
# Model based IVIVC and related considerations from ICHM15 and EMA concept paper on mechanistic models

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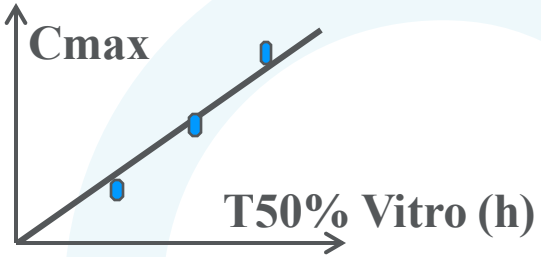
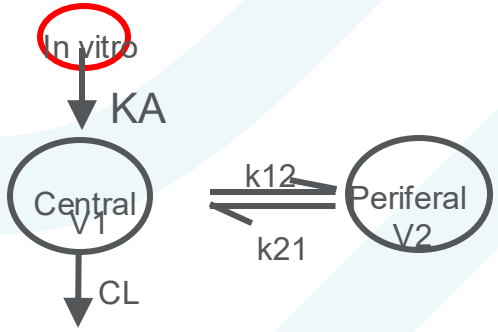
Moving Medicine Forward

# Introduction

- IVIVC: Mathematical model that describes relationship between *in vitro* property and *in vivo* response
  - **Assumption:** rate limiting absorption is due to drug product *in vivo* release properties and a method *in vitro* shows the same (or related) rate limitation
  - Level A, B, C

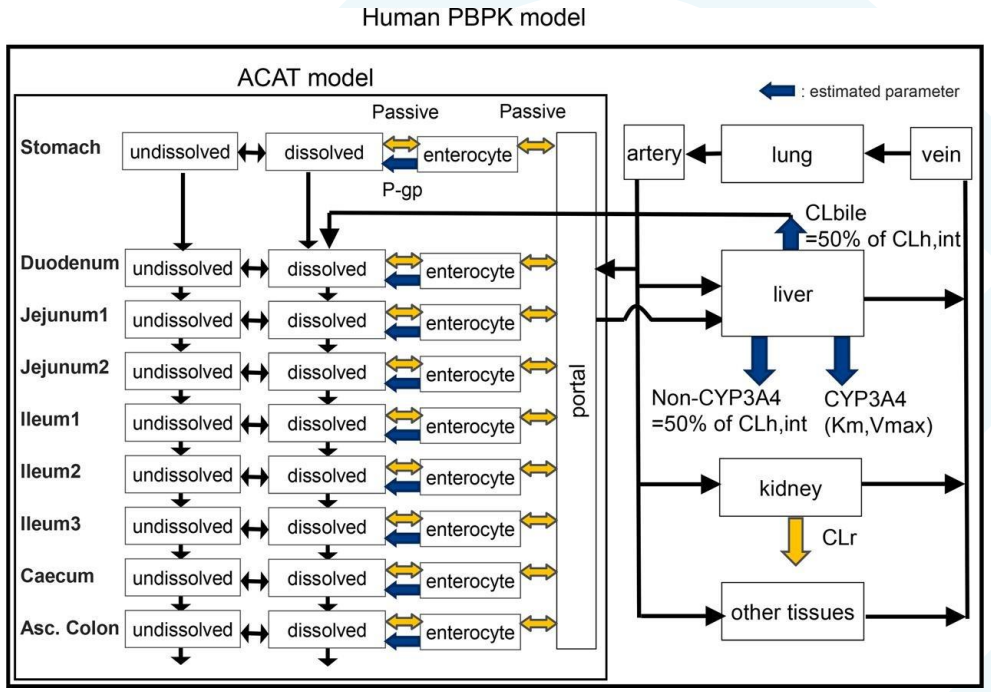



  - Population PK: Mathematical model that describes the data, Estimate parameters and variability, Assess model fit, Explore what explains variability (e.g. weight, comed)
    - *In vitro* is fit as a PK compartment



# Introduction

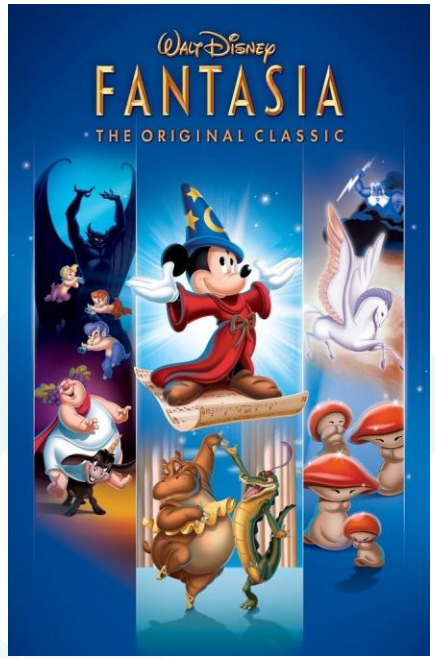
- Mechanistic models, i.e. mathematical models that integrate biopharmaceutical, physico-mechanical, (patho)physiological and pharmacological processes, along with population characteristics
  - Physiologically Based Biopharmaceutics (PBBM) which are based on PBPK models:




From Kato, 2021

# Introduction

- Pharmaceutical and Analytical scientists: art of galenical development, pharmaceutical technology
  - *Artists, Chemists, Engineers*
  - *Accuracy and Precision: ±5-10%*
- Pharmacometricians: math and statistics
  - *Rock Stars*
  - *Precision and Bias: ±25%? Within 2 fold? 90% of observations within 95% of predictions? No visible deviation trend? With or without uncertainty? Recently published qualification method by…*
- Regulatory science strategists
  - *Masters of the Universe*
  - *Accuracy and Precision and Bias: Is this level of detail really necessary?*
- All are artisans: learn from others but mostly by experience
  - Different schools of thought, preferences, "traumas"
  - Different ways of addressing the same issue; assumptions for some are truth for others
  - There will always be a new suggestion and discussions can be never ending
    - "The AI" (e.g. ChatGPT) is a new player…
- Who can coordinate and integrate all of these angles?
  - *ICHM15 has increased the involvement of the regulatory group*



