PBPK Drug-Drug-interaction (DDI) Network Qualification and Regulatory Application

Thomas Wendl, Bayer AG
OSP Community Conference
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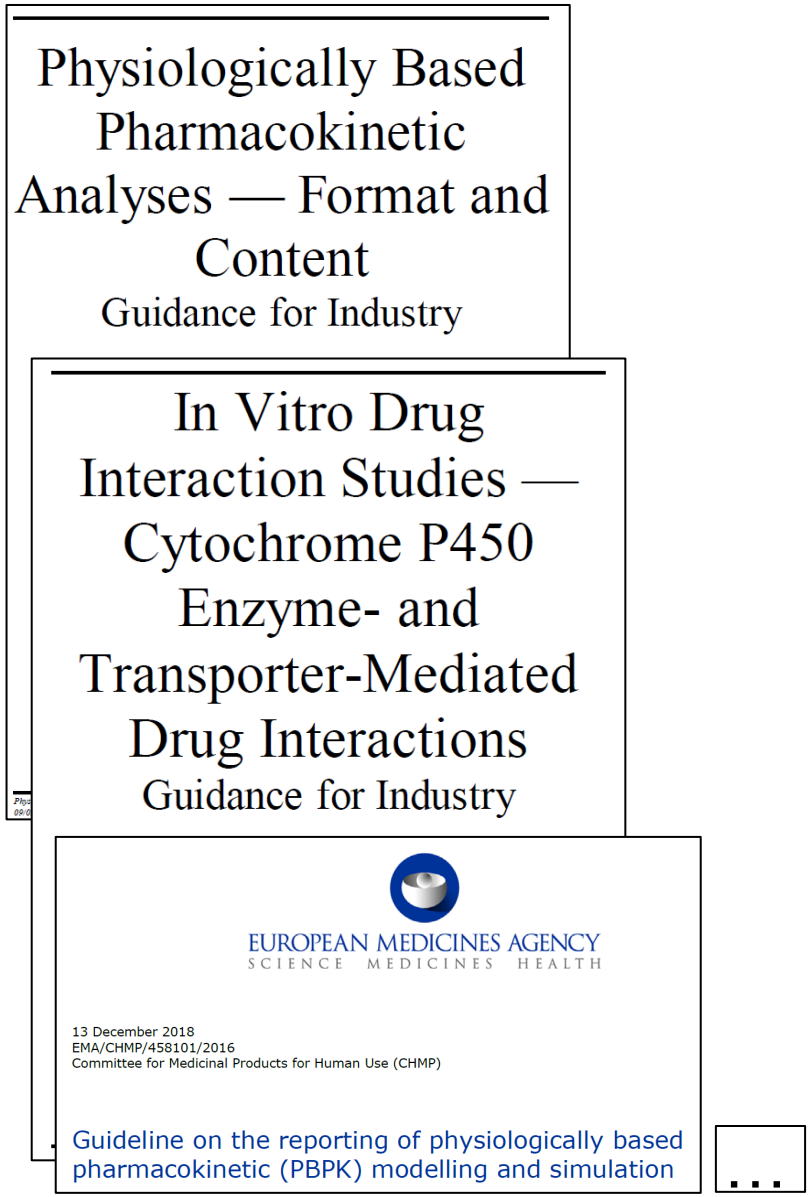
Regulatory guidelines / guidances



Guidelines

- Focus on pharmacokinetic DDIs
- Promote the use of PBPK **modelling in lieu of** conducting clinical DDI studies

Require:

- **PBPK platform qualification** including the models for the intended use of predicting DDIs
- **Model verification** of the investigational drug product, i.e. comparison to clinical DDI studies
- Assessment of **parameter uncertainty**

