EMA
EUROPEAN MEDICINES AGENCY

HMA
Heads of Medicines Agencies

Industry experience and discussion from a PBPK working group on the predictive performance of PBPK model for DDI applications.

Kunal S. Taskar, PhD.
DMPK, GSK.
O.b.o. EFPIA and PBPK Working Group

GSK

Acknowledgments

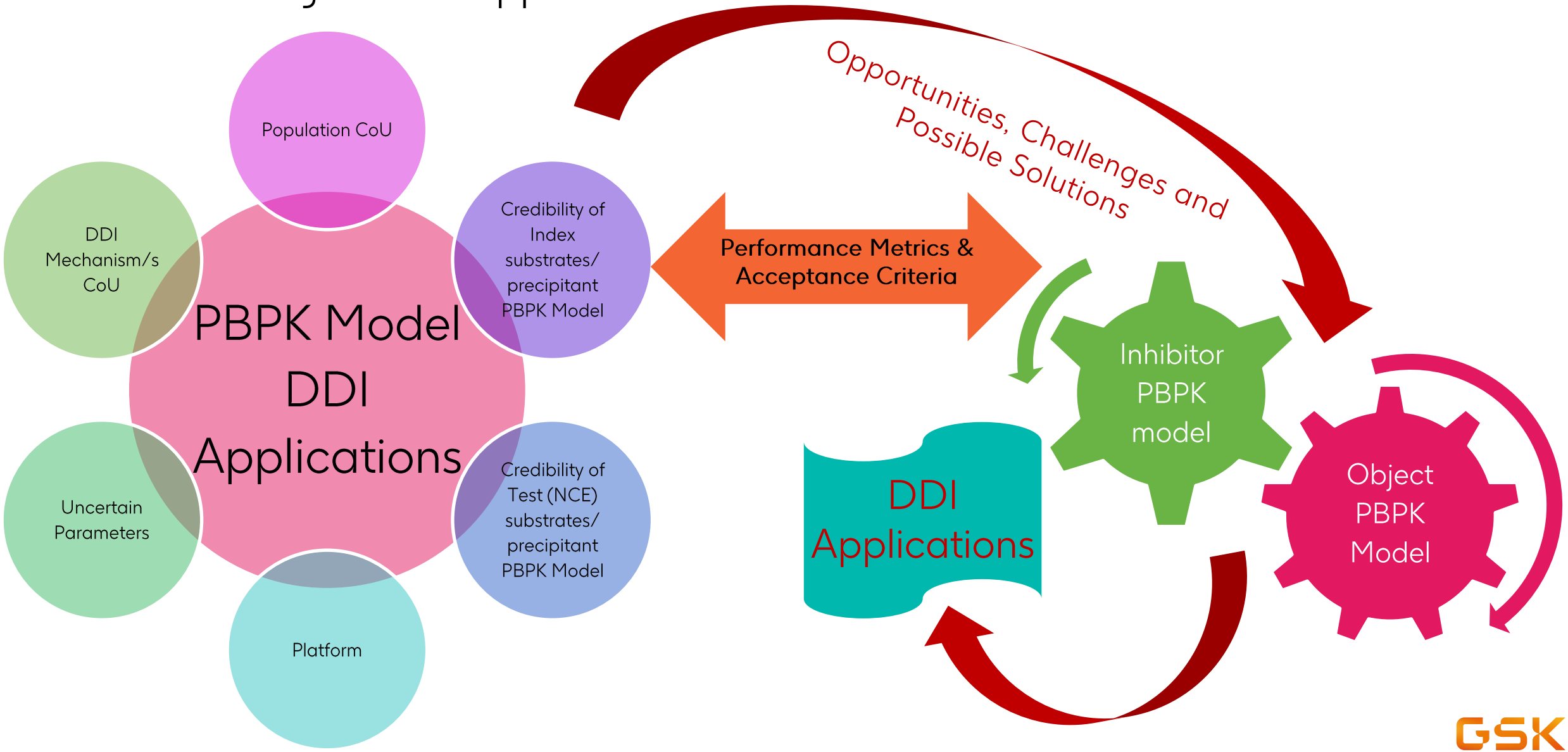
EFPIA
Pharma Industry PBPK Expert Team:
Loeckie de Zwart - Johnson & Johnson
Neil Parrot – Roche
Pradeep Sharma – AstraZeneca
Ivana Tomic – Novartis
Caroline Sychterz – BMS
Theunis Goosen – Pfizer
Gareth Lewis – GSK
Kunal Taskar - GSK
Priyanka Kulkarni –Takeda
Mary Choules – Astellas
Ryota Kikuchi – AbbVie
Maria Posada - Lilly
Sonya Chapman – Lilly
Ivelina Gueorguieva – Lilly
Jialin Mao - Genentech

DMPK GSK Team Members

The presentation represents the collected experience and opinions of multiple Pharmaceutical Industry experts in PBPK modelling who have united efforts for the purpose of delivering optimal input to this meeting.
The discussions were facilitated by Pharma Industry PBPK Expert Team (SMDG)
Final application and coordination was facilitated via EFPIA
We appreciate the opportunity to participate in this EMA multi-stakeholder workshop and thank the organizers for their work

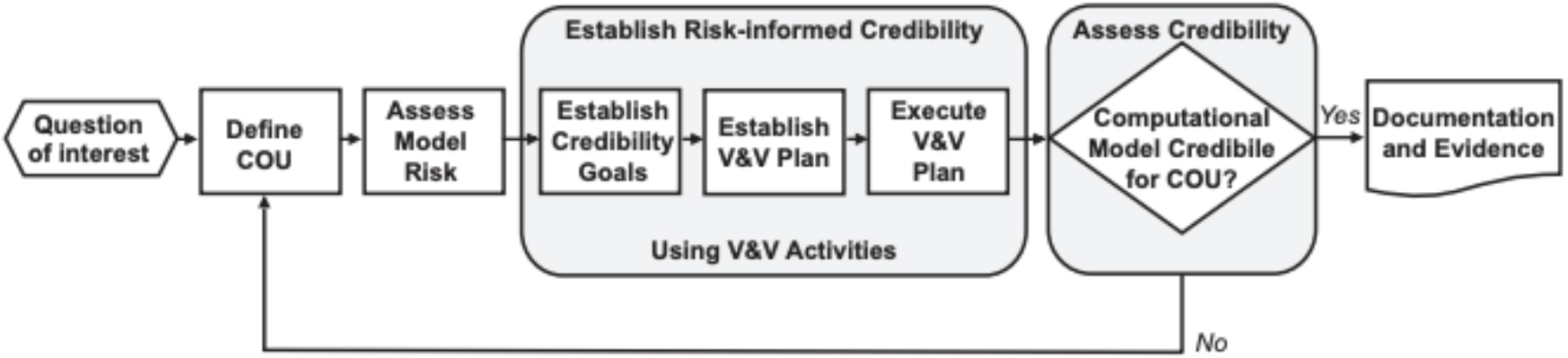
Summary of Discussion Topics

PBPK modeling for DDI Applications



Performance Metrics and Acceptance Criteria

Industry Approach – Catering to All Regulatory Guidelines



PBPK Model Documentation, Communication and Evidence should be aimed to cover:

- Clear objectives and scope
- Detailed description of model construction and assumptions
- Detailed description of software qualification
- Model codes, workspaces, compound files, PBPK package detailed contents
- Validation and uncertainty analysis
- Alignment with regulatory guidelines
- Clear presentation of clinical impact and practical implications

Citation: CPT Pharmacometrics Syst. Pharmacol. (2020) 9, 21–28; doi:10.1002/psp4.12479

WHITE PAPER

Consideration of a Credibility Assessment Framework in Model-Informed Drug Development: Potential Application to Physiologically-Based Pharmacokinetic Modeling and Simulation

Colleen Kuemmel[1,*], Yuching Yang[1], Xinyuan Zhang[1], Jeffry Florian[1], Hao Zhu[1], Million Tegenge[2], Shiew-Mei Huang[1], Yaning Wang[1], Tina Morrison[3] and Issam Zineh[1]

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

13 December 2018
EMA/CHMP/458101/2016
Committee for Medicinal Products for Human Use (CHMP)

Guideline on the reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation

Pmda
独立行政法人 医薬品医療機器総合機構
Pharmaceuticals and Medical Devices Agency

PSEHB/PED Notification No. 1221- 1
December 21, 2020

Guidelines for Analysis Reports Involving Physiologically based Pharmacokinetic Models

FDA U.S. FOOD & DRUG ADMINISTRATION

GUIDANCE DOCUMENT

Physiologically Based Pharmacokinetic Analyses — Format and Content Guidance for Industry

SEPTEMBER 2018

GUIDANCE DOCUMENT

The Use of Physiologically Based Pharmacokinetic Analyses — Biopharmaceutics Applications for Oral Drug Product Development, Manufacturing Changes, and Controls

Draft Guidance for Industry

SEPTEMBER 2020

Performance Metrics and Acceptance Criteria

Industry Approach – Using Regulatory Guidelines

ICH harmonisation for better health

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 November 2024
EMA/CHMP/ICH/496426/2024
Committee for Human Medicinal Products

ICH M15 Guideline on general principles for model-informed drug development
Step 2b

ICH M15 Guideline

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 • Context of Use • Model Influence • Consequence of Wrong Decision • Model Risk • Model Impact	• Appropriateness of Proposed MIDD • Technical Criteria for model evaluation and model outcomes[1] These should be documented (e.g., in a Model Analysis Plan [MAP]).	• Verification • Validation • Applicability assessment	• Model Analysis Report(s) (MAR)	• Regulatory documents, including + Outcome of MIDD Evidence Assessment + 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

GSK

Performance Metrics and Acceptance Criteria in PBPK DDI Applications

Considerations

Precision

- • **Consistency Across Simulations:** Precision refers to the consistency in model predictions when the same simulation is repeated (e.g., multiple runs with similar parameter distributions or within different software versions _ Industry practice to repeat SD/MD simulation for confirmation).
- • **Statistical Variability:** For large number of simulations (often via Monte Carlo methods), precision can be evaluated in terms of the variability (e.g., standard deviation or coefficient of variation) of key outputs such as Cmax, AUC, or AUC ratios between object and precipitant drugs.
- • **Confidence or Prediction Intervals:** Narrow prediction intervals that consistently capture observed data can indicate a high level of precision in model predictions- Depends on available clinical sample size and extrapolation CoU.