# Introduction aplicable guidelines

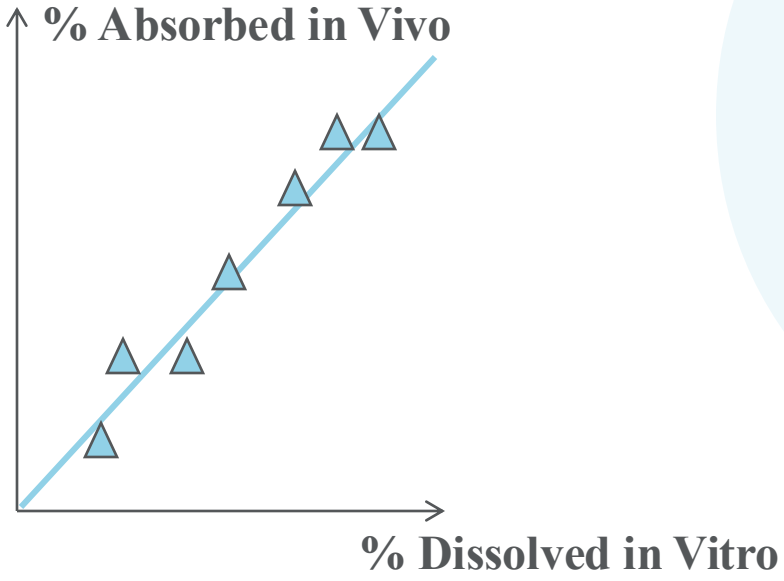
- FDA
  - PBPK for CMC guidance *2020*
  - SUPAC MR *1997*
  - MR IVIVC *1997*
- EMA
  - MR guideline includes differential equation based approaches for IVIVC *2014*
  - Guideline on reporting PBPK (highlights DDI application) *2018*
    - SimCYP simulator now qualified for some CYP mediated interactions using data from **220 studies** for model verification/qualification *2025*
      - *Context of Use 1: predict weak and moderate when a clinical study with a strong CYP inhibitor of the same enzyme has been conducted*
  - Concept paper assessment and reporting of mechanistic models used in the context of model informed drug development *2025*
- ICHM15 general principles for model-informed drug development *2025*

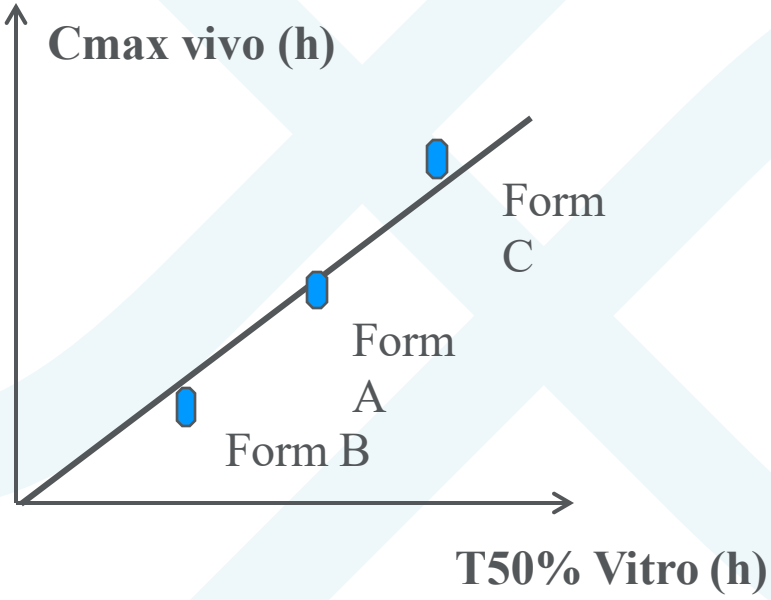
# EMA concept paper mechanistic models

- Concerns align with ICH M15:
  - Complex structure and high number of interconnected parameters can lead to issues related to structure identifiability: What is this model?
  - Mechanistic justification and plausibility: Is it aligned with human physiology and drug pharmacology?
    - Note: state of the art and knowledge evolves from year to year
    - E.g. higher exposure in fed of an osmotic pump system due to more time taking in water in the stomach leading to better release efficiency or due to delivery of more drug in the lower GI tract where less efflux transporter activity is expected?
      - Should determine amount remaining in formulation after defecation to assess, other…
  - Assumptions need to be justified: There are many many assumptions!
    - Examples: *in vitro in vivo* extrapolation of enzyme and transporter activities, regional permeability/impact of excipients on permeability (rat perfusion technique, cell lines?), compartment volumes, distribution rates
  - Data from different sources are used to inform parameter values: propagation of uncertainty!
  - Tools and data for assessing predictive performance: based on intended use!
  - Virtual population and simulation scenarios: based on intended use!

# ICH M15 Model Informed Development

- ICH M15 applies: “strategic use of computational M&S methods that integrate…information…data…knowledge..to generate evidence
  - PBPK mentioned in the guidance
  - Are level A and level C IVIVC (e.g. regression line) models for the context of ICHM15?
    - Hopefully not, as specific topic guidelines are available



# ICH M15 overview

**Table 1: Guideline Overview: Sequence of MIDD in Relation to the Relevant Guideline Sections**

| Stages | Planning and Regulatory Interaction | | Implementation, Reporting, and Submission | | |
|---|---|---|---|---|---|
| **Sequence of Activities** | **Key Assessment Elements** | **Additional Considerations for Interaction with Regulator and to Inform Decision-Making** | **Model Evaluation** | **Model Analysis Reporting** | **Documentation for Regulatory Interactions and Submissions** |
| | • Question of Interest<br>• Context of Use<br>• Model Influence<br>• Consequence of Wrong Decision<br>• Model Risk<br>• Model Impact | • Appropriateness of Proposed MIDD<br>• Technical Criteria for model evaluation and model outcomes[1]<br><br>These should be documented (e.g., in a Model Analysis Plan [MAP]). | • Verification<br>• Validation<br>• Applicability assessment | • Model Analysis Report(s) (MAR) | • Regulatory documents, including<br>+ Outcome of MIDD Evidence Assessment<br>+ References to all relevant MAPs and MARs |
| **Relevant Guideline Section** | Section 2.1 and Appendix 1 | Sections 2.2 and 4.1 and Appendix 1 | Section 3 | Section 4.2 and Appendix 2 | Sections 2 and 4.3 and Appendix 1 |

Note: Terms used in this table are defined in relevant guideline sections.

