Elevating PBPK as Primary Evidence: A Collaborative Best-Practice Framework for Regulatory Qualification and ICH M15 Alignment

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Aim and outline of this presentation

Awareness of and walkthrough
the recently published
Best Practice paper in PBPK

Outline

- The motivation
- Aim
- Method
- Results: Overview
- Case study
- Concluding remarks

Motivation: the “why”

- Despite its long history, a significant gap persists between model quality and regulatory expectations.
- Relatively little practical guidance from industry for PBPK planning, development, evaluation, application and documentation, in the public domain.

Current Use of Physiologically Based Pharmacokinetic modeling in New Medicinal Product Approvals at EMA

Polly Paul[1], Pieter J. Colin[1,2], Flora Musuamba Tshinanu[3,4], Carolien Versantvoort[5], Efthymios Manolis[1] and Kevin Blake[1,*]

The Aim

From PBPK model to credible regulatory evidence



QUALITY

Robust and reliable analyses



CONSISTENCY

Aligned practices across projects



REGULATORY ACCEPTANCE

Greater confidence of decision-making

ICH M15 now provides the regulatory framework → our paper translates this into practical best practice.

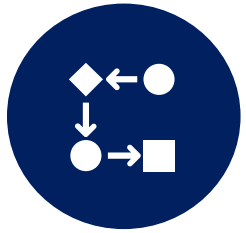
Method: the “how”



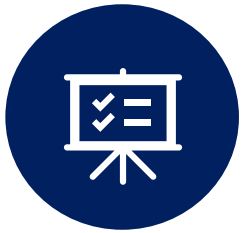
Share & Align, within a group of experts, current practices in planning, developing, evaluating, applying & reporting PBPK models.



Harmonize with the ICH M15 guidance.



Keep it tool agnostic.



Exemplify with case studies.



Publish it as a peer reviewed white paper in an open-source journal.

Results: the “what”