Predictive Accuracy

- • **Comparison with Observed Data:** Predictive accuracy assesses how close the PBPK model's outputs (e.g., concentration–time profiles, extent of DDI as measured by changes in AUC or Cmax) are to observed clinical outcomes.
- • **Quantitative Metrics:**
  - Metrics like root mean square error (RMSE) or mean absolute error (MAE) can be used to quantify the deviation between predicted and actual values.
  - Geometric mean ratios (GMRs) for key exposure metrics comparing predicted versus observed data—especially in scenarios where the magnitude of the DDI effect is important—are also commonly applied.
- • **Visual Predictive Checks :** Overlaying observed concentration data with simulated percentiles (e.g., 5th, 95th) helps assess how well the model approximates the overall behavior of the system during a DDI scenario.

Bias Assessment

- • **Systematic Over- or Under-Prediction:** Bias quantifies whether the model systematically overpredicts or underpredicts drug exposures in the presence (or absence) of an interacting drug.
- • **Mean Prediction Error (MPE):** Calculating the average difference between observed and predicted parameters (expressed either as an absolute difference or a percentage) can highlight consistent trends.
- • **Graphical method** can be employed to visualize the agreement between observed and predicted values, providing insights into any systematic bias over the range of data: e.g. Bland-Altman Analysis data, Forest Plots etc.
- • **DDI-Specific Considerations:** It is crucial to check if the model accurately predicts the magnitude of interaction (for instance, changes in the metabolic clearance) rather than just the parent drug concentrations, as even small biases here can considerably affect conclusions regarding dose adjustments

Uncertain Parameters for PBPK DDI Applications

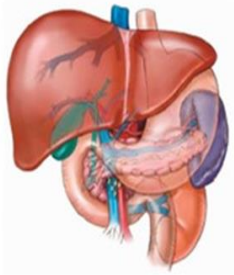
Identify Origins

System specific factors

Demographic and genetic factors

Age
Weight
Height
Sex
Genetics
Race
Disease

Anatomical and physiological factors

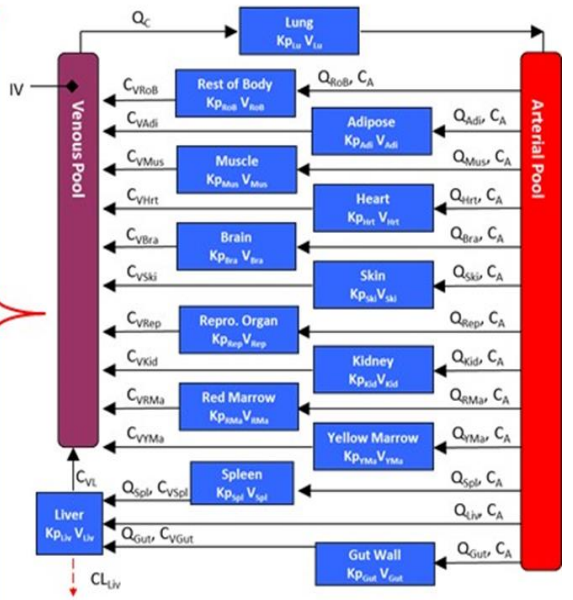


Organ size
Blood flow
Enzymes
Transporters
Plasma protein
Haematocrit
Transit time
pH

Drug specific factors

MW
pK_a
Log P
PSA
Solubility
Permeability
K_m, V_{max}
fu, B:P, fu_{inc}

Mechanistic PBPK



Disease impact,

Abundance of DMETs

Identify and incorporate/ update based on relevant in vitro and clinical datasets

Robust In vitro Assays

- Absorption inputs
- DMETs - IC50 or Ki or EC50 –Emax or Ki/kinact
- Transporter/enzyme Km/Vmax or Clint
- Plasma protein binding

Uncertainty Quantification for PBPK DDI Applications

Sources and Impact

Safety Risks

1) Under or overestimation of DDI Magnitude

2) Inaccurate IVIVE Scaling – enzyme transporter abundance

3) Physiological and Population Variability

4) Quality and Source of Experimental data

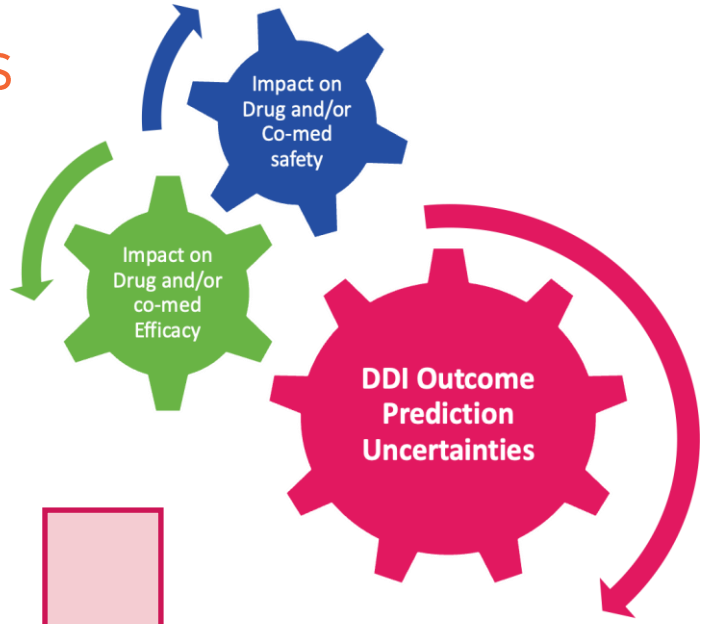
5) Time dependant nature of DDI effects

6) Combined Effects of Multiple DDIs – synergistic or antagonistic effect to maintain efficacy or avoid tox.

7) Regulatory and Translational Impact

8) Sensitivity Analysis – Range definition overtly conservative or done without any clinically relevant basis

Therapeutic Effect



Uncertainty Quantification

'Results of sensitivity analyses for uncertain parameters should be discussed in the context of the simulation conditions and potential clinical relevance.' FDA PBPK Guidance

A 'worst-case' approach is recommended e.g. for CYP enzymes 10-fold, for transporters 30-fold. EMA PBPK Guidance

Sensitivity Analysis Range for PBPK Analysis of Enzyme/Transporter Inhibition/Induction Mediated DDIs

FACT

It is important to identify uncertain/sensitive parameters and strategize and conduct a suitable sensitivity analyses for that PBPK Model DDI application.

REALITY

- **Lack of Industry wide uniform approach** to strategize Sensitivity Analysis Range.
- **Variability in *in vitro* assays** systems/methods and resultant measured IC50 or Ki values across labs regarded as an arbitrary rationale for a wide range of a Sensitivity Analysis selection; e.g. 100-, 30-, 10-fold more potent than actual measured values.
- **Lack of general guidance on sensitivity analysis** range selection rationale that can be used as a starting point.
- **PBPK Models for drug transporter Inhibition** mediated DDI assessments not consistently evaluated or accepted by Regulatory agencies.