[1] Results derived from M&S (i.e., via model-based predictions or simulations) and associated conclusions that are typically aligned to a Question of Interest.

**Inform Decision-Making**

# ICH M15 Key Assessment elements example

- Question of Interest
  - Will a “product” with different dissolution profile/different PSD/polymorph content/etc provide adequate PK behaviour?
    - In generic context “adequate” is bioequivalent to reference product (or to test biobatch for variations)
    - In a NCE/hybrid context “adequate” can consider thresholds of effect/safety and/or exposure matching to biobatch used in pivotal study/phase III
- Context of Use
  - Explicit description of the model, the **data** used to build the model, the specific role of the model outcomes, and the other data or evidence that will contribute to the answer to the Question of Interest.
- Model Influence: intended weight of the model outcomes in decision-making considering the contribution of other relevant information
  - “product” within side batches studied *in vivo*? Standard formulation and manufacturing process? High risk product? changes within SUPAC criteria? Can exclude other potential differences (e.g. pH dependence, transit times)?

# ICH M15 Key Assessment elements example

- Consequences of wrong decision (patient efficacy safety)
  - *Release batches with Cmax at BE limit (e.g. T/R 120 or 85) but drug with broad therapeutic index, very broad dose escalation steps (exposure response is not sharp), safety concerns are not associated with peak values*
- Model Risk (contribution of the model outcomes to a possible wrong decision depending on contribution to totality of evidence)
  - Low, medium, high: impacts model evaluation expectations
- Model Impact
  - Low (exploratory, mechanistic understanding), medium (model and clinical data) , high (risk/benefit assessment; SmPC)
  - *Medium (e.g. specifications totality of evidence includes clinical data, CMC data, manufacture of registration and commercial batches)*

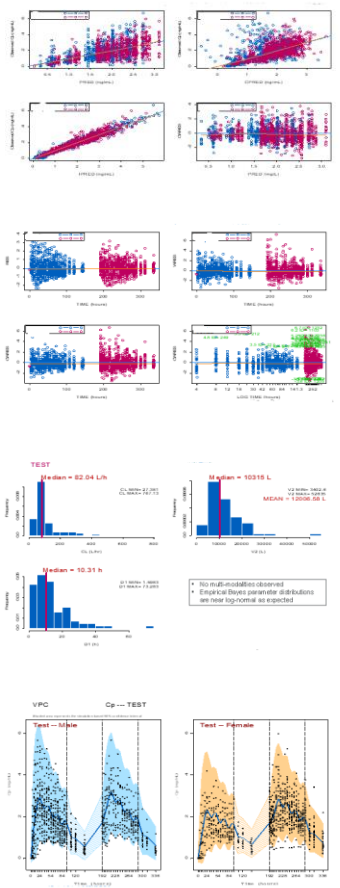
# ICH M15 Model Evaluation

- Verification: Is the coding correct? Error free? accurate?
  - Documentation available for review
  - QA of software
- Validation: comparison of the model versus data, prior information, and knowledge
  - data selection, associated transformations, and imputations should be specified, justified, and documented (plan and report)
  - model structure and parameters should be consistent with the available knowledge
  - Assumptions described, justified, alternatives considered
  - Method issues considered (e.g. overfitting, knowledge gaps, selection bias)

# ICH M15 Model Evaluation

- Validation: comparison of the model versus data, prior information, and knowledge (cont)
  - Robustness: examples: sensitivity analysis for critical parameters, leave-one out approach for batches; popPK parameter estimates from bootstrap are within the 90% CI
  - Model performance (precision and bias)
    - Standard predictive checks and goodness of fit
    - Prioritize metrics that relate to the Question of Interest and associated analysis objective(s)
      - Examples for PBBM: Cmax, AUC, partial AUC, profile shape, emphasis on absorption phase, apparent elimination if flip-flop PK, etc
      - Bioequivalence results? GMR T/R? This goes way beyond standard model performance requirements
  - External validation (encouraged)
  - Simulation method and scenarios described in detail, accounting for parameter and assumption uncertainties
    - Virtual bioequivalence? Sample size, population characteristics and number of studies (e.g. 10,100,200?a million?)
- Applicability (fit for purpose): to answer Question of Interest

# Predictability: Cmax, AUC and PROFILE SHAPE!



IVIVC
PE less than 15% per product
PE less than 10% on average

Sample size sufficient to characterise PK, does not need to be for 80% powered BE study