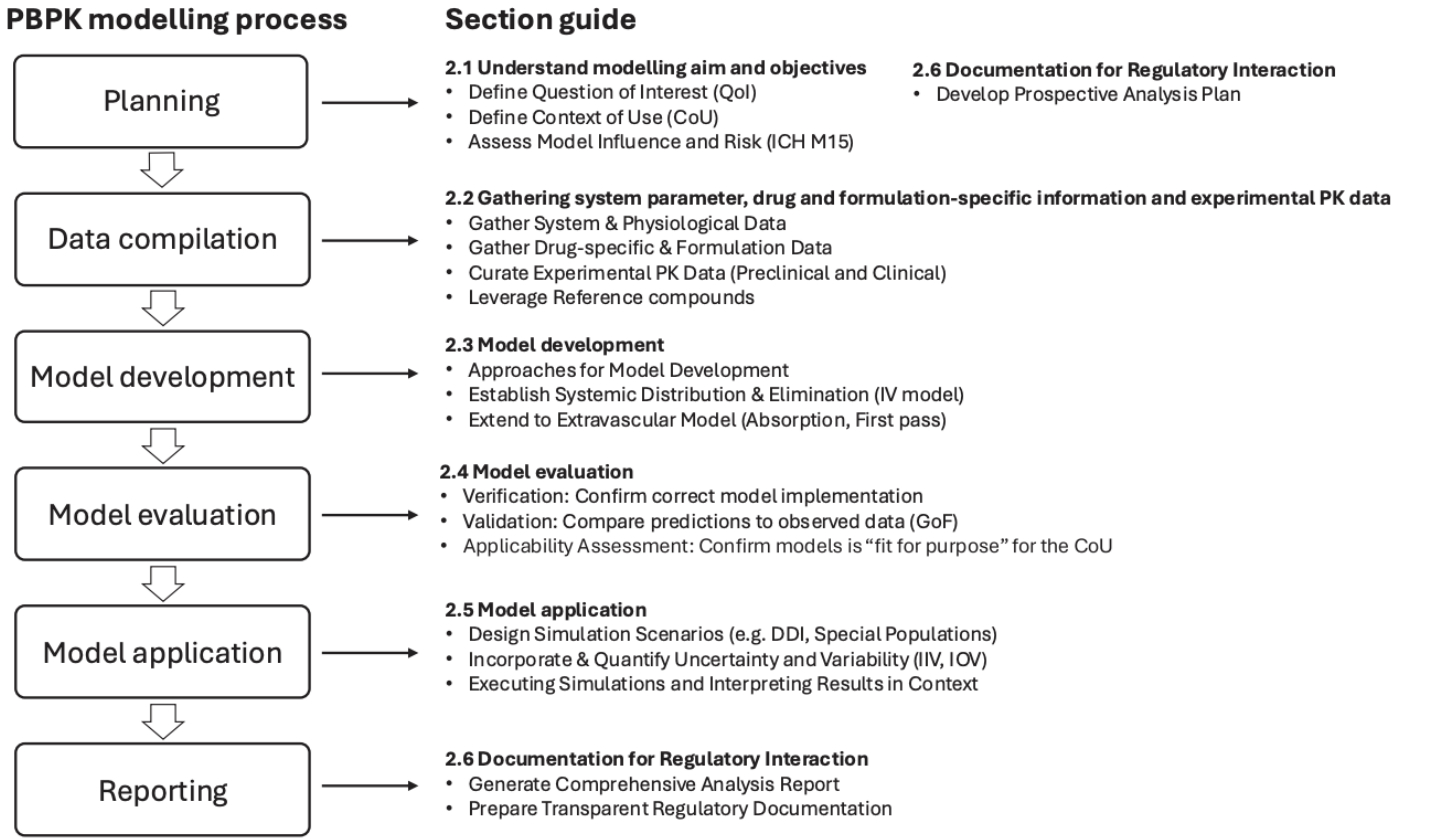


FIGURE 1 | The PBPK best-practice framework. A visual overview of the sequential process for PBPK model planning, development, evaluation, application and reporting as detailed in this manuscript.

- Target audience: practitioners at first, clinical pharmacologists, DMPK scientists.
- The overall structure follows the different steps of a PBPK modelling process.
- General principles and points to consider at the different steps.
- Adopt the ICH M15 lingo and concepts and align with existing regulatory guidance.
- Provide case studies to exemplify.

