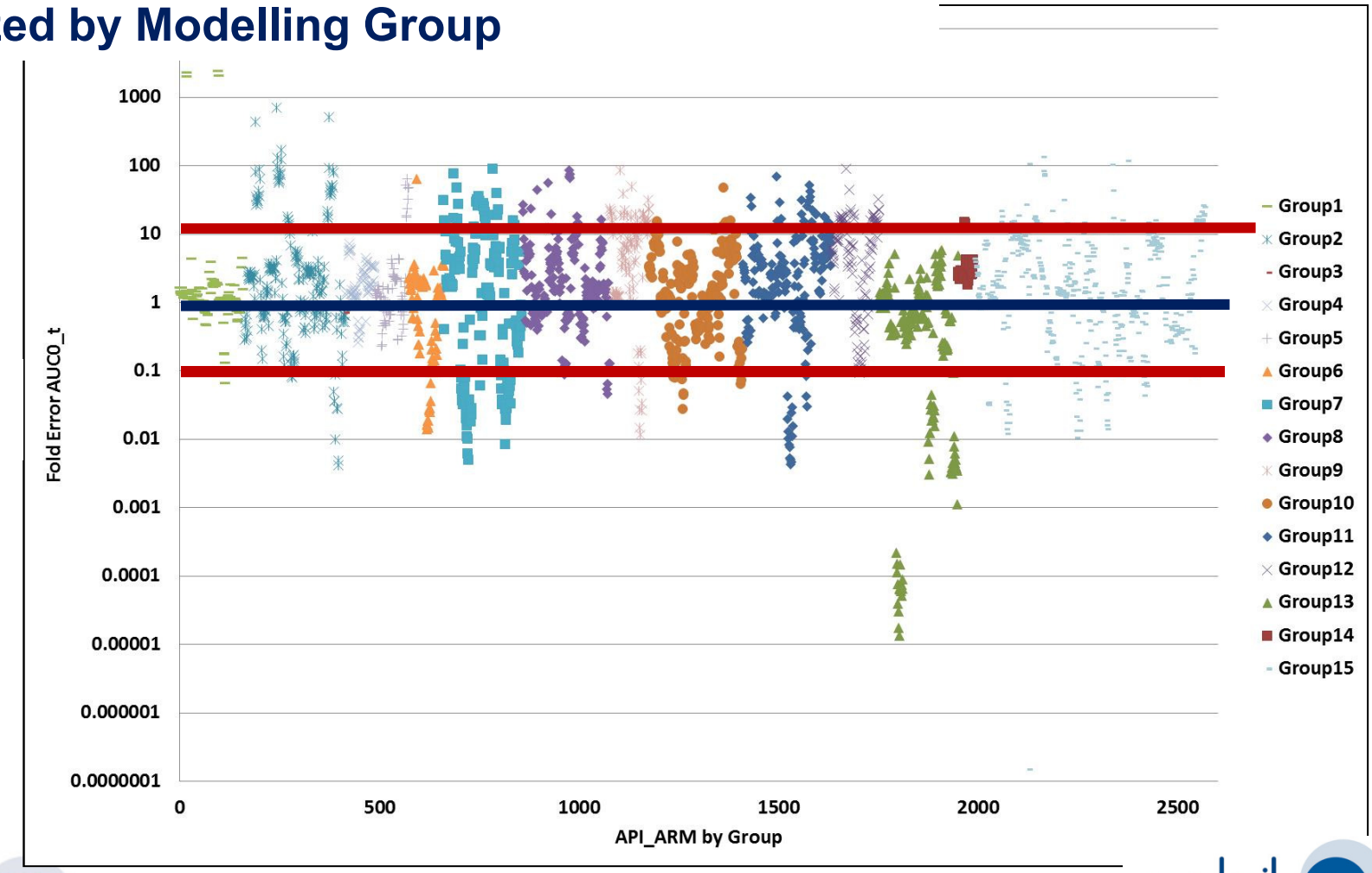
Fold error of AUClast predictions for all API simulations, organized by Modelling Group