Addressing Uncertainty – IC50/Ki/EC50 In vitro Values

Possible Approach for Reasonable Sensitivity Analysis

Enzyme/ Transporter	Substrate	Inhibitor/Inducer
CYP3A4/5	Midazolam	Itraconazole and hydroxy metabolite/ Multiple dose Rifampicin
CYP1A2	Caffeine	Fluvoxamine
CYP2C8	Repaglinide	Gemfibrozil
CYP2C9	S-warfarin	Fluconazole
CYP2C19	Omeprazole	Fluvoxamine
CYP2D6	Desipramine	Fluoxetine
P-gp	Digoxin	Verapamil
BCRP	Rosuvastatin	Cyclosporine
OATP1B1/1B3	Rosuvastatin	Single dose Rifampicin
OAT1	Furosemide	Probenecid
OAT3	Furosemide	Probenecid
OCT2,	Metformin	Dolutegravir
MATE1/2-K	Metformin	Pyrimethamine

Reference: ICH M12 Guideline.[3]

In vitro Assay Inhibition or Induction values for Test Drug along with Selected Probe Substrate– Index Inhibitor/Inducer Pair

+

Clinical DDI study for Selected Probe Substrate- Index Inhibitor Pair

+

Qualified PBPK Model for Probe Substrate-Index Inhibitor/Inducer Verified using Clinical DDI Studies

Establish correlation between the in vitro measured Inhibition or Induction Value for Probe Substrate-Index Inhibitor Pair and establish the Excursion Factor

Use excursion factor to rationalize suitable Sensitivity Analysis range for Test Drug

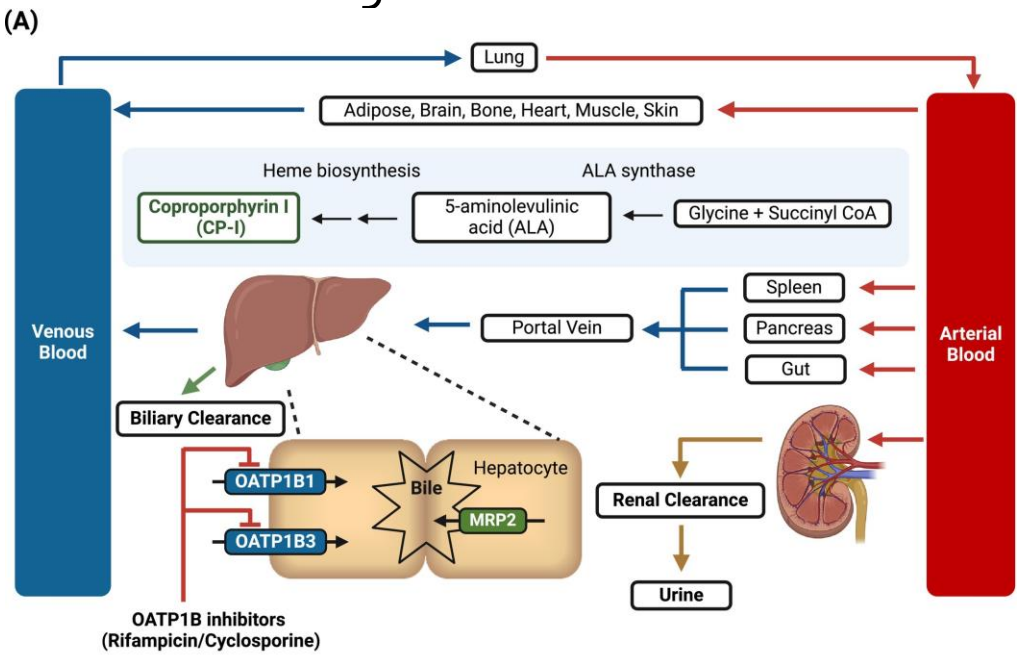
In vitro Run #	Rifampin EC50 (µM) values from several runs	Fold of clinically calibrated EC50 value of Rifampicin of ~ 0.32 µM*	SA range determination with clinically calibrated
1	0.21	0.7	No SA necessary
2	0.38	1.2	
3	0.42	1.3	
4	0.45	1.4	
5	0.45	1.4	
6	0.49	1.5	SA with up to 2x more potent EC50
7	0.49	1.5	
8	0.49	1.5	
9	0.51	1.6	
10	0.51	1.6	
11	0.57	1.8	
12	0.59	1.8	
13	0.59	1.8	
14	0.61	1.9	
15	0.63	2.0	
16	0.64	2.0	
17	0.66	2.1	
18	0.66	2.1	
19	0.69	2.2	
20	0.70	2.2	
21	0.71	2.2	
22	0.74	2.3	SA with up to 3x more potent EC50
23	0.75	2.4	
24	0.76	2.4	
25	0.76	2.4	
26	0.77	2.4	
27	0.78	2.4	
28	0.79	2.5	
29	0.80	2.5	
30	0.81	2.5	
31	0.83	2.6	
32	0.89	2.8	
33	0.89	2.8	
34	0.90	2.8	
35	0.90	2.8	
36	0.91	2.8	
37	0.91	2.8	
38	0.92	2.9	
39	0.97	3.0	
40	0.98	3.1	
41	1.00	3.1	
42	1.05	3.3	
43	1.07	3.4	
44	1.08	3.4	
45	1.13	3.5	
46	1.15	3.6	
47	1.16	3.6	
48	1.16	3.6	
49	1.18	3.7	
50	1.21	3.8	SA with up to 4x more potent EC50
51	1.21	3.8	
52	1.21	3.8	
53	1.21	3.8	
54	1.23	3.8	
55	1.29	4.0	
56	1.31	4.1	
57	1.31	4.1	
58	1.31	4.1	
59	1.34	4.2	
60	1.35	4.2	
61	1.39	4.3	
62	1.39	4.3	
63	1.42	4.4	
64	1.42	4.4	
65	1.44	4.5	SA with up to 5x more potent EC50
66	1.47	4.6	
67	1.47	4.6	
68	1.48	4.6	
69	1.50	4.7	
70	1.50	4.7	
71	1.53	4.8	
72	1.55	4.8	
73	1.66	5.2	
74	1.71	5.4	
75	1.73	5.4	
76	1.78	5.6	SA with up to 6x
77	1.83	5.7	
78	1.90	5.9	more potent EC50
79	1.96	6.1	
80	1.98	6.2	
81	2.01	6.3	
82	2.01	6.3	
83	2.21	6.9	SA with up to 7x more potent EC50
84	2.47	7.7	SA with up to 8x more potent EC50
85	2.73	8.5	SA with up to 9x more potent EC50
86	2.90	9.1	
87	2.93	9.1	

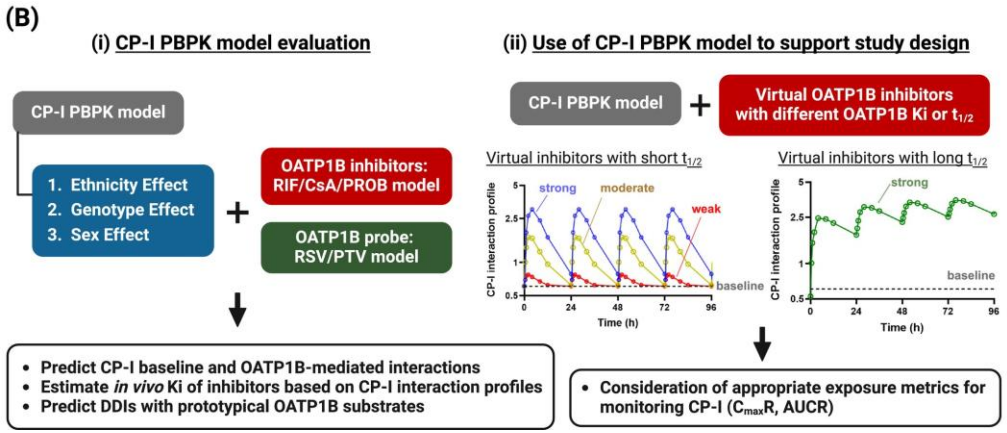
*Please note that these data values are examples from an internal dataset and will vary between labs. Sensitivity analysis must be tailored to specific in vitro assay conditions and the PBPK platform used. They require re-optimization and justification if assay conditions or test systems change.

*Reddy et al. IQ paper 2024.[7]

Using Clinical Data to Calibrate/Confirm Uncertainty Quantification

Use of Endogenous Biomarkers along with PBPK Modeling for DDI Applications





(I) Phase-1 dose escalation study for a new chemical entity (NCE) to obtain in vivo $K_{i,OATP1Bs}$ using CP-I as an endogenous probe

(II) Calculation of *in vivo* $K_{i,OATP1Bs}$ for probe substrate drugs (e.g. statins) using *in vivo* $K_{i,OATP1Bs}$ for CP-I obtained in (I), and *in vitro* $K_{i,OATP1B}$ for CP-I and probe substrate drugs