Establishing IVIVC

Tablet X In vivo-In vitro data

IVIVC

Internal predictability

Establishing IVIVC

Tablet X In vivo-In vitro data

IVIVC

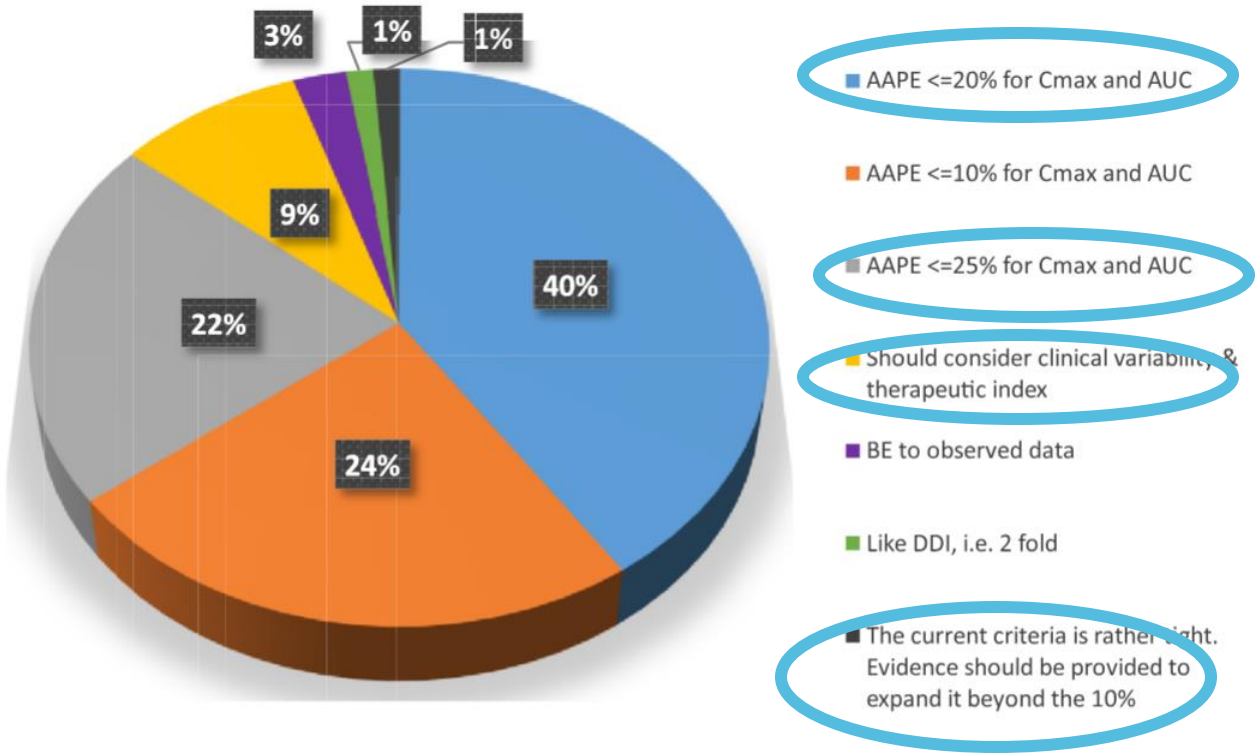
Simulated vs observed plasma data

External predictability

Tablet Y in vitro data

GOF, Distributions, VPC, PPC, Bayesian predictions, comparison between models, sensitivity analysis, assess bias, uncertainty….

# Predictability acceptance criteria



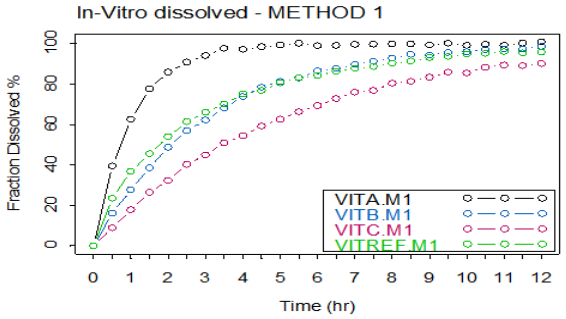

¾ of workshop participants suggest to widen it

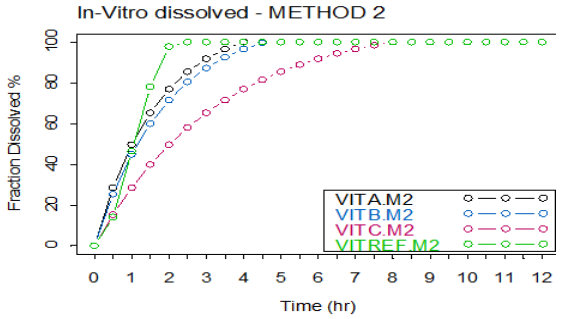
**Figure 10.** Question 10: Assuming full PBPK model and PBBM validated on all rich PK data during development (e.g., 1 SAD, 1 MAD, 1 food effect study, 1 ARA study, 1 fit for purpose study with 3 variants), what should the average absolute prediction error (AAPE) for PBBM validation be?

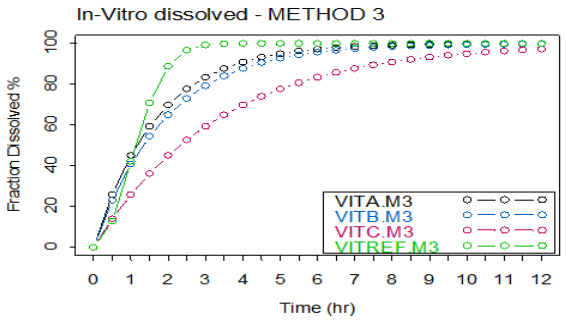
Mackie C, Arora S, Seo P, Moody R, Rege B, Pepin X, Heimbach T, Tannergren C, Mitra A, Suarez-Sharp S, Borges LN, Kijima S, Kotzagiorgis E, Malamatari M, Veerasingham S, Polli JE, Rullo G. Physiologically Based Biopharmaceutics Modeling (PBBM): Best Practices for Drug Product Quality, Regulatory and Industry Perspectives: 2023 Workshop Summary Report. Mol Pharm. 2024 May 6;21(5):2065-2080.

