CRDS Webinar 18 May 2021

Absorption PBPK models in regulatory applications: The EMA experience

Aris Dokoumetzidis
Associate Professor, Pharmacy Department, University of Athens
Member of MSWP of EMA

Disclaimer:
The opinions in this talk are mine and I am not representing EMA or MSWP
I am an academic member of MSWP (external expert) not an employee of EMA or any other National Regulatory Authority

Overview

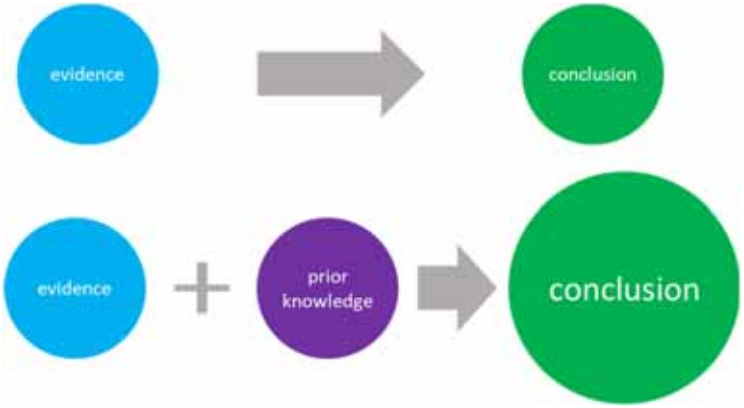
- PBPK models and applications
- The EMA guideline on PBPK
- Case study A: PBPK for IVIVC
- Case study B: PBPK for VBE
- Steps to advance uptake of PBPK in regulatory setting

Why use mathematical models?

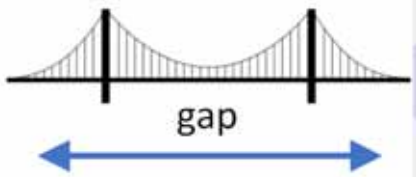
Applications of M&S is Drug Development are increasing in the context of Pharmacokinetics and Pharmacidynamics

A. Quantifying high dimensional systems D>2 (complexity)
   - In **1-D** it is easy to measure something and use it
   - In **high dimensions** must be quantified by mathematical models

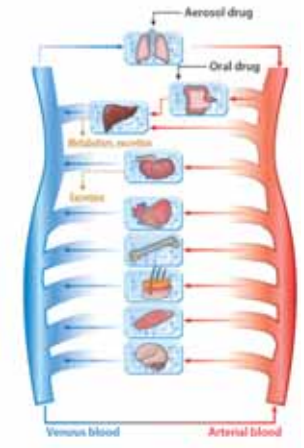
B. Introducing assumptions / prior knowledge
   - Assume something we know to learn from data something we don't

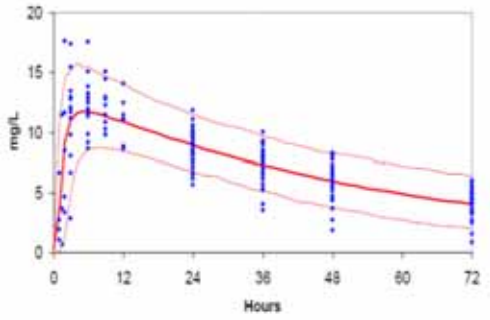


What kind of mathematical models are used?