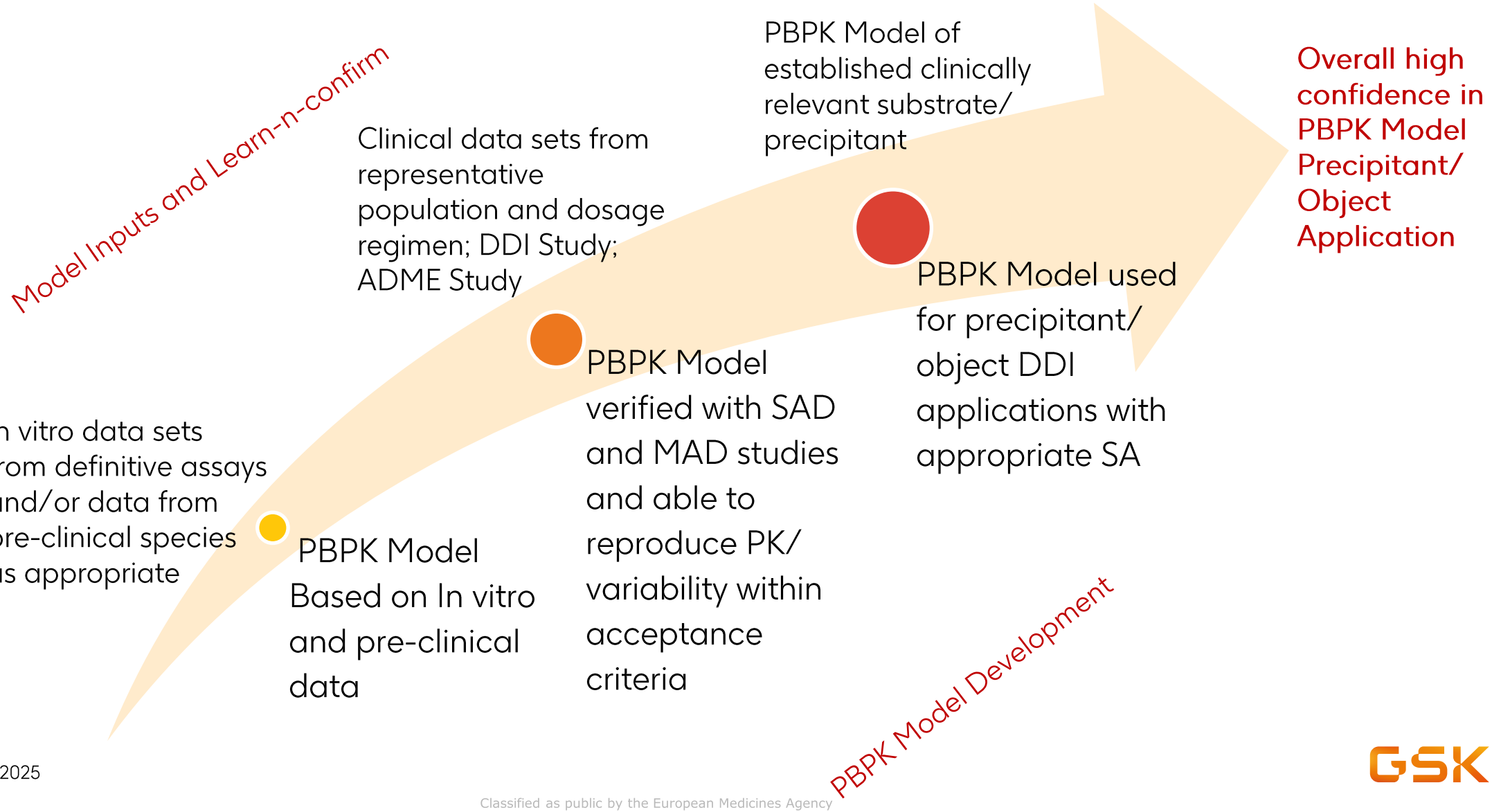
$$in\ vivo\ K_{i_{OATP1Bs(Drug)}} = in\ vivo\ K_{i_{OATP1Bs(CPI)}} \times \frac{in\ vitro\ K_{i_{OATP1Bs(Drug)}}}{in\ vitro\ K_{i_{OATP1Bs(CPI)}}}$$

(III) Prediction of changes in concentration-time profiles, AUC and C_{max} of probe substrate drugs caused by a NCE by PBPK modeling and simulation

- Yoshikado T, Toshimoto K, Maeda K, Kusuhara H, Kimoto E, Rodrigues AD, Chiba K, Sugiyama Y. PBPK Modeling of Coproporphyrin I as an Endogenous Biomarker for Drug Interactions Involving Inhibition of Hepatic OATP1B1 and OATP1B3. CPT Pharmacometrics Syst Pharmacol. 2018 Nov;7(11):739-747. doi: 10.1002/psp4.12348. Epub 2018 Sep 30. PMID: 30175555; PMCID: PMC6263667.
- Ujihira, Y., Tan, S.P.F., Scotcher, D. and Galetin, A. (2025), Genotype, Ethnicity, and Drug–Drug Interaction Modeling as Means of Verifying Transporter Biomarker PBPK Model: The Coproporphyrin-I Story. CPT Pharmacometrics Syst Pharmacol, 14: 941-953. https://doi.org/10.1002/psp4.70008

PBPK Model Application for a Precipitant or Object

Confidence-building for DDI Application

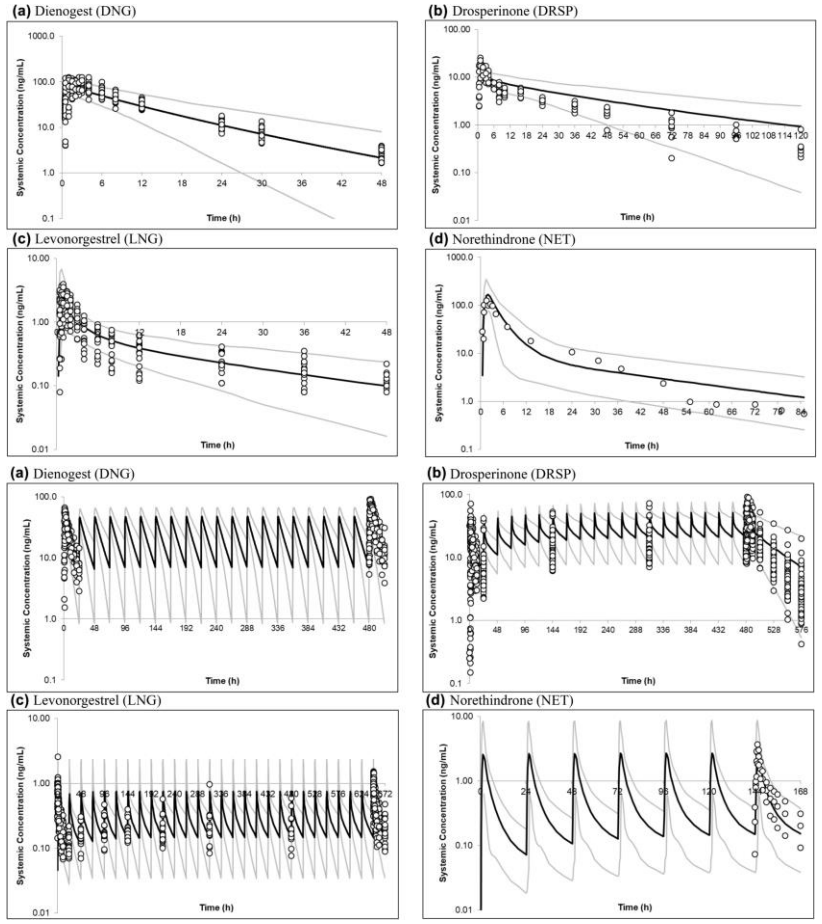


PBPK Model Application DDI Assessment

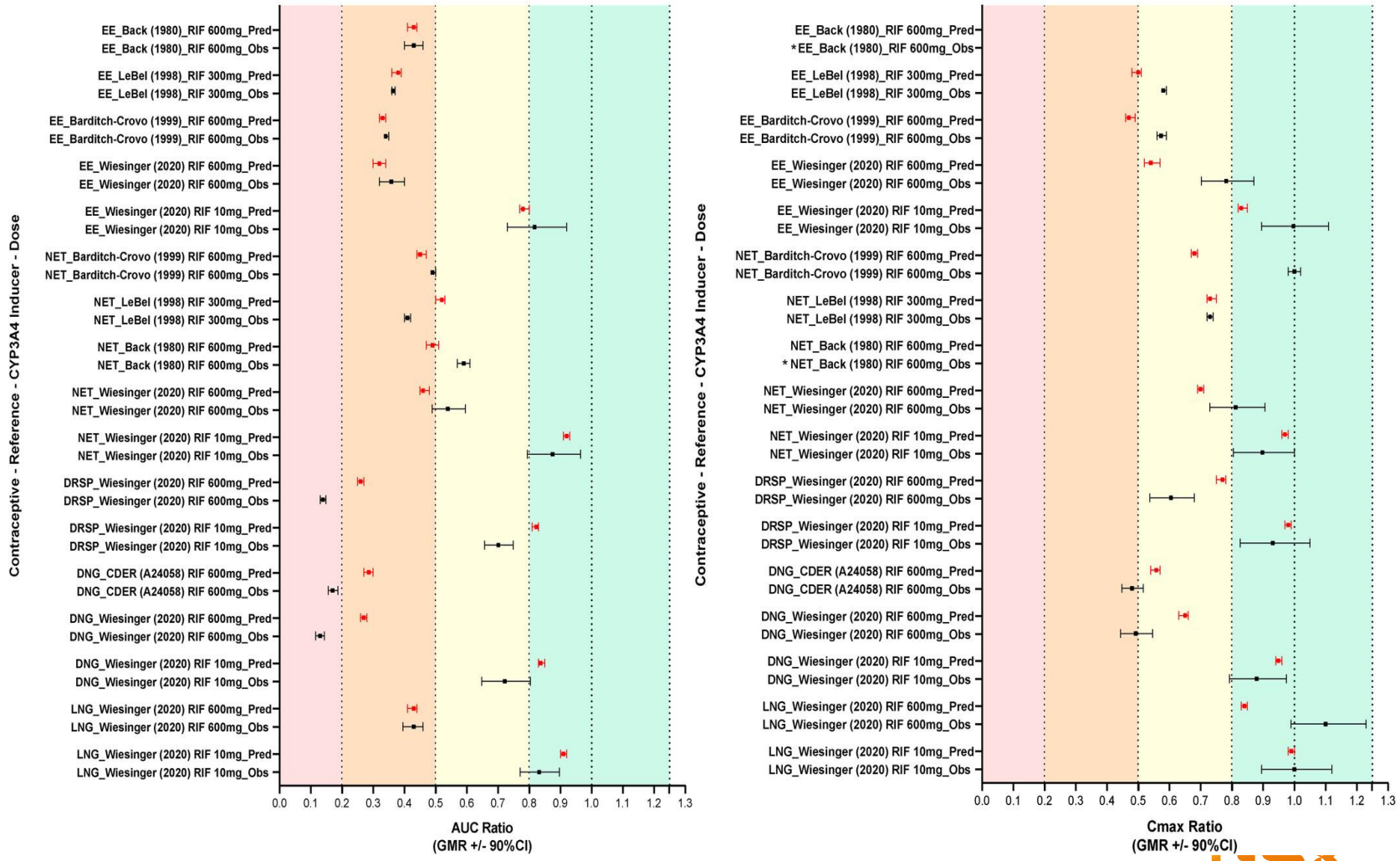
Matrix Based Approach Additional Example: Oral Contraceptives