10 – fold higher

1 – fold

10 – fold lower

Note!
Blinded bottom up



PBPK gap analysis – preliminary conclusions

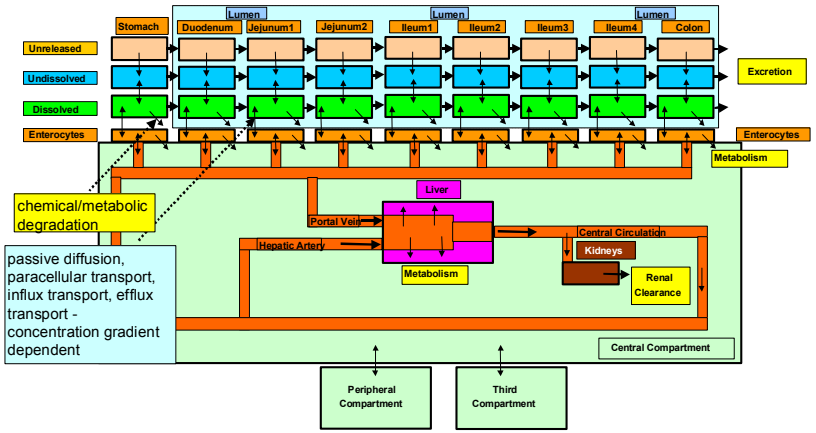
Room for improvements

- Solubility-limited compounds are challenging
  - Dissolution extent for BCS II is underestimated
  - Precipitation is not well anticipated for weak bases
- Formulation
  - Integration of *in vitro* release profiles could be improved
- Training of modellers & input data quality

5 manuscripts planned from gap analysis

PBPK based IVIVC – a logical next step in context of development and biowaivers

PBPK



Classic IVIVC

Based on physiological understanding modelling and first principle modelling

Take into account how other absorption factors influences effect of dissolution

Based on empirical mathematical models

Assumes dissolution proportional to absorption

Apply same criteria for validation prior to use for biowaivers

⇒ ***Greater confidence in IPD/PBPK based biowaivers***

⇒ ***Possibility for biowaivers for all type of products, not only controlled release***

PBPK based IVIVC already recognised in Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms, 2014

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 November 2014
EMA/CHMP/EWP/280/96
Committee for Medicinal Products for Human Use (CHMP)

Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms
(EMA/CPMP/EWP/280/96 Corr1)

Draft Agreed by Pharmacokinetics Working Party	October 2012
Adoption by CHMP for release for consultation	21 February 2013
End of consultation (deadline for comments)	15 September 2013
Agreed by Working Party	23 October 2014
Adoption by Committee	20 November 2014
Date for coming into effect	1 June 2015

This guideline replaces Guideline on Modified Release Oral and Transdermal Dosage Forms Section II (Pharmacokinetic and Clinical Evaluation (EMA/CPMP/EWP/280/96 Corr1)

Keywords	*Modified release, prolonged release, delayed release, transdermal drug delivery systems (TDDS), bioequivalence, pharmacokinetics, biowaiver, in vitro dissolution, generics, oral, intramuscular and subcutaneous*

Excerpt from 3. IVIVC development and validation

Two general categories of mathematical approaches to IVIVC modelling are one- and two-stage methods. The two-stage method is deconvolution-based. One stage approaches include convolution-based and differential equation-based methods and use of physiologically-based pharmacokinetic (PBPK) models.