# Some issues for the context of bioequivalence

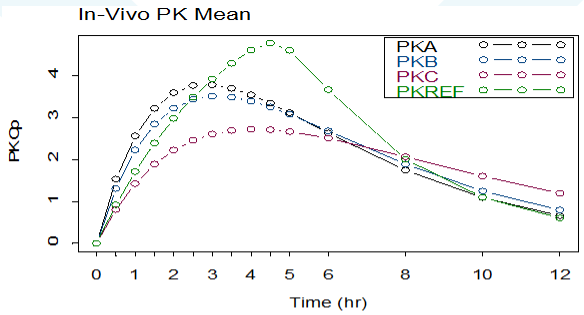
- Very similar products yield very similar PK that may not be BE
  - Differences can be within variability and uncertainty
  - Use data from batches with clearly different properties to develop the model and to select most relevant dissolution method(s) as input

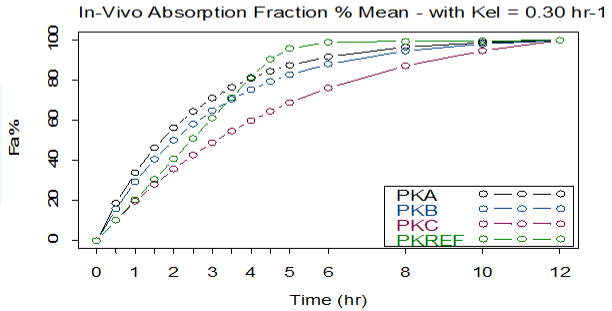



Check in vitro and in vivo rank order first!



# Example for virtual bioequivalence

- Virtual bioequivalence trial using a mechanistic absorption model to compare the bioavailability of drug product batches with different amounts of spiked X:
  - Relative BA studies used to build and validate the model in addition to iv data
    - 240 mg Study PCR1007: Relative BA study of **seven** tablet **formulations** to the capsule formulation
    - 240 mg Study PCR1011: Relative BA study of **three** tablet **formulations** to the capsule formulation
    - 60 mg Study PCR1015: Crossover study of tablet formulation with **varying particle size distribution**
    - 60 mg Study PCR1017: Crossover study of tablet formulation from **different manufacturing sites**
  - Developed a “physiology based dissolution” for the model, not the QC method
  - Mechanistic model of absorption based on the physico-chemical properties (two solubility inputs: **amorphous and crystalline**), the PBD profiles of each formulation
    - precipitation seen in vitro from some formulations was not relevant in vivo
- Virtual BE trials: Virtual BE trials were performed to evaluate the exposure between drug product containing with the drug product containing different amounts of material
  - The results of the 10 virtual trials show that drug product batches with up to X% are bioequivalent while drug product batches with more than Y%
  - are not bioequivalent: 10 enough as have BE and non-BE scenarios
- Applied for setting specifications of X content
- **Model risk:** Low as CMC data (solubility, dissolution of different forms) and relative BA data contribute to the assessment
- **Model impact:** medium (model and clinical data): FDA classifies as supportive to set the specifications

- In what context would a generic product development stand such an investment in time and expense?

[1]FDA. 210951Orig1s000 Product Quality Review (s). Erleada®. February 2017

# Example for virtual bioequivalence

- Model validation: The mean modeling and simulation results were compared to the results of the BA studies (Cmax and AUC)

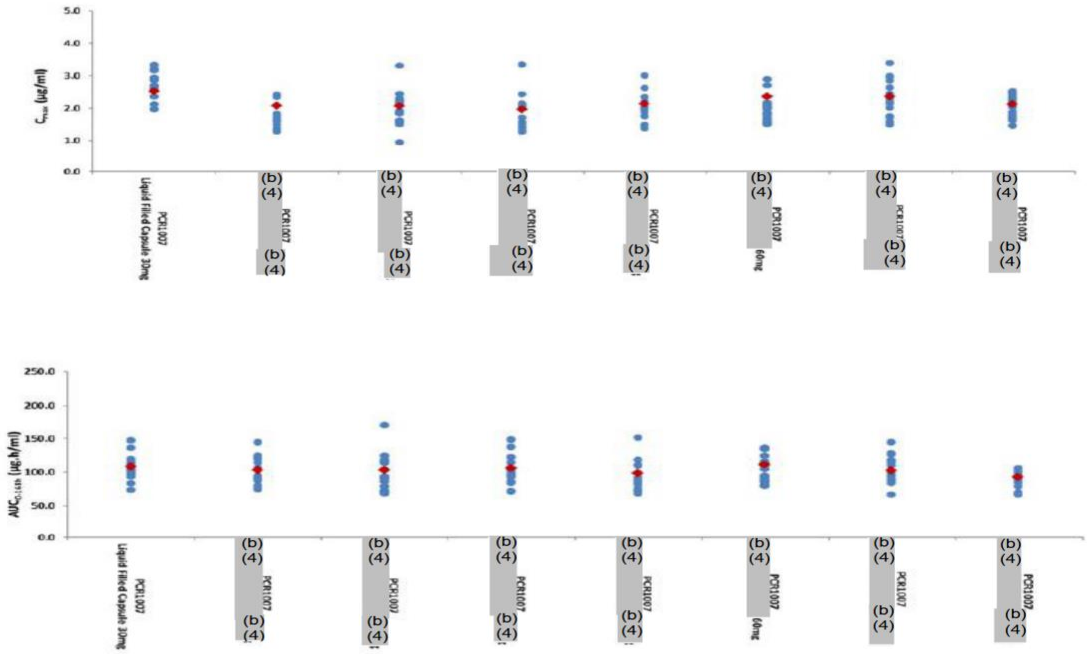


**Figure 14. Individual Cmax (top panel) and AUC (bottom panel) values The in vivo data Study 1007 (blue) versus predicted in silico (red)**