Acceptance Criteria – Guest Criteria or Suitable Statistical analysis for PBPK Model DDI Application

Single and Multiple Dose Verification



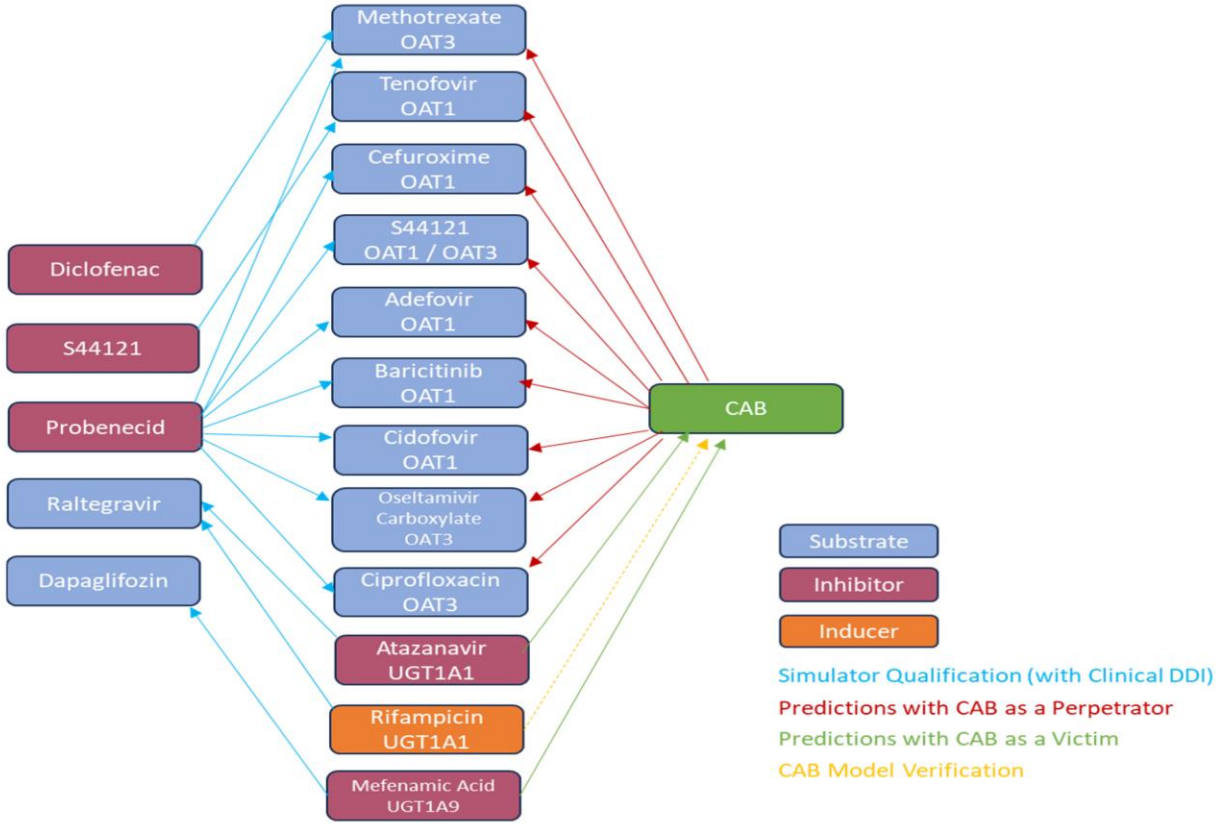
DDI Prediction Verification

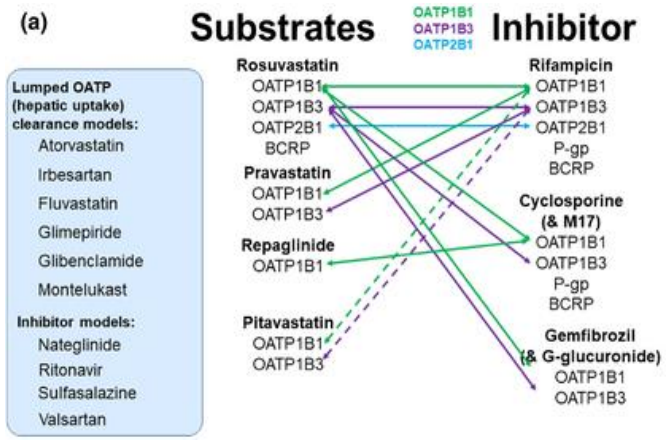


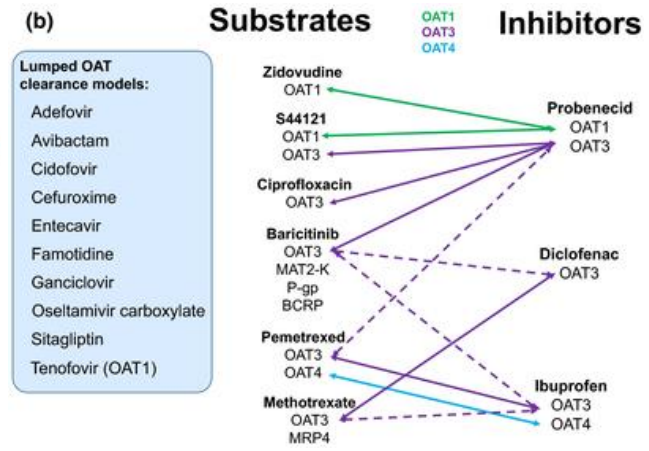
Lewis GJ, Ahire D, Taskar KS. Physiologically-based pharmacokinetic modeling of prominent oral contraceptive agents and applications in drug-drug interactions. CPT Pharmacometrics Syst Pharmacol. 2024 Apr;13(4):563-575. doi: 10.1002/psp4.13101. Epub 2024 Jan 15. PMID: 38130003; PMCID: PMC11015076.