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/11/WC500177884.pdf

Physiological based pharmacokinetic modelling (PBPK) in drug drug interaction guidelines

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

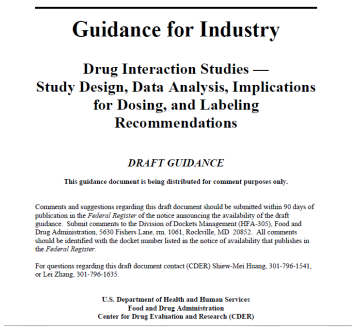
21 June 2012
CPMP/EWP/560/95/Rev. 1 Corr.*
Committee for Human Medicinal Products (CHMP)

Guideline on the Investigation of Drug Interactions

Final

Discussion in the Efficacy Working Party (EWP)	June/October 1996 February 1997
Transmission to the CPMP	March 1997
Transmission to interested parties	March 1997
Deadline for comments	September 1997
Re-submission to the EWP	December 1997
Approval by the CPMP	December 1997
Date for coming into operation	June 1998

PBPK simulations may be used to evaluate the *in vivo relevance of competitive or mechanism based* inhibition (MBI) observed *in vitro*



Guidance for Industry

Drug Interaction Studies — Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations

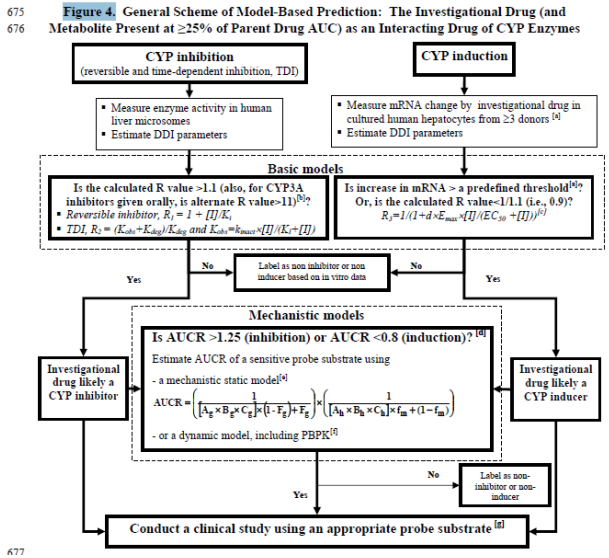
DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (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 (CDER) Shiew-Mei Huang, 301-796-1541, or Lei Zhang, 301-796-1635.

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



675 **Figure 4. General Scheme of Model-Based Prediction: The Investigational Drug (and**
676 **Metabolite Present at ≥25% of Parent Drug AUC) as an Interacting Drug of CYP Enzymes**

677

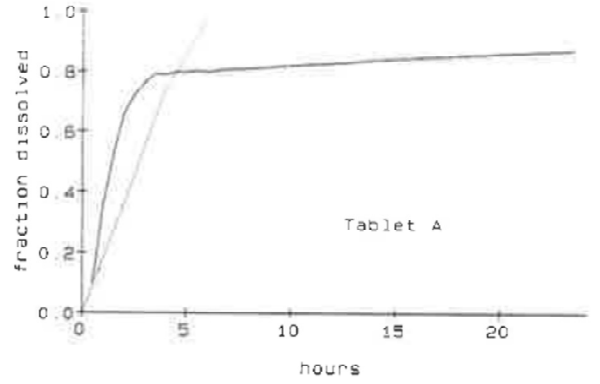
EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

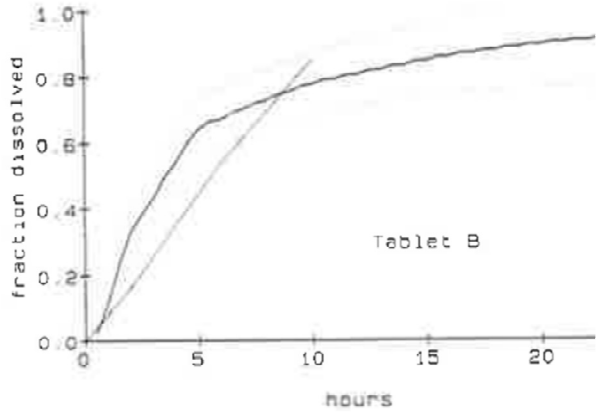
26 June 2014
EMA/CHMP/211243/2014
Committee for Medicinal Products for Human Use (CHMP)