**Table 9. Overview of the virtual trial simulations and the ration of the in silico results with the vivo observed data**

| Study | Formulation | Dose | $C_{max}$ (µg/ml) | | | | | $AUC_{last}$ (µg.h/ml) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | *in vivo* | | *in silico* | | ratio | *in vivo* | | *in silico* | | ratio |
| | | | mean | stdev | mean | stdev | | mean | stdev | mean | stdev | |
| PCR1007 | Liquid Filled Capsule 30mg | 240mg | 2.73 | 0.38 | 2.59 | 0.37 | 0.95 | 107.30 | 18.63 | 110.03 | 23.88 | 1.03 |
| PCR1007 | (b) (4) | 240mg | 1.75 | 0.37 | 2.06 | 0.25 | 1.18 | 103.00 | 20.74 | 102.32 | 17.25 | 0.99 |
| PCR1007 | | 240mg | 1.94 | 0.54 | 1.91 | 0.32 | 0.98 | 99.89 | 26.46 | 95.50 | 20.65 | 0.96 |
| PCR1007 | | 240mg | 1.88 | 0.54 | 1.94 | 0.18 | 1.03 | 102.38 | 22.87 | 103.51 | 18.41 | 1.01 |
| PCR1007 | | 240mg | 2.01 | 0.43 | 2.12 | 0.29 | 1.05 | 92.86 | 22.80 | 99.85 | 26.18 | 1.08 |
| PCR1007 | | 240mg | 1.97 | 0.41 | 2.34 | 0.33 | 1.19 | 102.99 | 18.81 | 113.60 | 29.76 | 1.10 |
| PCR1007 | | 240mg | 2.30 | 0.58 | 2.36 | 0.19 | 1.03 | 105.40 | 20.10 | 105.13 | 30.13 | 1.00 |
| PCR1007 | | 240mg | 2.04 | 0.35 | 2.25 | 0.18 | 1.10 | 88.22 | 12.35 | 97.66 | 26.93 | 1.11 |
| PCR1011 | | 240mg | 2.70 | 0.49 | 2.33 | 0.23 | 0.86 | 98.64 | 14.03 | 96.79 | 21.11 | 0.98 |
| PCR1011 | | 240mg | 2.58 | 0.46 | 2.57 | 0.40 | 1.00 | 109.60 | 15.13 | 108.36 | 22.21 | 0.99 |
| PCR1011 | | 240mg | 2.42 | 0.38 | 2.42 | 0.32 | 1.00 | 120.48 | 25.72 | 107.40 | 25.71 | 0.89 |
| PCR1011 | | 240mg | 2.05 | 0.41 | 2.03 | 0.33 | 0.99 | 107.77 | 22.83 | 101.60 | 19.54 | 0.94 |
| PCR1011 | | 240mg | 2.36 | 0.72 | 2.35 | 0.38 | 1.00 | 117.98 | 31.34 | 104.29 | 19.66 | 0.88 |
| PCR1015 | | 60mg | 0.593 | 0.096 | 0.555 | 0.043 | 0.94 | 26.55 | 4.25 | 24.23 | 5.65 | 0.91 |
| PCR1015 | | 60mg | 0.573 | 0.107 | 0.564 | 0.077 | 0.98 | 29.47 | 4.01 | 24.87 | 6.61 | 0.84 |
| PCR1015 | | 60mg | 0.615 | 0.109 | 0.596 | 0.092 | 0.97 | 27.25 | 4.21 | 25.96 | 7.72 | 0.95 |
| PCR1015 | | 60mg | 0.620 | 0.104 | 0.588 | 0.078 | 0.95 | 27.86 | 4.83 | 25.29 | 6.39 | 0.91 |
| PCR1015 | | 60mg | 0.668 | 0.081 | 0.643 | 0.104 | 0.96 | 29.56 | 5.19 | 28.11 | 4.96 | 0.95 |
| PCR1017 | | 60mg | 0.633 | 0.123 | 0.595 | 0.075 | 0.94 | 26.60 | 5.77 | 25.89 | 5.80 | 0.97 |
| PCR1017 | | 60mg | 0.628 | 0.143 | 0.603 | 0.058 | 0.96 | 26.54 | 5.19 | 26.70 | 6.73 | 1.01 |
| PCR1017 | | 60mg | 0.614 | 0.133 | 0.614 | 0.091 | 1.00 | 26.16 | 5.05 | 25.66 | 7.16 | 0.98 |

[1]FDA. 210951Orig1s000 Product Quality Review (s). Erleada®. February 2017

# Example for virtual bioequivalence

- Model validation (cont):
  - 95% modeling and simulation results were compared to individual observations (per product and study)

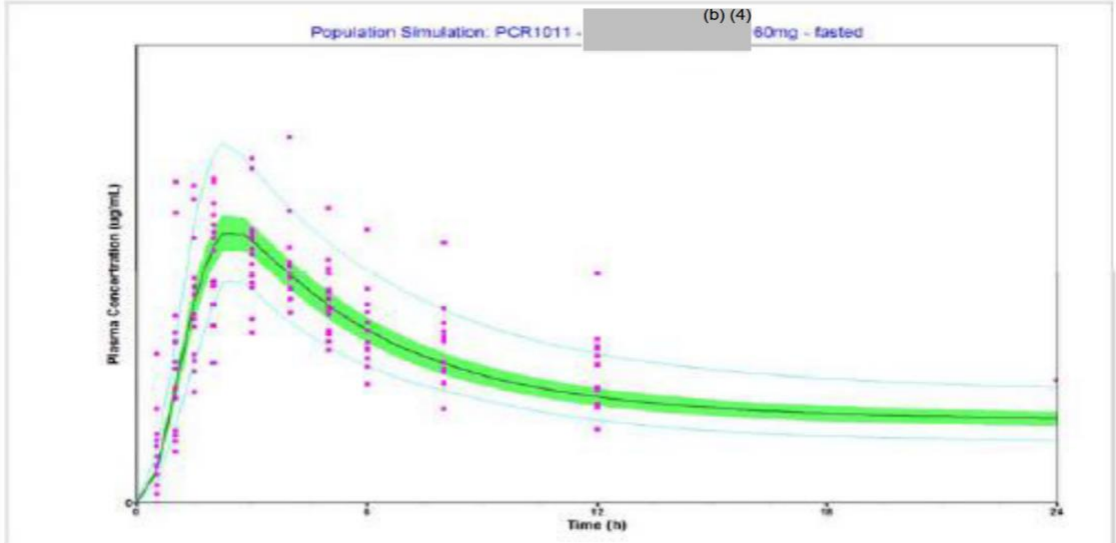



**Figure 15. PBPK predicted (green) concentration time profile with the 95% probability plots (blue dash lines) as compared to the observed (pink squares) concentration vs time data of the proposed drug product**