PBPK Model Application – Case Study: Transporter Inhibitor

Matrix Based Approach for Performance Metrics and Acceptance Criteria





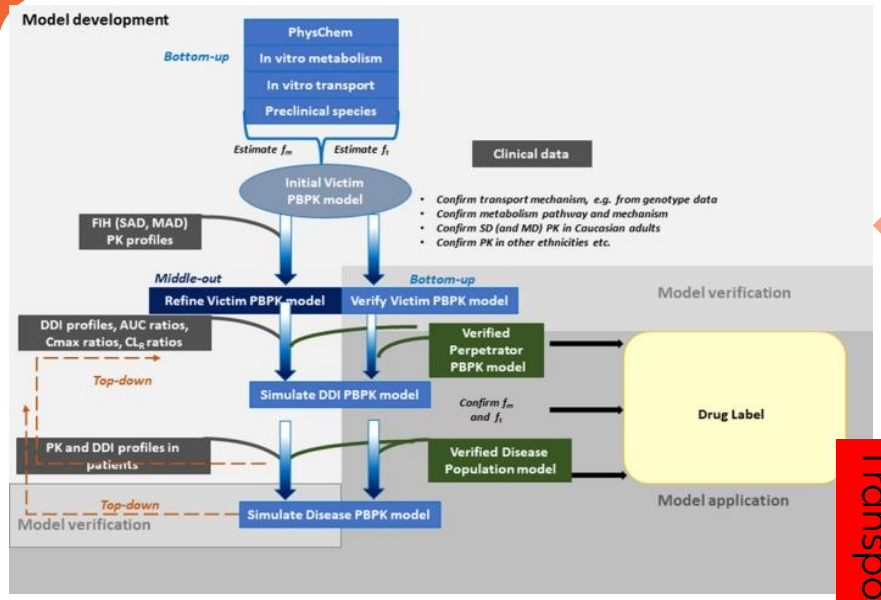


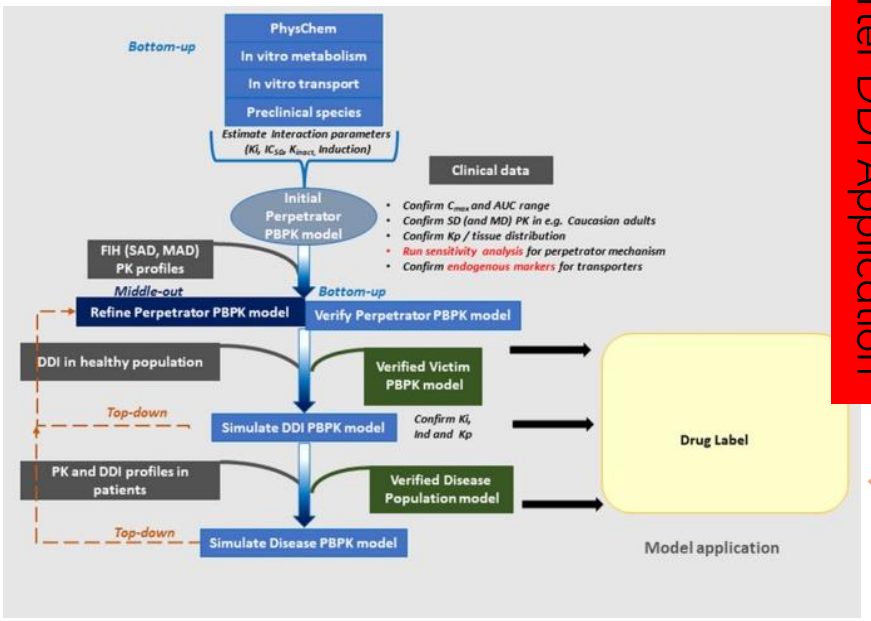
Matrix Based Approach:

- Involves testing and gaining confidence in the mechanism of DDI for the NCE precipitant or object drug model with DDI models of clinically relevant object or precipitant drug models, respectively.
- Effective for DDI applications involving single or multiple DDI mechanisms

- Tracey, H.; Bate, S.T.; Ford, S.; Patel, P.; Bloomer, J.; Patel, A.; Taskar, K.S. Matrix Approach Assessment of Cabotegravir Drug–Drug Interactions with OAT1/OAT3 Substrates and UGT1A1/UGT1A9 Inhibitors Using Physiologically-Based Pharmacokinetic Modeling. *Pharmaceutics* **2025**, *17*, 531. https://doi.org/10.3390/pharmaceutics17040531.
- Hariparsad N, Ramsden D, Taskar K, Badée J, Venkatakrishnan K, Reddy MB, Cabalu T, Mukherjee D, Rehmel J, Bolleddula J, Emami Riedmaier A, Prakash C, Chanteux H, Mao J, Umehara K, Shah K, De Zwart L, Dowty M, Kotsuma M, Li M, Pilla Reddy V, McGinnity DF, Parrott N. Current Practices, Gap Analysis, and Proposed Workflows for PBPK Modeling of Cytochrome P450 Induction: An Industry Perspective. Clin Pharmacol Ther. 2022 Oct;112(4):770-781. doi: 10.1002/cpt.2503. Epub 2021 Dec 24. PMID: 34862964.