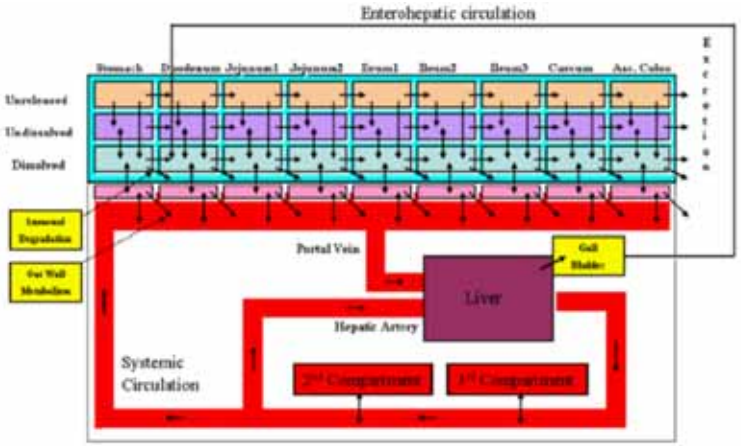
Empirical		Mechanistic
• PopPK / PKPD		• PBPK / QSP
Top-down / Data driven	VS	Bottom-up / Knowledge driven
Regression		Simulation
Fewer assumptions		More assumptions
Good for interpolation		Good for extrapolation
Clinical		Preclinical

Mechanistic PBPK models: In vitro in vivo extrapolation





- Complex compartmental models with anatomical and physiological representation of entire body
- Integration of physicochemical properties of API, in vitro data, and the physiology
- Detailed submodels for GI, Liver, Brain, Lung, and other organs or tissues of interest such as tumours
- Implementation: Home made models and Platforms
- Active research particularly to characterise variability



Applications of PBPK

- Preclinical to clinical
- Drug Drug interactions
- First dose in man
- Paediatric extrapolation
- Special populations (obese, pregnant, etc)
- Tissue PK, e.g. organs or tumours
- Toxicokinetics
- Candidate selection with high throughput PBPK
- **Absorption (mostly oral, but other routes of administration)**
  Physiologically Based Biopharmaceutics Models (PBBM)

- Closely linked to its PD counterpart: Quantitative Systems Pharmacology

Quality by Design

- Drug product quality cannot be tested into drug products but should be built into drug products by design

- QbD Studies critical quality attributes and creates a **Design Space**

- **Quality attributes include:**

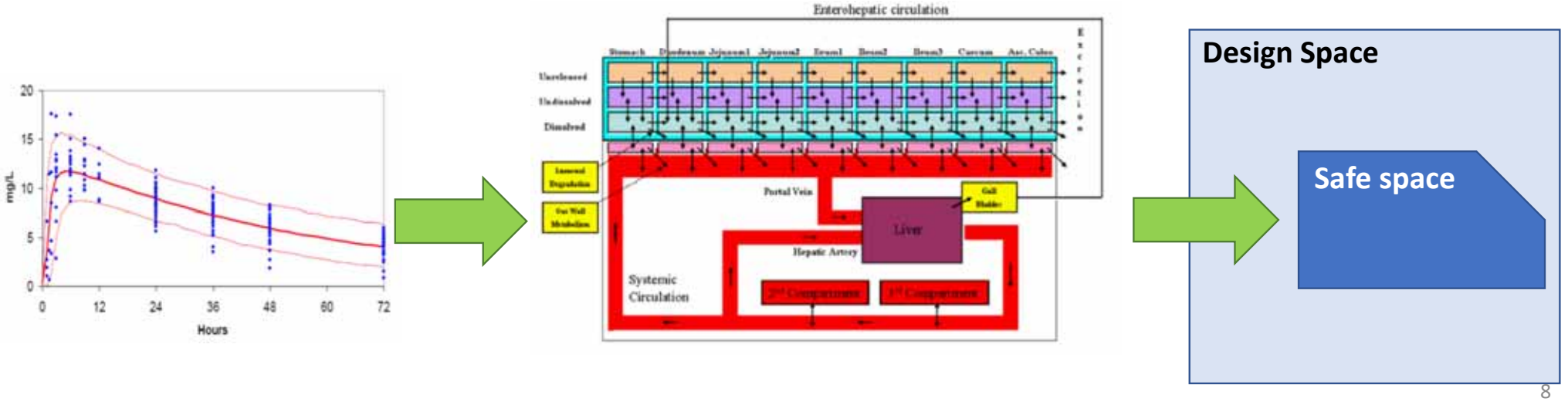
➢ Drug substance attributes : particle size distribution, physical form, etc
➢ Excipient quality attributes: type / level of release rate controlling excipient
➢ In-process quality attributes: granule particle size, coating weight gain
➢ Finished drug product attributes: disintegration
➢ Manufacturing process parameters: coating parameters, compression force.