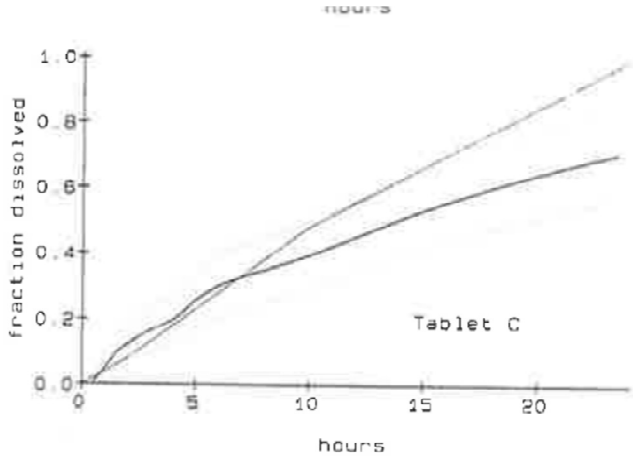
Concept paper on qualification and reporting of physiologically-based pharmacokinetic (PBPK) modelling and analyses

- Qualification of the model
- Version control of the software
- Support of its predictive performance of software
- Justification of assumptions made and impact on the results
- Justification of system parameters

Case example Biowaiver for BCS II drug, felodipine, as ER tablet for manufacturing site change part I







In vitro/in vivo dissolution

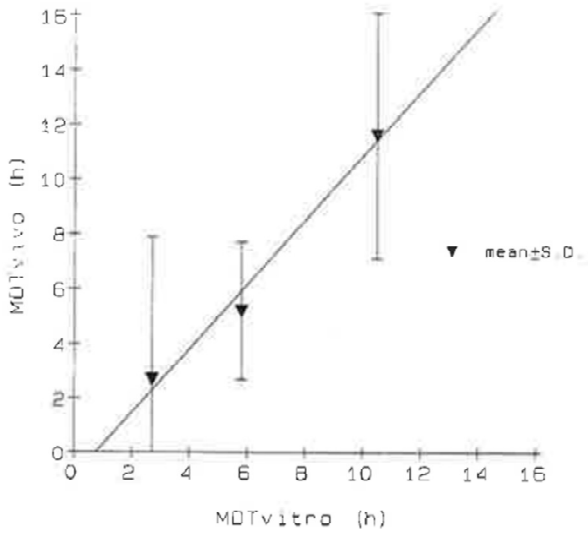


Fig. 3. Mean dissolution time in vivo (MDT_{vivo}) for felodipine ER tablets as a function of the mean dissolution time in vitro (MDT_{vitro}). The mean of the 16 individual regression lines was $Y = 1.17X - 0.86$ and the correlation coefficient was $r = 0.76 \pm 0.35$ (mean ± S.D.).

Level B correlation obtained by use of classical approach

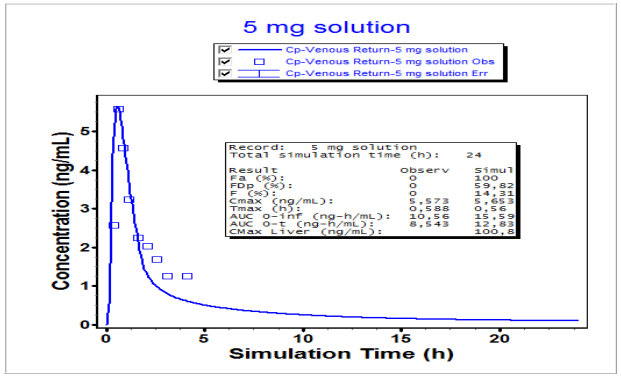
Wingstrand, Abrahamsson, Edgar Int J Pharm 1990

Case example Biowaiver for BCS II drug, felodipine, as ER tablet for manufacturing site change part II