Justify data selection to inform model structure and evaluation

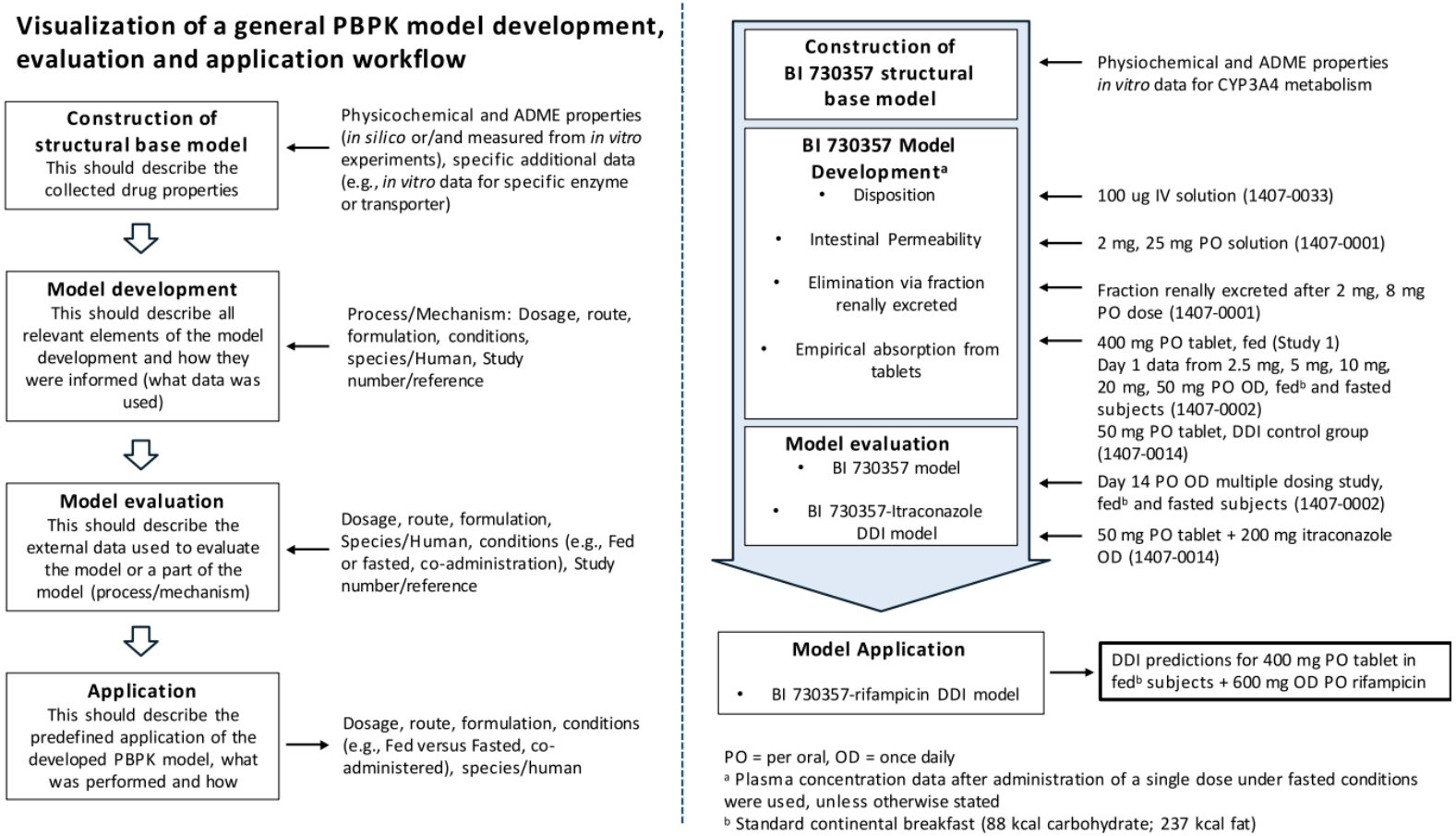


FIGURE 2 | Visualization of the PBPK modeling workflow and corresponding data sources used for model development, validation and application, and to the right a case example adopted from Kanacher et al. [44].

Relationship between context of use, model risk and credibility requirements

TABLE 1 | Relationship between context of use (CoU), model risk, and credibility requirements for PBPK applications.

Application (CoU)	Primary goal	Model risk considerations	Key credibility factors	Regulatory outcome
DDI assessment	Predict changes in exposure (AUC, C_{max}) during co-administration	Safety risks if interaction is missed or underestimated; unnecessary restrictions if over-predicted	Accurate K_i/IC50/E_{max}; mechanistic interaction dynamics; recovery of known clinical DDI magnitudes	Waiving clinical DDI studies; informing drug–drug interaction sections of the product label
Special populations				
Pediatrics	Inform dose selection to match adult exposure or therapeutic windows	Significant safety (overdosing) or efficacy (underdosing) risks in children	Validated ontogeny functions (metabolism/transporters); age-dependent physiological scaling; sparse data validation	Dose selection for pediatric trials; support for pediatric labelling when data is limited
Organ impairment	Guide dosing adjustments for renal or hepatic impairment	Toxicity or loss of efficacy due to incorrect adjustment	Accurate representation of ADME changes (GFR, liver blood flow, expression/function of transporters and enzymes); validation against healthy and impaired PK data	Dose adjustment recommendations in the "Special Populations" section of the label
Formulation & food effects	Predict bioavailability, assess virtual BE (vBE), or quantify food impact	Promoting sub-optimal formulations; unethical exposure in futile bioequivalence studies	In vitro solubility/dissolution; mechanistic absorption models; parameterization of fed-state GI physiology	Generating evidence for bioequivalence via virtual bioequivalence simulation; support for biowaivers; determining food effect labelling; bridging formulation changes
FIH dose projections	Predict human PK from preclinical data to select safe starting doses	Unsafe or sub-pharmacological starting doses, particularly in oncology patients	Quality of multi-species data; IVIVE integrated into PBPK; animal model validation; uncertainty/sensitivity analysis	Approval of FIH trial protocols; defining safe starting doses and escalation increments
Biologics (mAbs)	Understand TMDD and factors influencing mAb exposure/response	Mischaracterizing non-linear PK impacts efficacy and safety predictions	Representation of mAb mechanisms (FcRn recycling, lymphatic uptake, target binding/TMDD)	Informing dose-exposure-response; characterization of non-linear clearance for biologics