- How is Design Space mapped to clinical performance ?

- Clinically relevant in vitro specifications

Role of PBPK in Quality

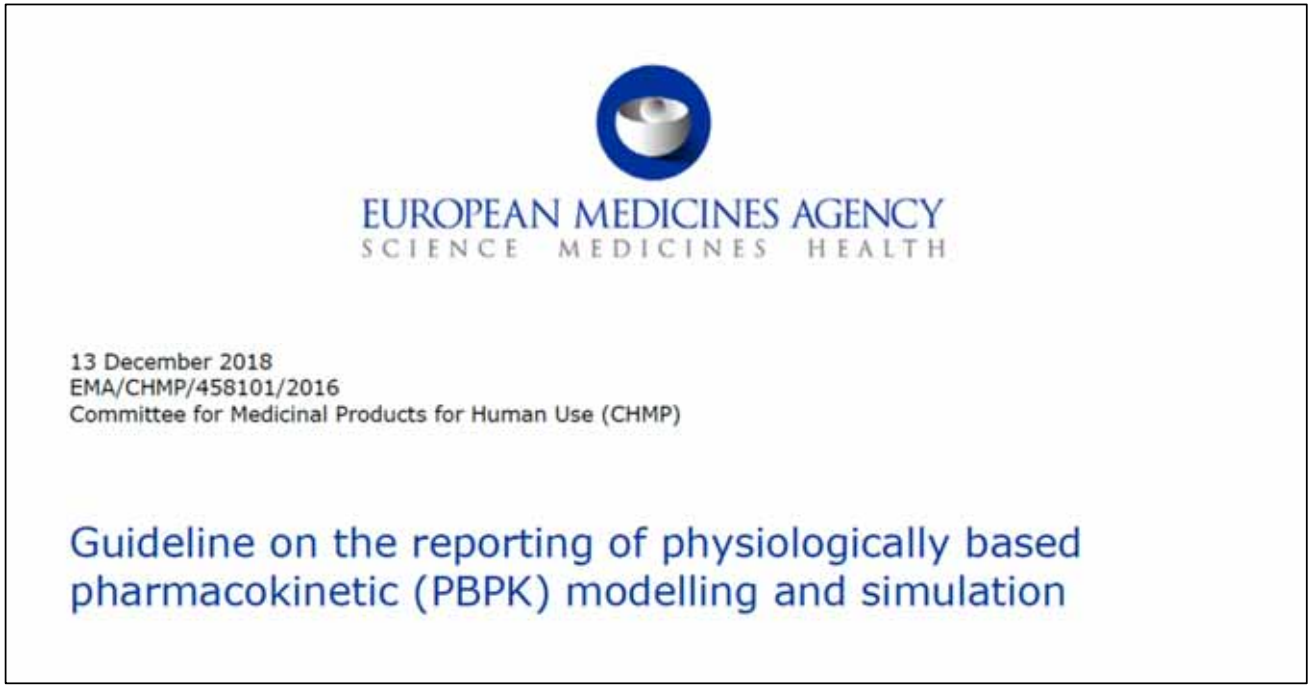
- Multiple clinical studies to explore Design Space, not feasible
- PBPK can explore Design Space in silico to define a Safe Space
- **Safe space:** *the boundaries defined by in vitro specifications, within which drug product variants are anticipated to be bioequivalent to one another*
- How the clinical boundaries (BE limits) translate back to the in vitro specs
- Parameter Sensitivity Analysis / Virtual Bioequivalence studies



Regulatory questions addressed by Absorption PBPK models

- Mechanistic IVIVC
- Virtual BE for waiving clinical studies
- Bridge between formulations
- Develop clinically relevant in vitro specifications – Safe Space

The EMA guideline on PBPK



"Qualification of the PBPK platform for the intended purpose"

Concept of model qualification was introduced :

Basically means that sufficient evidence needs to be provided demonstrating that the model is capable of simulating what it is supposed to (same concept in recent FDA guidance is referred to as validation)

…For the Intended purpose (or CoU, context of use)

The same model depending on the scope may need different qualification.