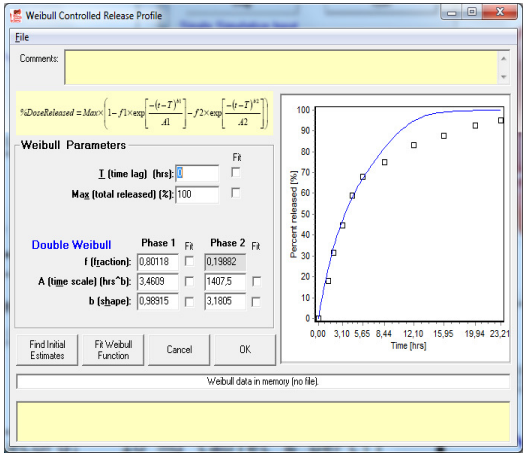
1. Input for basic model

- MW 384.3 g/mol, log P = 5.58[1], fu,p = 0.4%[2], B:P=0.7[2], Caco2 permeability scaled to 1.7 10^{-4}cm/s human jejunal Peff, aqueous solubility = 0.9-1.2 µg/mL, FaSSIF sol= 54.5 µg/mL. Vmax and Emax from human liver microsomes.

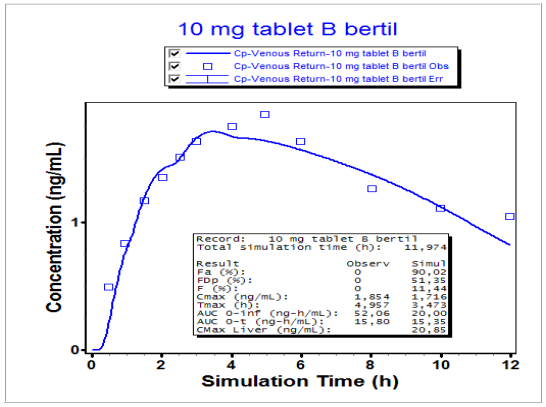
2. Validation vs oral solution



3. Fit ER tablet in vitro dissolution to Weibull function



4. Predict plasma profiles For ER tablets



5. Validation

Level A correlation suitable for biowaiver

Celine Ollier, Stephane Beilles, Xavier Pepin, Sanofi, Poster at OrBiTo/APGI meeting in Paris June 2015

Case example - Application of Absorption Modeling to Support Biowaiver for IR tablet of class II basic drug

RESULTS

Figure 1. Dissolution of etoricoxib tablets at three pH conditions

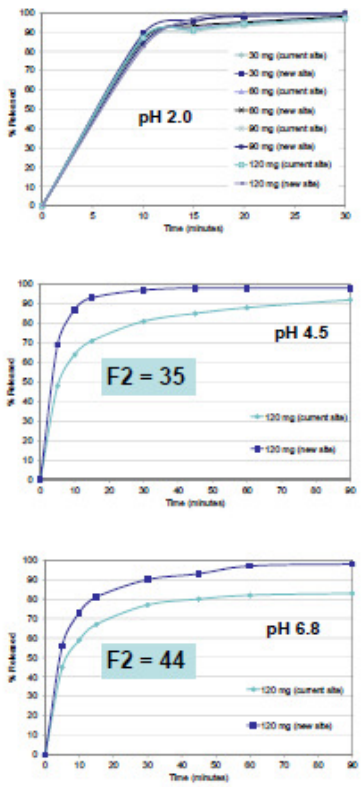


Figure 2. Predicted (line) vs observed (squares) PK profiles of 120 mg etoricoxib tablets for three clinical studies

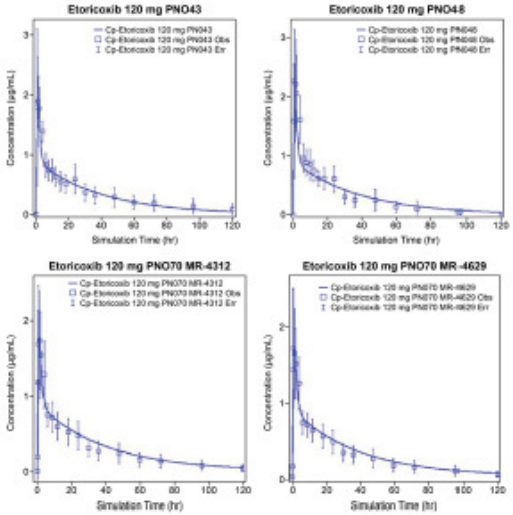


Figure 3. Predicted PK profiles of 30, 60, 90, and 120 mg etoricoxib tablets manufactured at current and new site