The ICH M15 Table for Assessment of MIDD Evidence, tested retrospectively against Vericiguat

TLDR

The completed assessment table is the applicant's account. The FDA reviewer re-derived key PBPK input parameters and predicted a higher AUCR, yet the applicant's conclusion held.

VERICIGUAT + ATAZANAVIR

AUCR **1.12** vs. **1.27**

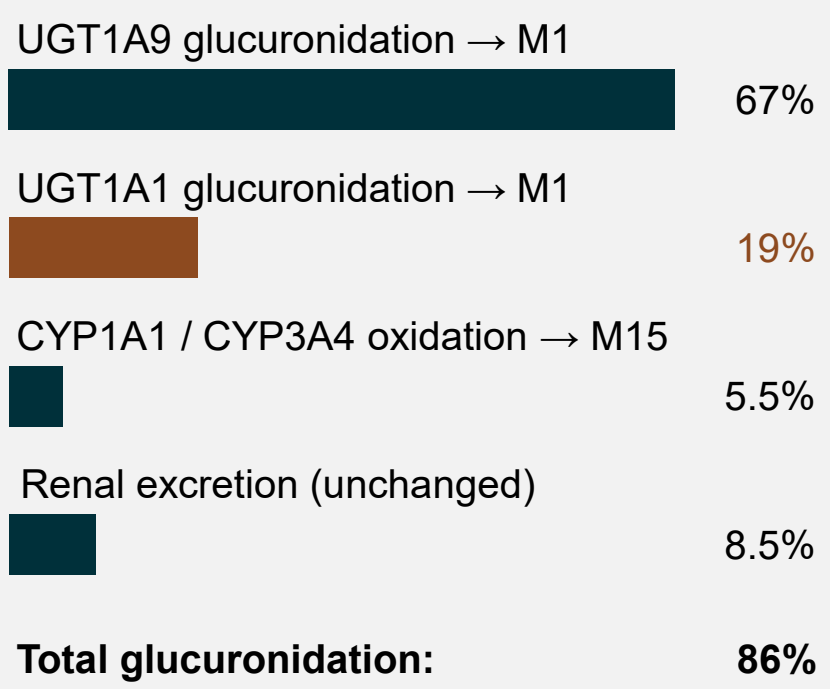
applicant vs. FDA reviewer

Label: no clinically significant DDI

Context of Use

- **Vericiguat:** Orally administered direct soluble guanylate cyclase stimulator co-developed by **Bayer/MSD** to manage and treat heart failure with reduced ejection fraction.
- **PBPK model** was developed using 12 clinical studies (incl. mass balance, abs BA, food effect study) + 29 in vitro studies.
- Major metabolic pathway: glucuronidation to **M-1**
- Relative contribution of **UGT1A9** vs. **UGT1A1** to hepatic glucuronidation of vericiguat in vitro: 60% vs. 40%
- M1 is eliminated via renal and biliary secretion with deconjugation in the intestinal lumen (→ reconversion to vericiguat)

Vericiguat disposition in PBPK model



Source: Frechen et al. CPT Pharmacometrics Syst Pharmacol. 2024. doi: 10.1002/psp4.13059.

Question of Interest

- The dominant role of UGT1A1/9 in vericiguat elimination indicated the possibility of a DDI liability with respect to UGT perpetrators.
- **DDI liability with respect to UGT1A9** was assessed in a clinical study with mefenamic acid (UGT1A9 inhibitor). The observed inhibition effect was deemed to be not clinically meaningful:

Parameter	Observed GMR (%CV)	Observed 90% CI
AUCR	1.20 (8.3%)	1.13 – 1.27
CmaxR	0.97 (9.6%)	0.90 – 1.03

Source: Frechen et al. CPT Pharmacometrics Syst Pharmacol. 2024. doi: 10.1002/psp4.13059.