Verification is different to Qualification but a prerequisite
Correctness of the mathematical form of the model and its implementation
Mostly applicable to home-made models not platforms
Platforms provide some assurance that are verified (added value)

What does it take to qualify a PBPK model?

Depends on the impact.

High : e.g. Replace or waive studies
Medium: e.g. Design studies
Low: Have a supportive role without making decisions

In **high impact** submissions and in the **absence of clinical data** for the product:

Similar, predictive exercises of other examples should be provided to show that the approach works.

How many other examples? Guidance says 8 – 10.

PBPK guidance is general enough but is oriented towards DDI because this is the majority of submissions

However one of the examples refers to Absorption

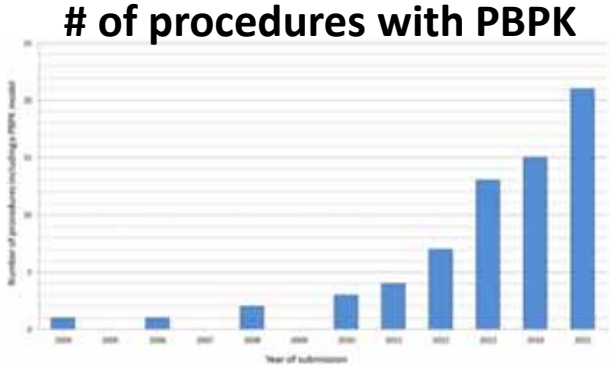
Example 4: Biopharmaceutical application- particle size specification

To qualify a model for biopharmaceutical applications e.g. to define product specifications for particle size in the absence of any clinical data, it should be demonstrated that the effect of particle size versus dissolution and PK exposure (AUC and C_{max}) is captured by the model for a number of drugs with similar physicochemical and biopharmaceutical properties and over a similar range of particle sizes.

Qualification sounds very demanding and may deter applicants
But it is necessary because combines high impact and extrapolation with no clinical data

Submissions to EMA with PBPK

- Number of submissions with PBPK models is rising
- Majority of submissions (64%) has been about DDI (Luzon et al 2016 CPT)



Luzon et al 2016 CPT

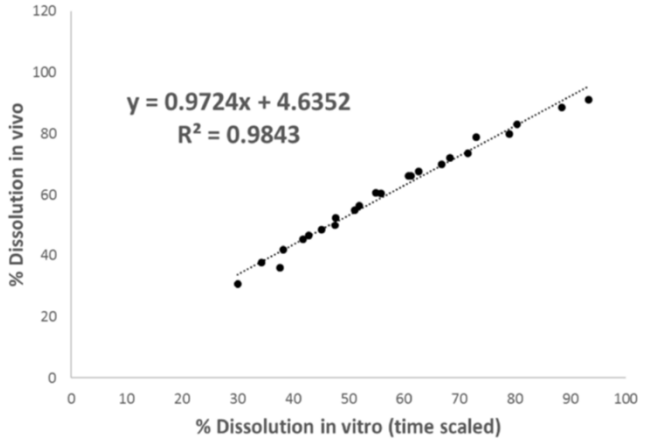
- With help of two colleagues from EMA:
  Evangelos Kotzagiorgis and Efthymios Manolis
  5 products with PBPK on quality related questions identified
  Recent applications mostly from 2019/20 apart from one from 2017

- **Product A:** PBPK for IVIVC
- **Product B:** Virtual BE to waive clinical studies
- Product C: PBPK for clinically relevant specifications
- Product D: PBPK for solubility and precipitation
- Product E: PBPK for paediatric formulation bridging

Product A: PBPK for IVIVC

Scientific Advice for development a **level A IVIVC** for a MR, BCS 2, Narrow TI drug, suitable for biowaivers for post-approval variations, changing manufacturing site