[1]FDA. 210951Orig1s000 Product Quality Review (s). Erleada®. February 2017

# Example food effect

- Food effect characterised for 40 mg dose and PBPK for highest dose

**Q9. Can PBPK analyses predict the effects of food on the PK of asciminib?**

No, the absorption model of asciminib was not mechanistic to allow evaluation of the effect of food on the exposure of asciminib at higher dose levels. The Applicant optimized the absorption parameters (fa and ka) with the observed food effect at asciminib 40 mg single dose and assumed the same negative food effect would be extrapolated to 80 mg QD and 200 mg BID. The Applicant concluded the food effect was independent of the dose. However, this was an assumption incorporated in the model; not a simulation outcome. Detail assessment is as follows:

Importance of considering alternative assumptions and clearly identifying knowledge gaps
Fa linked to solubility?
Ka linked to dissolution rate?
First pass, Other?

Result: PK study to characterise food effect for final market product and dose

# Example PPI

**Q12. Can the ADAM-PBPK model evaluate the effect of elevated gastric pH on the PK of asciminib following a 200 mg oral administration?**

Yes, the asciminib ADAM-PBPK model, along with the in vitro dissolution data and clinical DDI study with the ARA rabeprazole [Study A1101], was adequate to evaluate the effect of elevated gastric pH on the exposure of asciminib following 200 mg dose.

The ADAM-PBPK model of asciminib was validated against the observed PK in healthy subjects and in patients in the dose range of 40 mg to 200 mg (Table 56), and the clinical DDI study (A1101) with rabeprazole (Table 57).

**Table 57: ADAM-PBPK model Predicted and observed PK parameters following oral administration of 40 mg asciminib with and without co-administration of rabeprazole**

| Scenario | Geometric Mean Cmax (ng/mL) | | | Geometric Mean AUCinf (ng·h/mL) | | |
|---|---|---|---|---|---|---|
| | Observed | Predicted | Pred/Obs | Observed | Predicted | Pred/Obs |
| Asciminib alone (40 mg) | 943 | 849 | 0.90 | 9850 | 7949 | 0.81 |
| Asciminib with rabeprazole | 856 | 844 | 0.99 | 9710 | 7949 | 0.82 |
| Ratio (with/without rabeprazole) | 0.908 (0.849, 0.972) | 0.994 | 1.09 | 0.986 (0.959, 1.01) | 1.00 | 1.01 |

Observed values are reported as the adjusted geometric mean values from Study A1101. Simulated trials:10 trials of 10 subjects (n=100) with age range and proportion of females matching the actual demographics of the respective clinical studies. The virtual population model was the Japanese model (same population as study A1101) with the advanced fluid volume dynamic model selected and gastric mean residence time of 0.4 h. The DDI ratios were comparisons of asciminib PK simulated with a normal gastric pH, i.e. default value of 1.5 (asciminib alone simulations) with asciminib PK simulated with a gastric pH of 5.0 (asciminib with rabeprazole simulations). (Source: Applicant's response to Clinical Pharmacology IR submitted on September 16, 2021).

Prediction error less than 50%(!!!) for Cmax and AUC observed PK: fit for purpose of characterising PK linearity

Validation versus DDI study was more stringent: Prioritize metrics that relate to the Question of Interest and associated analysis objective(s)

# Example PPI

- *In vivo solubility predicted by the model are consistent with in vitro values (0.032 versus 0.4; 10 fold difference!)*
- *Used particle radius of 10 µm in model, experimental result was 25 µm; sensitivity analysis of the impact was conducted by the FDA*
- *Partition coefficient between water and bile salts and critical saturation ratio; sensitivity analysis of the impact was conducted by the FDA*

*Conclusion*

- The ADAM-PBPK model simulations suggested that changes on gastric pH does not have much effect on asciminib exposure due to its high solubility in bile salts attributed to supersaturation, which override the pH effect. The predicted effect of elevated gastric pH on asciminib PK following 200 mg administration is unlikely to be clinically meaningful.