- **DDI liability with respect to UGT1A*1*** was assessed by PBPK modeling in lieu of a clinical DDI study – the model itself was used as sole evidence.

QUESTION OF INTEREST

"What is the vericiguat drug exposure change due to co-administration with the UGT1A1 inhibitor atazanavir?"

Key elements of the ICH M15 assessment table

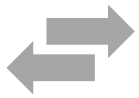
Element	Definition	Rating	Justification
Model influence	The intended weight of the model outcomes in decision-making considering the contribution of additional data or evidence.	HIGH	Modeling replaces a prospective clinical DDI study & informs the label.
Consequence of wrong decision	The potential negative effect (e.g., on patient safety and/or lack of efficacy) resulting from an incorrect decision based on all available information.	HIGH	Wrong co-medication labeling entailing an inaccurate benefit-risk assessment.[1]
Model risk	The contribution of the model outcomes to a possible wrong decision and subsequent potential undesirable consequences.	HIGH	Combination of model influence and consequence of wrong decision rating.
Model impact	The extent to which the proposed MIDD strategy varies from regulatory standards, or expectations when no regulatory standard is in place, for answering the question of interest.	MEDIUM	PBPK as substitute for DDI studies is generally accepted, OSP is qualified for UGT1A1/atazanavir – still less established for UGTs than for CYPs.

[1] Low to medium rating would be supported considering severity and likelihood of patient harm: vericiguat is titratable with a wide tolerated exposure range, changes in PD (blood pressure) are self-evident and monitorable. High rating is defensible only on a severity-weighted view: symptomatic hypotension/syncope with consequent falls and bone fractures in an elderly patient population.

Model risk drives rigor

MODEL RISK: influence × consequence

Characterizes the evaluation rigor.
Both model influence and consequence of wrong decision are rated high → high risk.



MODEL IMPACT : deviation from standards

Characterizes the communication / pre-alignment needs.

Consequences of "High risk" rating:

Positive control recovery
Required for both UGT pathways: mefenamic acid/dapagliflozin (UGT1A9); atazanavir/raltegravir (UGT1A1).

Independent UGT1A9 in vivo anchor
DDI study between mefenamic acid/vericiguat to constrain the fraction metabolized via UGT1A9 externally.

Platform qualification for intended use
Independent pre-qualification of the OSP platform for simulating UGT1A1/9-mediated DDIs.

Parameter sensitivity analyses
How do variations in key input parameters affect model output (i.e., predicted DDI magnitude)?

Pre-specified technical acceptance criteria

Base model (vericiguat + M-1)

- Dose range: 0.5 – 15 mg; IV infusion, oral solution, IR tablet; fasted and fed state.
- Data from several biological matrices: plasma, urine, and feces.
- Comparison of simulated/observed PK parameters for both vericiguat and M-1.
- Visual predictive checks for each study arm/cohort: overlay of simulated and observed concentration-time profiles + residual diagnostics.

Note: Generic go/no-go acceptance gates (e.g., “simulated PK parameters all within 2-fold of observed”) were not used.

DDI model (vericiguat/M1 + UGT perpetrators)

- Predicted/observed AUCR and CmaxR within 2-fold error range & Guest criterion
- Geometric mean fold error (GMFE)

Applied to:

- **UGT1A1:** atazanavir (inhibitor) / raltegravir (victim)
- **UGT1A9:** mefenamic acid (inhibitor) / dapagliflozin (victim)
- **UGT1A9 in vivo anchor:** mefenamic acid (inhibitor) / vericiguat (victim)

The UGT1A1 / 1A9 split is poorly informed

CONSTRAINED (mass balance + metabolite ID)

Glucuronidation ≈ 86% • Non-glucuronidation ≈ 14%



POORLY CONSTRAINED (identifiability gap)