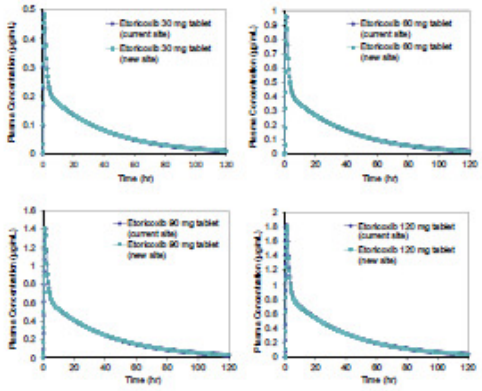


Table 1. Predicted $AUC_{0\text{-}120hr}$ and C_{max} from virtual trial simulation of 120 mg etoricoxib tablets manufactured at current and new site

	$AUC_{0\text{-}120\ hr}$ (%CV)	C_{max} (%CV)	Relative $AUC_{0\text{-}120\ hr}$	Relative C_{max}
120 mg (current site)	35.9 (15.8%)	1.81 (14.8%)	–	–
120 mg (new site)	37.1 (15.3%)	1.85 (14.4%)	1.03	1.02

Table 2. Bioequivalence study results and statistical analysis of the data comparing etoricoxib tablets manufactured at two sites at a dose of 120 mg

PK Parameters	Treatment A	Treatment B	Geometric Mean Ratio (A vs B)	90% Confidence Internal (A vs B)
$AUC_{0-\infty}$ (µg*hr/mL)	32.3 ± 13.1	32.1 ± 14.6	1.01	0.97, 1.06
C_{max} (µg/mL)	1.94 ± 0.47	1.98 ± 0.41	0.97	0.89, 1.06
T_{max} (hr)	1.25 (0.5-2.0)	1.00 (0.5-4.0)	–	–

Treatment A = tablets manufactured at the new site, Treatment B = tablets manufactured at the current site.
AUC and C_{max} reported as geometric mean ± SD; T_{max} reported as median with range.

SUMMARY: Dissolution testing at pH 4.5 and pH 6.8 media failed to show comparability of the tablets manufactured at the two sites, primarily due to poor aqueous solubility of etoricoxib at pH >3.0. However, simulations presented here demonstrate that dissolution in 0.01N HCl (pH 2) media is the most relevant to assess bioperformance of the etoricoxib tablets. Virtual trials conducted using the 0.01N HCl dissolution showed similarity in AUC and C_{max} for all tablet strengths for batches manufactured at the two manufacturing sites. These predicted results were verified in a definitive bioequivalence study. In cases such as etoricoxib, absorption modeling could be used to support a waiver of in vivo bioequivalence of different formulation batches.