PBPK Modeling Workflow for Precipitant or Object NCE DDI Assessment





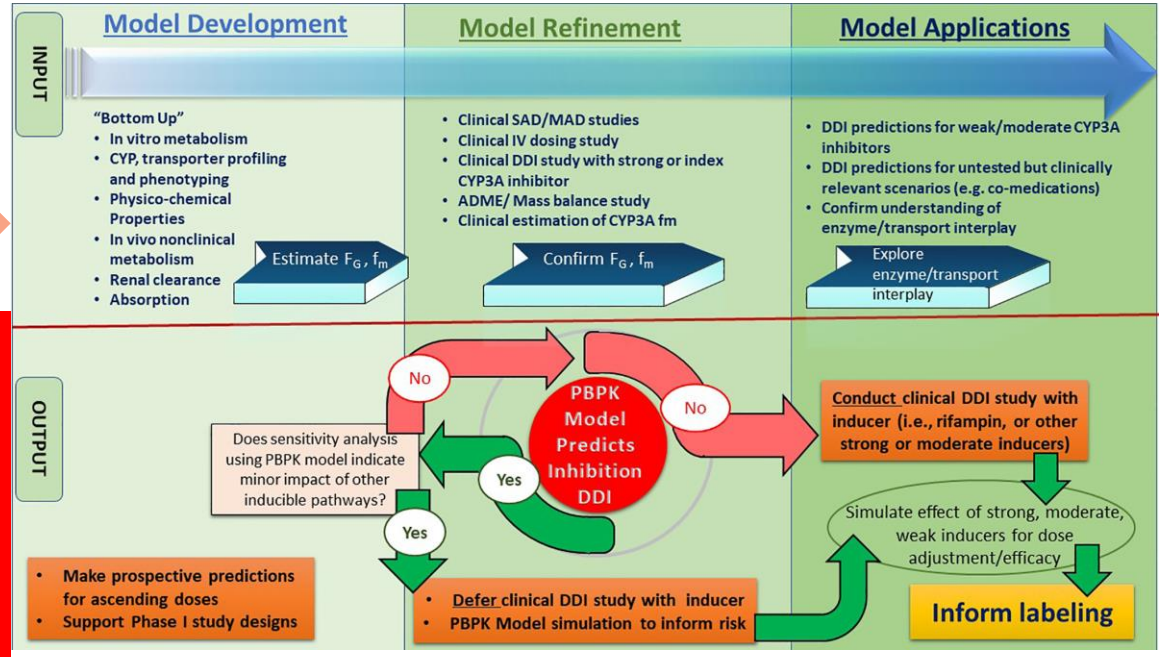
Substrate PBPK Model Development

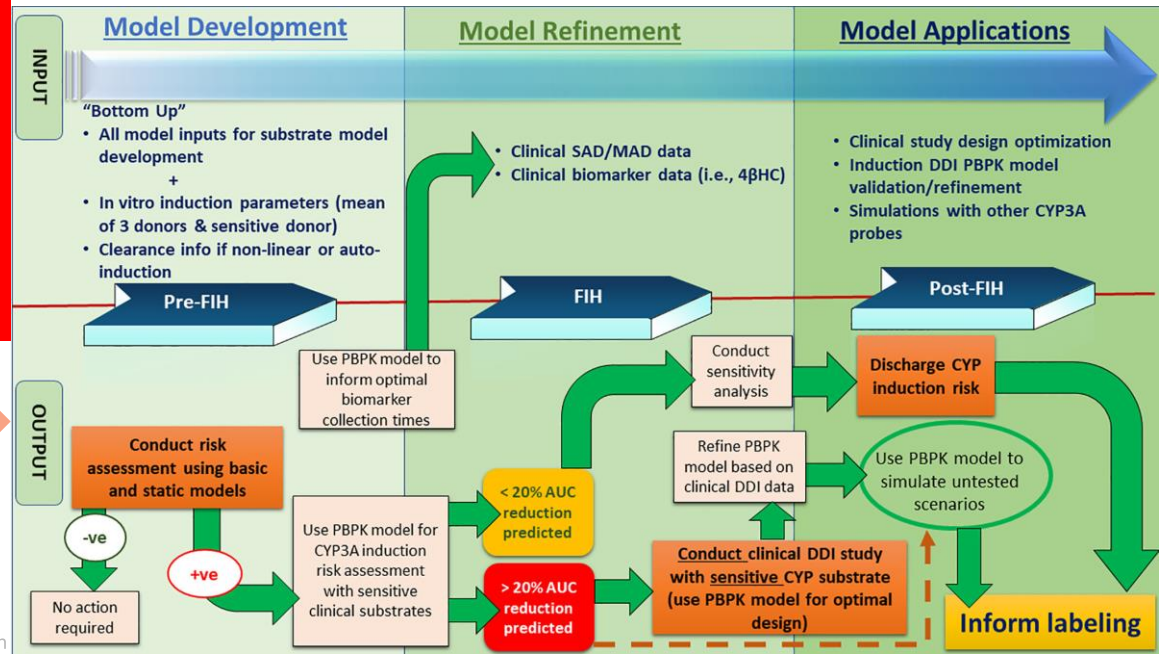
Transporter DDI Application

Targeted workflow for PBPK DDI Model CoU

CYP3A Induction DDI Application

Precipitant PBPK Model Development

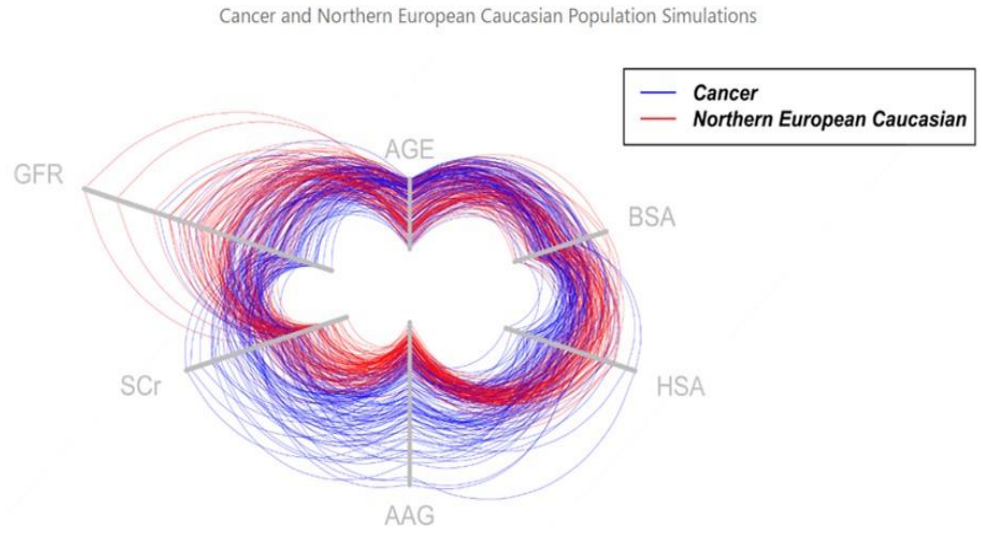




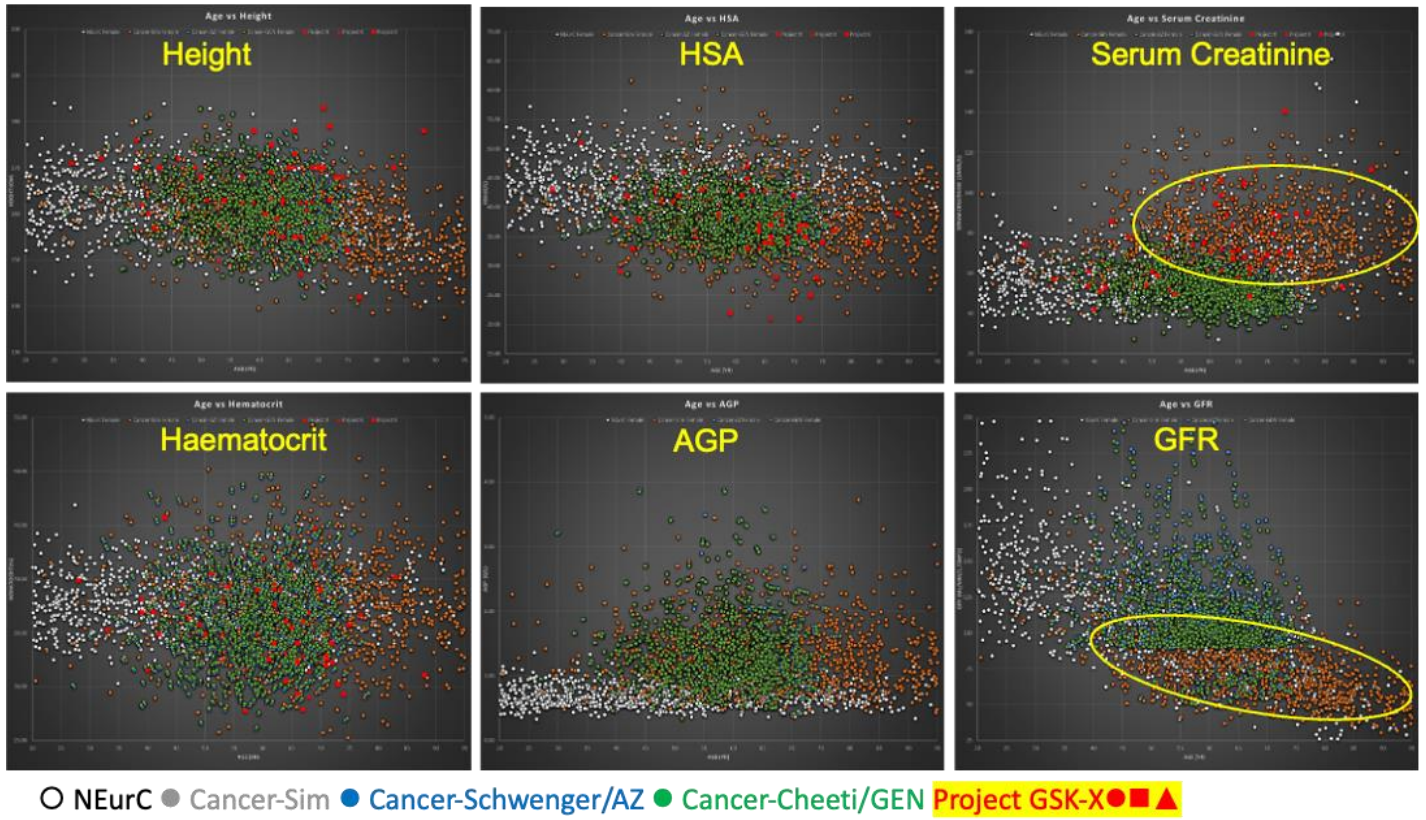
- Taskar KS, et al., Clin Pharmacol Ther. 2020 May;107(5):1082-1115.
- Hariparsad N, et al. Clin Pharmacol Ther. 2022 Oct;112(4):770-781..

Confirming Impact of Disease on Drug PK and DDI for PBPK Model Applications

The following Hive plot, where each strand represents an individual, provides a visualization of different parameter differences from a simulation of 1,000 individuals using the Northern European Caucasian (red) and Cancer (blue) populations.

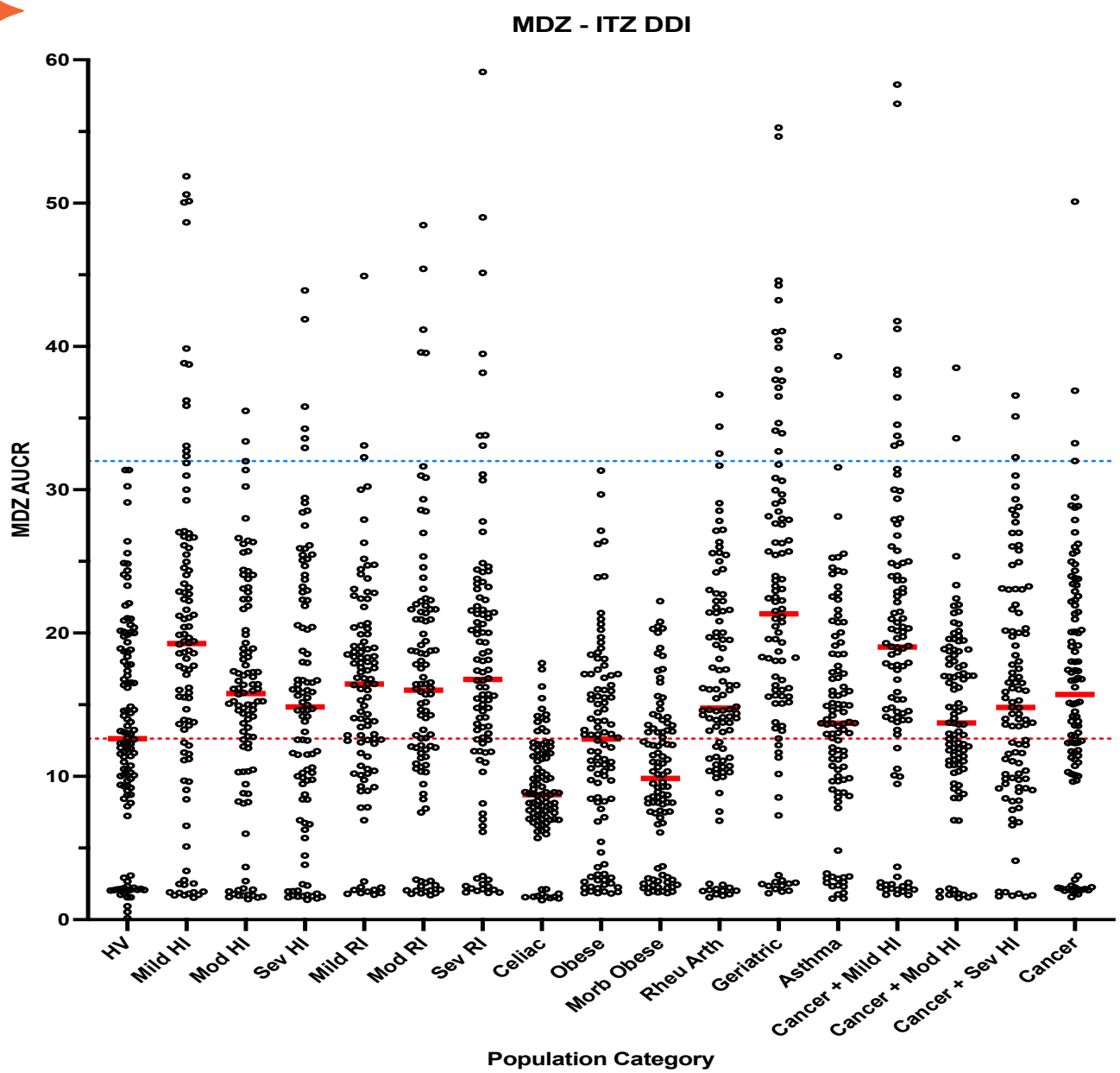


BSA: Body surface area
HSA: Human serum albumin
AAG: α_1-acid glycoprotein
SCr: Serum creatinine
GFR: Glomerular filtration rate