UGT1A1 : UGT1A9 split within the 86%

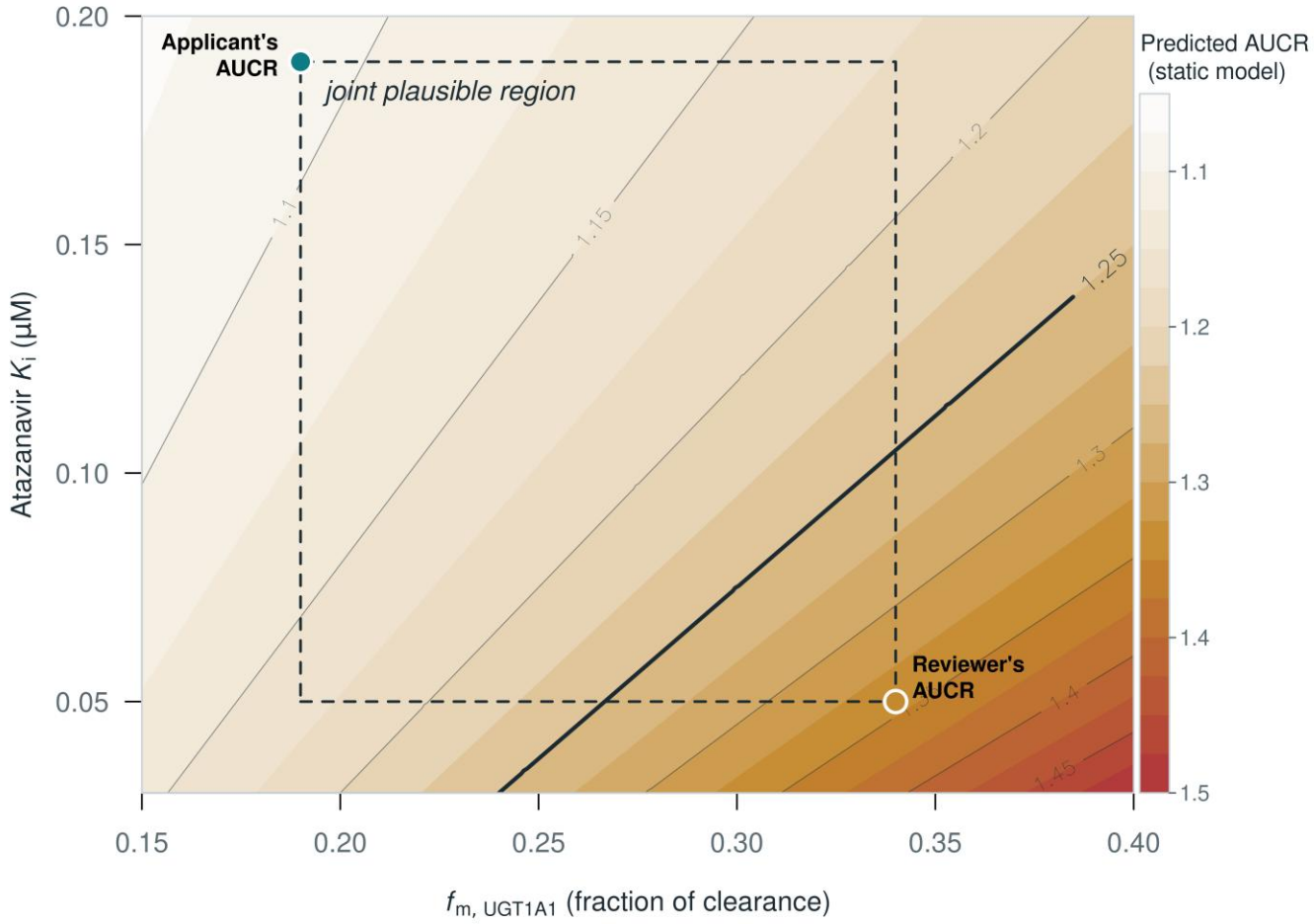
- The **relative contribution** of UGT1A1 vs. UGT1A9 to total glucuronidation is hard to determine.
- The **UGT1A9 in vivo anchor** has limitations:
  - Mefenamic acid is not a strong UGT1A9 inhibitor: The clinical DDI study between mefenamic acid / vericiguat found an **AUCR** of only **~1.20**.
  - This signal is **weak** and the simulated DDI is barely sensitive towards vericiguat's fm,UGT1A9.
- The atazanavir / vericiguat DDI is most sensitive to fm,UGT1A1, but neither the mass balance data nor the UGT1A9 in vivo anchor can fix fm,UGT1A1.
- In view of this uncertainty, the reviewer rebuild the PBPK model, **re-derived key input parameters** (namely Ki & fm,UGT1A1/9), and re-simulated the DDIs.