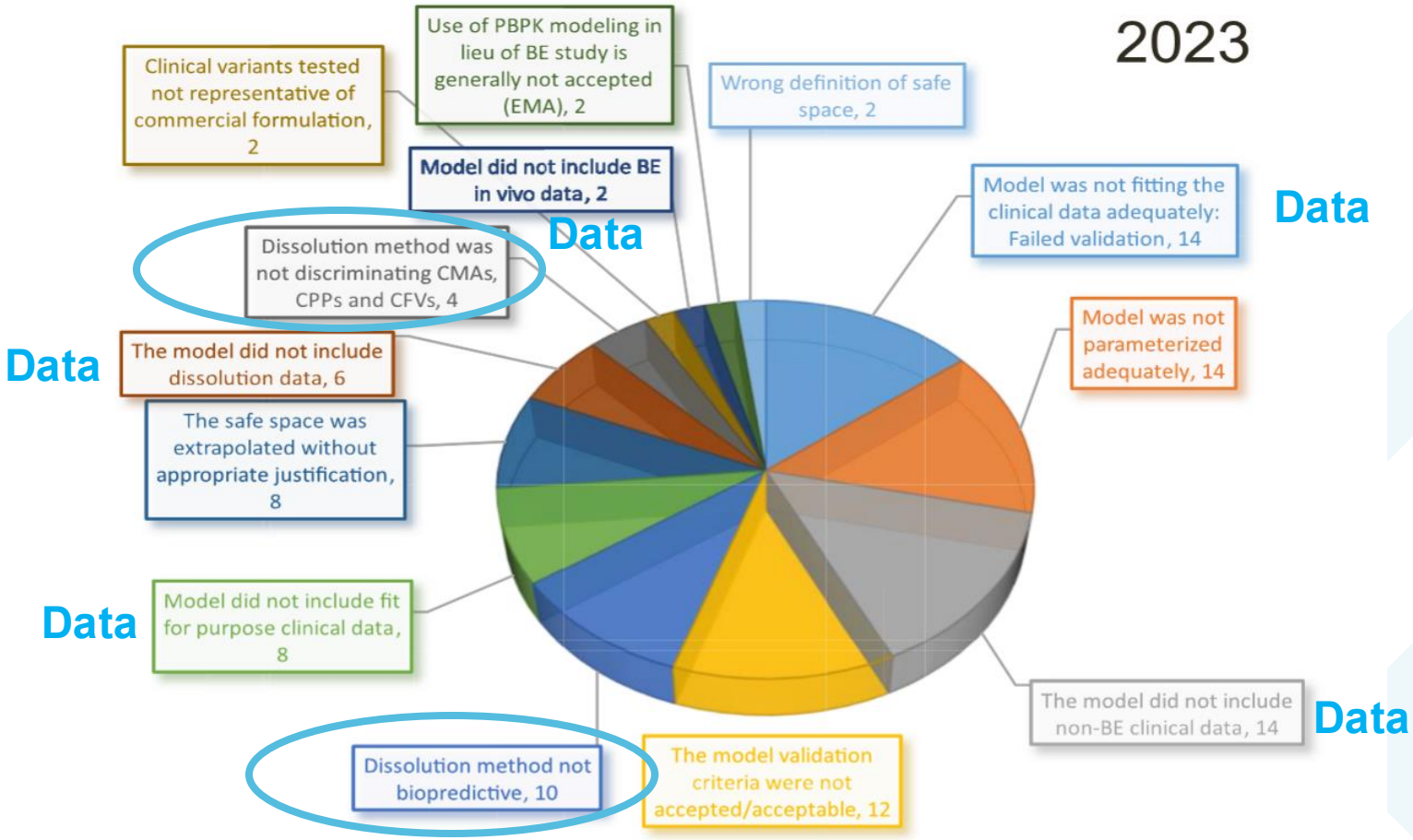
Importance of: model structure and parameters should be consistent with the available knowledge

# EMA common reasons for non qualification

- Review PBPK in EMA 8.3 MAA from 2022-2023
- Reasons for **non qualification**:
  - PBPK model structure (e.g. missing transporters, autoinhibition/induction, etc)
  - Lack of relevant data to assess predictive capacity
  - Poor prediction of clinical data
    - Acceptance criteria depends on regulatory impact
  - Insufficient justification of key assumptions (including input parameters)
    - uncertainty surrounding the source of the data (e.g., data from literature rather than from in-house studies) or methods used to determine assumptions of the model (e.g., determining the relative contribution of enzymes).
  - Insufficient number of compounds in qualification dataset

Paul P, Colin PJ, Musuamba Tshinanu F, Versantvoort C, Manolis E, Blake K. Current Use of Physiologically Based Pharmacokinetic modeling in New Medicinal Product Approvals at EMA. Clin Pharmacol Ther. 2025 Mar;117(3):808-817. doi: 10.1002/cpt.3525. Epub 2025 Jan 2. PMID: 39748538; PMCID: PMC11835421.

# What were the main reasons for the PBBM rejection?




Mackie C, Arora S, Seo P, Moody R, Rege B, Pepin X, Heimbach T, Tannergren C, Mitra A, Suarez-Sharp S, Borges LN, Kijima S, Kotzagiorgis E, Malamatari M, Veerasingham S, Polli JE, Rullo G. Physiologically Based Biopharmaceutics Modeling (PBBM): Best Practices for Drug Product Quality, Regulatory and Industry Perspectives: 2023 Workshop Summary Report. Mol Pharm. 2024 May 6;21(5):2065-2080.

# Closing remarks

- ICH M15 and EMA concept paper add structure to aspects critical for regulatory applications of models
  - Forces different types of experts to align and contribute to regulatory reporting
  - PBBM includes same players as standard IVIVC in addition to PBPK modelers
- M&S regulatory applications require validation with data and state of the art of all aspects included (e.g. dissolution, CMC,PK, transporters, absorption mechanisms, transit times, distribution kinetics, drug pharmacology)
  - Changes from year of model development to MAA submission time may require updates
- Qualification efforts, Model Master file might open the possibility of referring to main PBPK models and adapting to required context of use resulting in abridged model evaluation
- Evolution of “biopredictive methods” may inform initial analytical method developments for the PBBM models.
- Start in projects where clinical PK BE studies are hindered by feasibility constraints or are not fully informative (Manolis, 2023)

Manolis E, García-Arieta A, Lindahl A, Kotzagiorgis E, Limberg J, Holte Ø, Paixao P, Versantvoort C, Tshinanu FM, Blake K, Van Den Heuvel M. Using mechanistic models to support development of complex generic drug products: European Medicines Agency perspective. CPT Pharmacometrics Syst Pharmacol. 2023 May;12(5):556-559. doi: 10.1002/psp4.12906. Epub 2023 Jan 11. PMID: 36628987; PMCID: PMC10196408.

# Backup

CTI

# Guidelines

- https://www.fda.gov/regulatory-information/search-fda-guidance-documents/use-physiologically-based-pharmacokinetic-analyses-biopharmaceutics-applications-oral-drug-product
- https://www.fda.gov/media/70939/download
- https://www.fda.gov/media/70956/download
- https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-pharmacokinetic-and-clinical-evaluation-modified-release-dosage-forms_en.pdf
- https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-reporting-physiologically-based-pharmacokinetic-pbpk-modelling-and-simulation_en.pdf
- www.ema.europa.eu/en/documents/scientific-guideline/concept-paper-development-guideline-assessment-reporting-mechanistic-models-used-context-model-informed-drug-development_en.pdf
- https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-reporting-results-population-pharmacokinetic-analyses_en.pdf