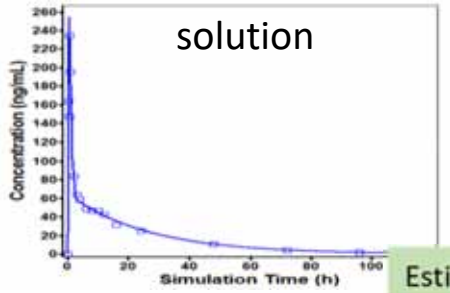
IVIVC developed following the guideline with use of PBPK model



- Descriptive dissolution method (fast / medium / slow)
- Deconvolution with administration of solution **(PBPK)**
- Time scaling with Levi plot
- Establish level A IVIVC
- Cross validation (check if every combination of 2 predicts 3rd)
- Apply IVIVC to waive studies for changing manufacturing site by comparing dissolution profiles by f2 similarity.
- No dissolution comparison needed for lower strengths

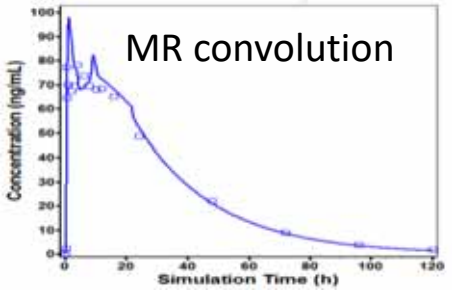
Role of PBPK model to establish of IVIVC was:

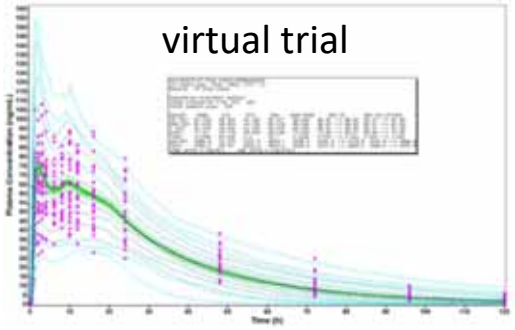
- Estimate 2-comp mode PK parameters for all subjects from solution formulation
- Deconvolute in vivo dissolution profiles for three MR formulations (Fast, Target, and Slow) from individual PK data in the study
- Convolute individual plasma concentration-time profiles for the three MR Formulations
- Simulate “virtual trial” to determine lower and upper in vitro dissolution limits

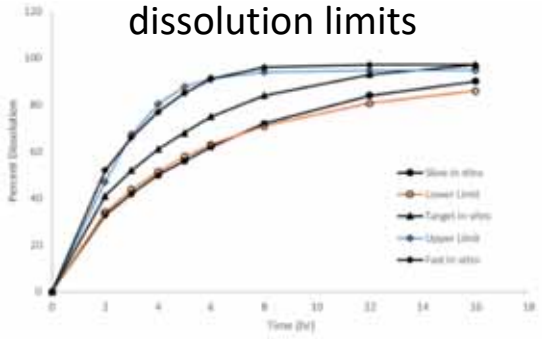


Estimate Weibull parameters

Subject	Max	A	b
1	51.467	3.7926	0.7838
2	100	3.9812	0.6007
3	100	3.2134	0.4622







SA question (the one related to PBPK):

Does the Agency agree that the approach employed to establish the Level A IVIVC, which used PBPK modelling, commercial **** software and cross-validation evaluation for external predictability, is appropriate to support its approval in the proposed MAA?