- Disease results in changes in drug metabolizing enzymes and/or transporters which are important determinant of drug clearance and disposition.
- Disease results in altered physiological changes such as plasma protein levels, blood flow changes, organ impairment etc. and such other physiological changes.
- Confirming Disease Models is crucial for qualifying, extending, or applying PBPK Population Models

DDI Extent in Various Disease - AUC ratio



Ratio of Median AUCR in Disease to AUCR in Healthy

Mild/Mod/Severe HI - 1.18 - 1.53

Mild/Mod/Severe RI - ~1.30

Geriatric – 1.69

Cancer – 1.25

Cancer with mild HI – 1.51

Obese – 1.01

Rheumatoid Arthritis – 1.17

Cancer with mod HI – 1.09

Cancer with severe HI – 1.17

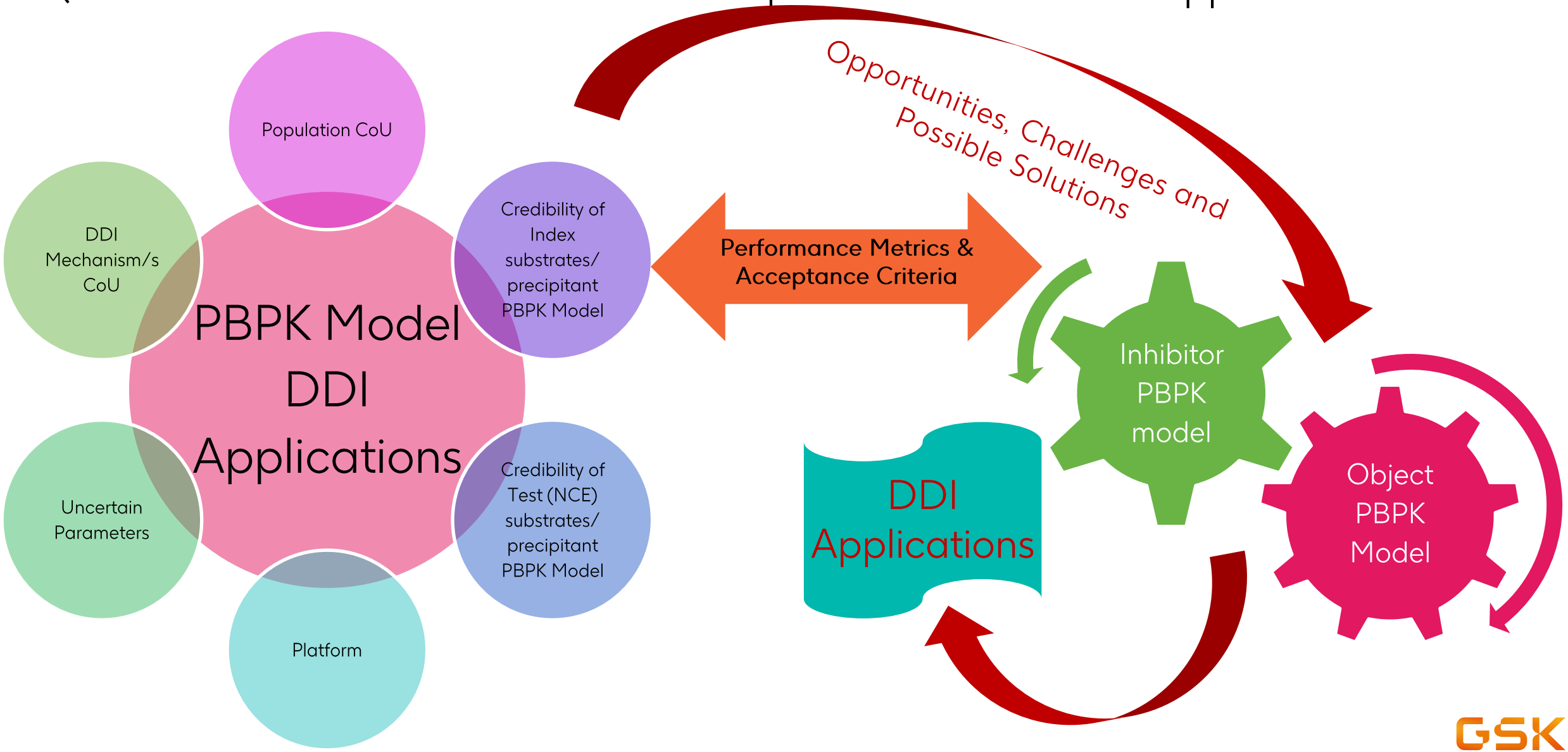
Celiac – 0.69

Morbidly Obese – 0.78

PBPK Simulations using Simcyp v24; Using either platform default or developed Disease Populations.

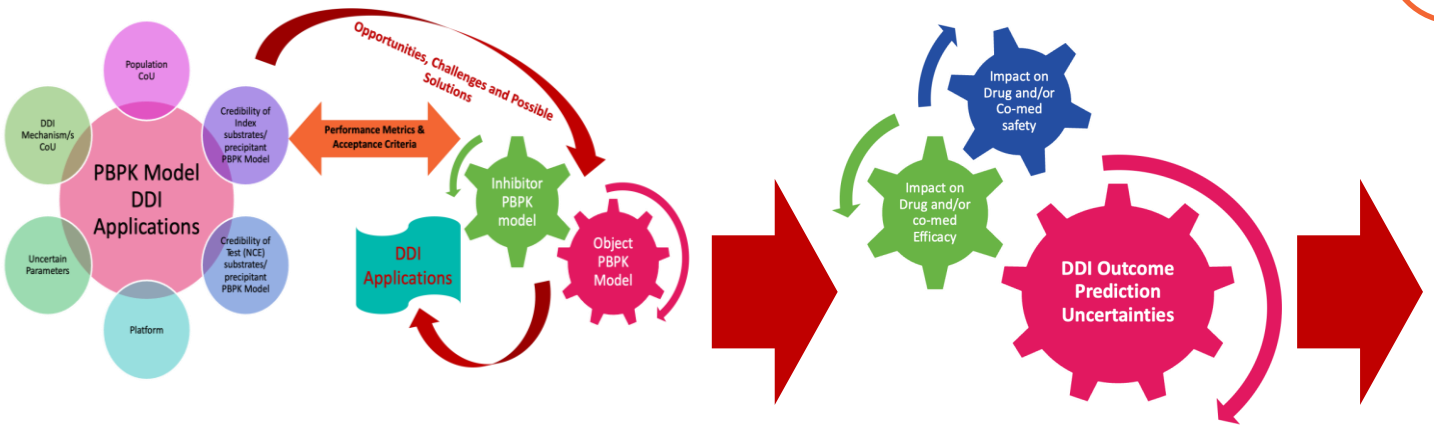
Piecing together the Jigsaw

Qualification of all identified critical components of PBPK DDI Applications



Expansion of 'Qualification' – Following up on the Momentum

Expand and Extend Considerations for PBPK Model/Platform Qualification for



- Enzyme Induction
- Transporter DDI Applications
- Complex DDI Mechanisms
- Specific Population: Pediatrics, Pregnancy-Lactation, Organ Impairment etc.
- Non-CYP Mediated Enzyme DDIs
- Biopharmaceutics Application

Practical Next Discussions:

- Consensus on re-use of Qualified/Verified Platform for DDI CoU
- Consensus on re-use of Qualified/Verified Substrate/Precipitant for DDI CoU
- Discussion on extension and expansion of previous specific CoU qualified platform for other applications

PBPK Modeling Working Group Collaborations

EMA Platform Qualification - Position Statement on Approach Used

The PBPK Working Group commends the European Medicines Agency for the qualification of the Simcyp Simulator. The group asserts that the Bayesian Framework approach employed is both suitable and comprehensive, facilitating a matrix-based PBPK DDI Model Qualification and Application.

- This framework enhances clarity in the submission and communication of similar DDI PBPK work packages.
- The Industry PBPK Working Group also highlights that several consortia, individual industries, and vendors have published similar 'Context of Use' approaches for DDI and additional PBPK applications.
- There is opportunity to leverage the gained momentum and EMA DDI Workshop for discussions on the suitability of additional PBPK applications beyond those covered in the current qualification document, thereby advancing Model-Informed Drug Development.

Next Steps:

Scope of Industry PBPK WG to collaborate with EMA on the next set of PBPK DDI and Specific Population Applications?