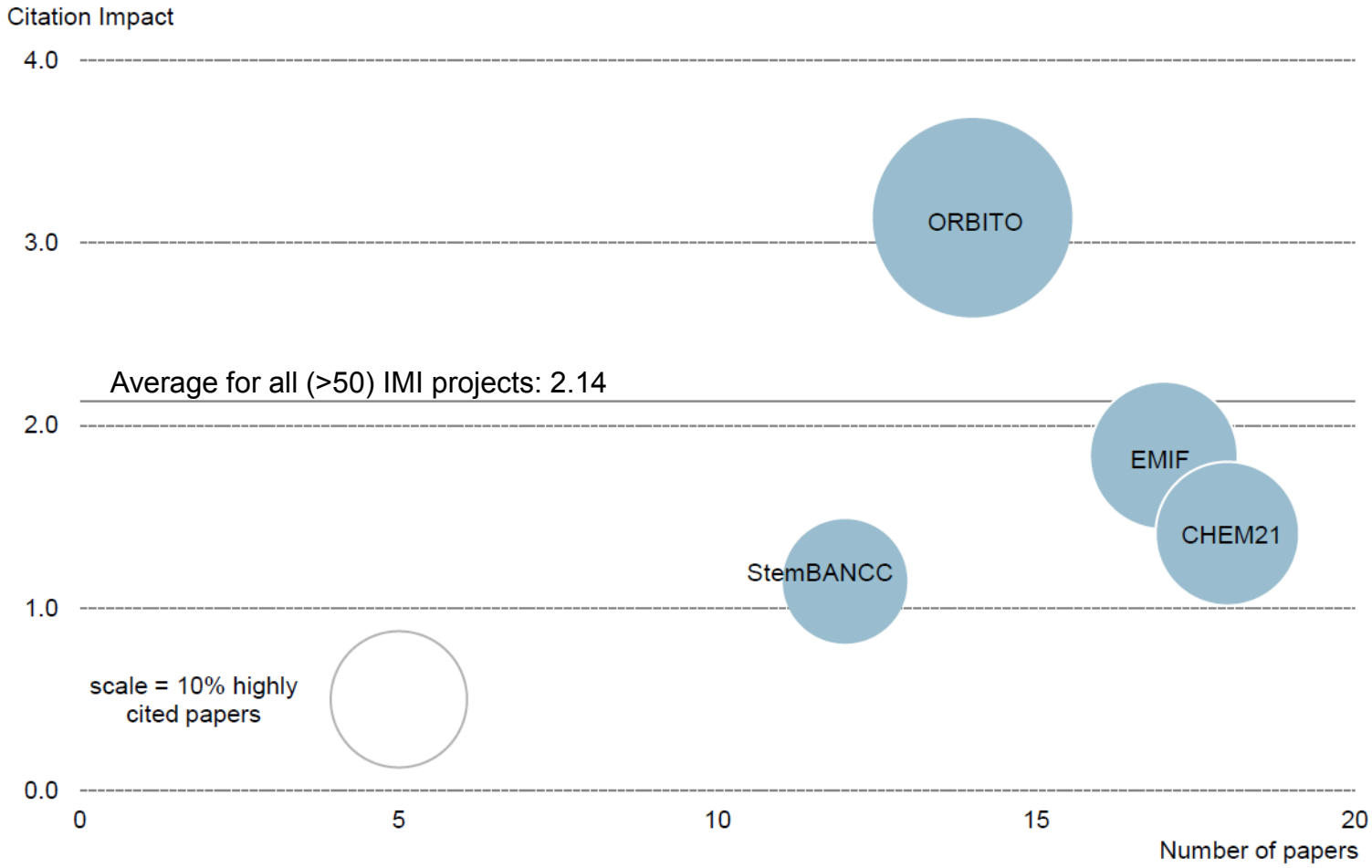
Amitava Mitra
Filippos Kesisoglou,
Merck US
Poster at
OrBiTo/APGI meeting
Paris, June 2015

AAPS PharmSciTech.
2015

Much more results on OrBiTo web site

>20 publicatíons

AVERAGE CITATION IMPACT AND SHARE OF HIGHLY-CITED RESEARCH FOR IMI PROJECTS – CALL 4, 2009-2014



Predictive oral biopharmaceutics tools as provided by OrBiTo project gathers significant interest!

IMI biobliometric analysis, 6th report June 2015
www.imi.europa.eu/sites/default/files/uploads/documents/BibliometricReports/IMI_bibliometric_report_2015.pdf

Conclusions

Progress in vivo predictive dissolution combined with PBPK provides an opportunity for taking a major new step in model based drug development and documentation (eg biowaivers)

Next step – IPD/PBPK based IVIVCs

Long term – extended space where predictive tools can be used without in vivo correlation (extend use BCS)

OrBito hopefully contribute to this progress