Assessment by EMA for PBPK model

- Cmax is underpredicted (Drug is Narrow TI, avoid high Cmax is the reason for developing MR).
- Encouraged to make more use of the model and use VBE dissolution limits

Assessment of other IVIVC aspects not about the PBPK model

- Dissolution test robustness assessment not considered adequate
- Concerns about the cross-validation methodology (good only as a minimal validation)
- Justification for using Weibull function instead of dissolution data is needed
- f2 as similarity factor to change sites not agreed, instead stricter limits based on VBE
- Proposal to waive comparative dissolution of lower strengths was not agreed (not proportional)

Conclusions for product A

- Despite issues with the IVIVC no major concerns about the PBPK model itself were raised
- No mentioning about further qualification
- IVIVC is in our comfort zone, data from the actual product are available
- Application of PBPK in IVIVC, not extrapolation, not proper mechanistic IVIVC
- Generally positive assessment

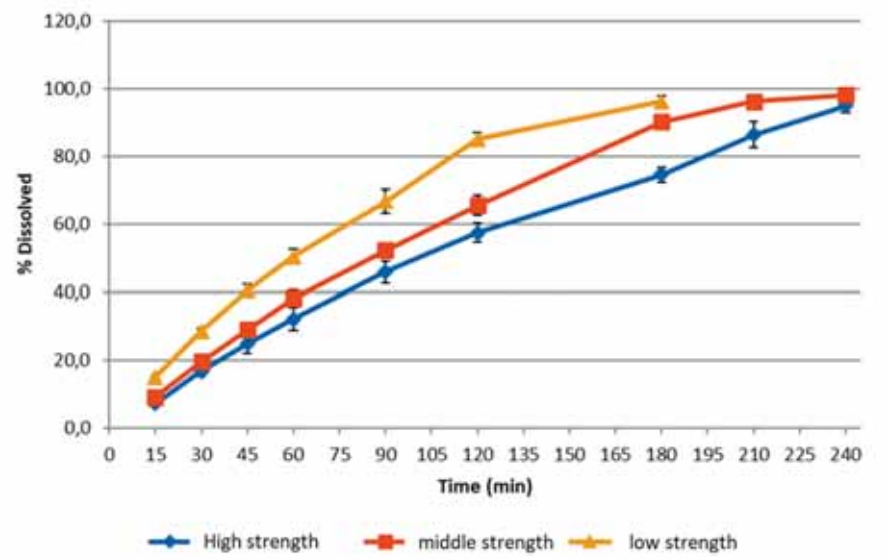
Product B: Virtual Bioequivalence

- A generic product in 3 strengths, BCS IV compound
- Question was to have a BE in higher strength and waive the lower strengths
- This is allowed if all of the following conditions are fulfilled:

- ☑ The pharmaceutical products are manufactured by the same manufacturing process.
- ☑ The qualitative composition of the different strengths is the same.
- ☑ The composition of the strengths is quantitatively proportional
- ☒ The dissolution profiles are similar under identical conditions for the additional strength and the strength of the batch used in the bioequivalence study.

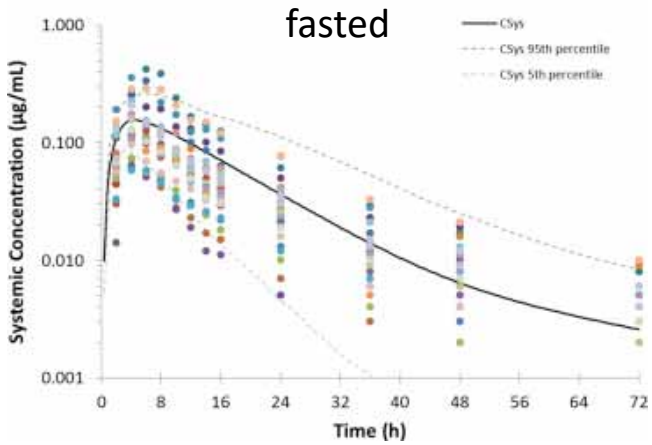
Fourth criterion, similarity of dissolution profiles between strengths is not met even for the reference product (f2 needs to be >50)

- f2 of middle strength compared to high is 52
- f2 of low strength compared to high is 34



The sponsor proposed:

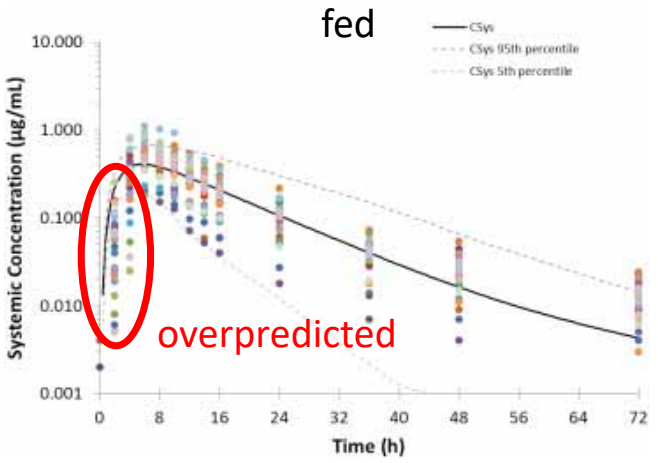
- **to use a PBPK platform to simulate a VBE of the lower strengths**
  Provided a literature PBPK model
- Plan B to compare in vitro profiles for each strength to respective reference product strength as per FDA product specific guidance



Assessment:

EMA SA discouraged the applicant for using a PBPK model on the basis that:

- Extensive qualification programme is needed for PBPK models
- Proposed PBPK model does not describe well the data, esp. in fed state
- No VBE study has ever been accepted by CHMP
- Better off pursuing plan B



Conclusions for Product B

- VBE is a valuable tool for drug development of generics
  It can guide formulation development and reduce pilot studies

- In drug approval at least in EMA VBE for biowaiver is one of the least likely M&S applications to be accepted.

- Indeed biowaivers based on VBE has been considered the application of PBPK with the **highest risk** in *Mitra et al 2020 JPharmSci.*

- Apart from risk VBE often addresses questions with low benefit, leading to **unfavourable B/R ratio** for the decision:
  - When feasibility of real study is not be an issue
  - Application of modelling to correct badly designed studies

B/R ratio and totality of data

- In other setting such as **paediatrics,** EMA could be more flexible.
  Key concept: **the totality of the data in a context of B/R**

- We are ready to consider posology in infants without clinical trials with a robust extrapolation concept and appropriate exposure matching

- This includes high risks and uncertainties
  BUT there is high medical benefit for the infants that outweighs the risk

- Still, often difficult feasibility problems arise in BE studies.
  - E.g. For SS BE studies for rare disease products carried out in patients because of safety concerns

Steps to advance uptake of PBBM in regulatory setting

- Novel approaches: Cetrain regulatory procedures such as Innovation Task Force and Qualification of Novel Methodologies are suitable for research innovative ideas and exchange of opinions.

- It is important that sponsors engage early with EMA about product development with SA

- Besides that we need to do more research to systematically build a M&S “confidence space”, such that research problems are solved by the time they are reviewed in regulatory setting

- Collaborations between Regulators , Industry and Academia to define questions and address them systematically. (With appropriate funding)

Steps to advance uptake of PBBM in regulatory setting

- Introduction of Standards for Good Practices and model assessment for PBPK. PopPK is more advanced than PBPK. Things are more difficult in QSP

- Standards could evolve to Guidelines which are lacking now, because applications are recent and due to the nature of M&S

- Develop approaches of how to make decisions with a model based approach as with standard statistical methods, in the context of the vision of in silico clinical trials.

- PBPK models is a field of active research with open questions particularly regarding characterisation of variability, transporters and drug specific biological processes. Also bridging with data-driven PopPK methods.

Closing remarks

- Regulatory questions related to Quality in order to determine clinically relevant specifications is a relatively recent application of PBPK modelling especially at EMA

- It is an emerging field of particular importance for industry that has been growing rapidly and in parallel to MIDD

- An active field of research both for technical methodological aspects as well as regulatory applications

- At the EMA and in the MSWP we encourage applications of PBPK models and M&S in general and are committed to improve uptake of such approaches.

Many thanks to:

- Evangelos Kotzagiorgis (EMA)
- Efthymios Manolis (EMA)
- MSWP (EMA)
- **All of you for listening**