The reviewer's re-derivation and DDI simulations

1. **Fit mefenamic acid Ki (UGT1A9): 0.30 → 0.15 µM**
   to recover observed AUCR for mefenamic acid / dapagliflozin DDI study.
2. **Retrieve new fm,UGT1A9 for vericiguat: 0.67 → 0.52**
   from mefenamic acid / vericiguat DDI with fitted Ki.
3. **Estimate new fm,UGT1A1 for vericiguat: 0.19 → 0.34**
   Non-glucuronidation fraction from mass balance: 0.14, so: fm,UGT1A1 = 1 – 0.52 – 0.14 = 0.34.
4. **Fit atazanavir Ki (UGT1A1): 0.19 → 0.05 µM**
   to recover observed AUCR from atazanavir / raltegravir DDI studies.
5. **Re-simulate atazanavir / vericiguat DDI : 1.12 → 1.27**
   with fm,UGT1A1 = 0.34 and atazanavir Ki = 0.05 µM.

Combination	Observed AUCR	Applicant's AUCR	Reviewer's AUCR
Mefenamic acid + dapagliflozin	1.51	1.33	1.51
Mefenamic acid + vericiguat	1.20	1.14	1.20
Atazanavir + raltegravir	~1.70	~1.44	~1.72
Atazanavir + vericiguat	na	**1.12**	**1.27**

AUCR across the joint parameter uncertainty



Caveat: Figure created using static inhibition, not a PBPK model.

Concluding remarks

Concluding remarks

- **Outcome of the vericiguat submission:** MIDD evidence accepted, no clinical UGT1A1 DDI study required. Text in US drug label:

  "No clinically significant differences on vericiguat pharmacokinetics were predicted with coadministration of atazanavir (UGT1A1 inhibitor)."

- The vericiguat case example is **retrospective**: a case re-described in ICH M15 vocabulary.
- A **negative case** example (e.g., reconcile agencies who disagreed) would be more insightful.

- This **Best practice paper** is a collaborative initiative aiming to improve the quality, consistency and regulatory acceptance of PBPK applications.
- Although it summarizes the best practices from a relatively small group (five organizations), we hope it will serve many, trigger discussion within PBPK community, and ultimately lead to **better acceptance** by regulators.

Further reading

White Paper "Best Practices in PBPK Modeling" with completed assessment table:
Chenel M, Dallmann A, Ince I, Meyer M, Schlender JF, Teutonico D, Sjögren E. Best Practices in Physiologically Based Pharmacokinetic (PBPK) Modeling. CPT Pharmacometrics Syst Pharmacol. 2026 Jul;15(7):e70295. doi: 10.1002/psp4.70295.

Vericiguat PBPK model and DDI simulations with atazanavir/mefenamic acid:
Frechen S, Ince I, Dallmann A, Gerisch M, Jungmann NA, Becker C, Lobmeyer M, Trujillo ME, Xu S, Burghaus R, Meyer M. Applied PBPK modeling to assess UGT-mediated drug-drug interactions for Vericiguat. CPT Pharmacometrics Syst Pharmacol. 2024 Jan;13(1):79-92. doi: 10.1002/psp4.13059.

Vericiguat Integrated Review, CDER. Application Number: 214377Orig1s000:
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/214377Orig1s000IntegratedR.pdf

Vericiguat Drug Label (US):
https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/214377s000lbl.pdf