Platform qualification for the intended use of predicting CYP3A4 DDIs

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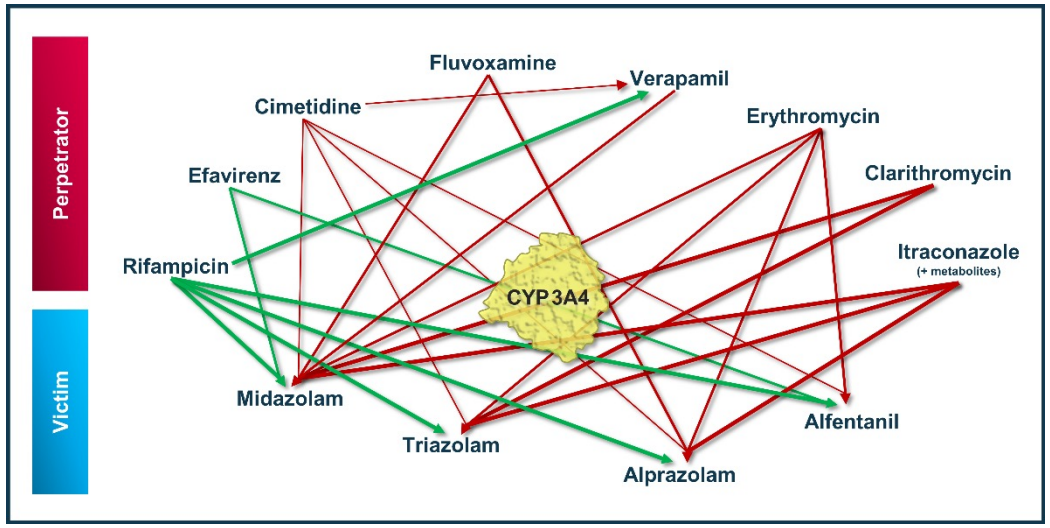
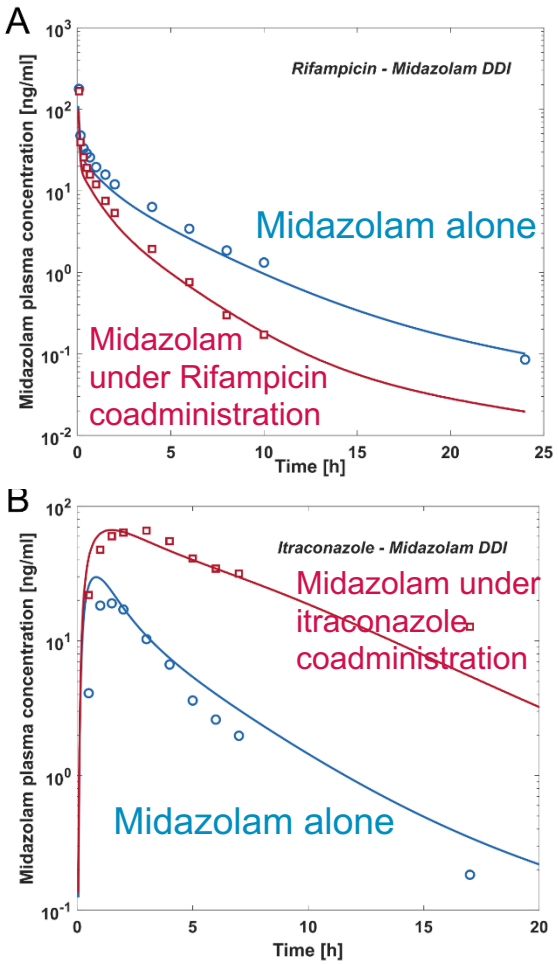
A Framework for the PBPK Platform Qualification of PK-Sim® and its exemplary Application Example to Predict CYP3A4-mediated Drug-Drug Interactions

Sebastian Frechen [1], Juri Solodenko [1], Thomas Wendl [1], André Dallmann [1], Ibrahim Ince [1], Thorsten Lehr [2], Jörg Lippert [1], Rolf Burghaus [1]

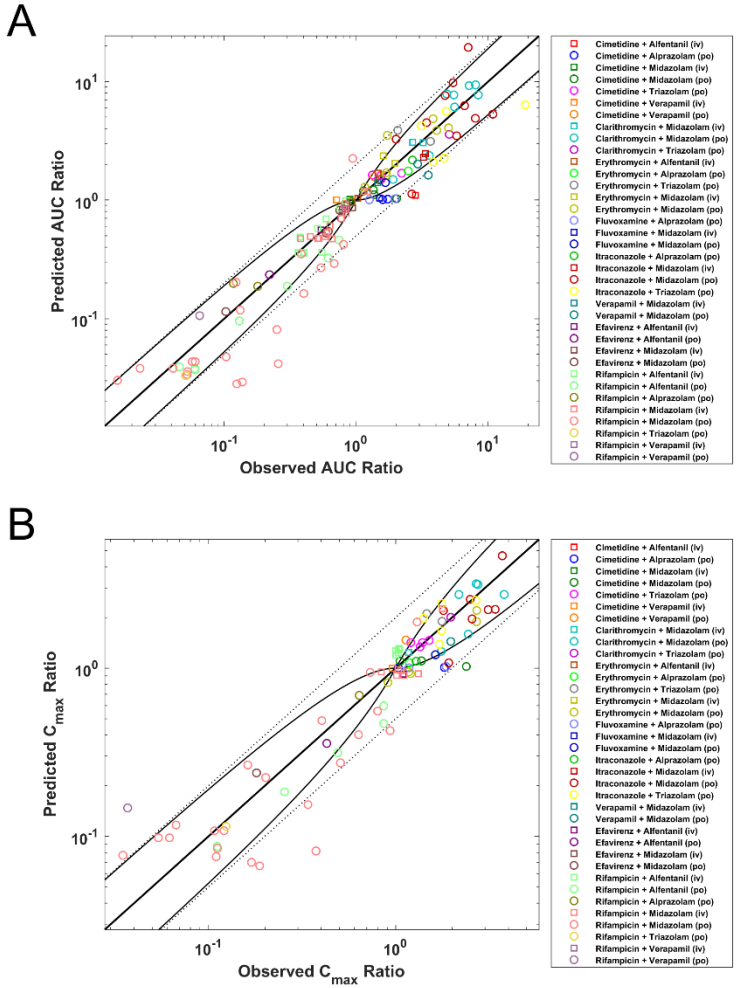
Published 2021



Simulation of DDI studies



Pred. vs obs. of all CYP3A4 DDI studies



Hanke *et al.* CPT Pharmacometrics Syst Pharmacol. 2018

Model verfication and application of CYP3A4 PBPK DDI platform to finerenone (Kerendia®)

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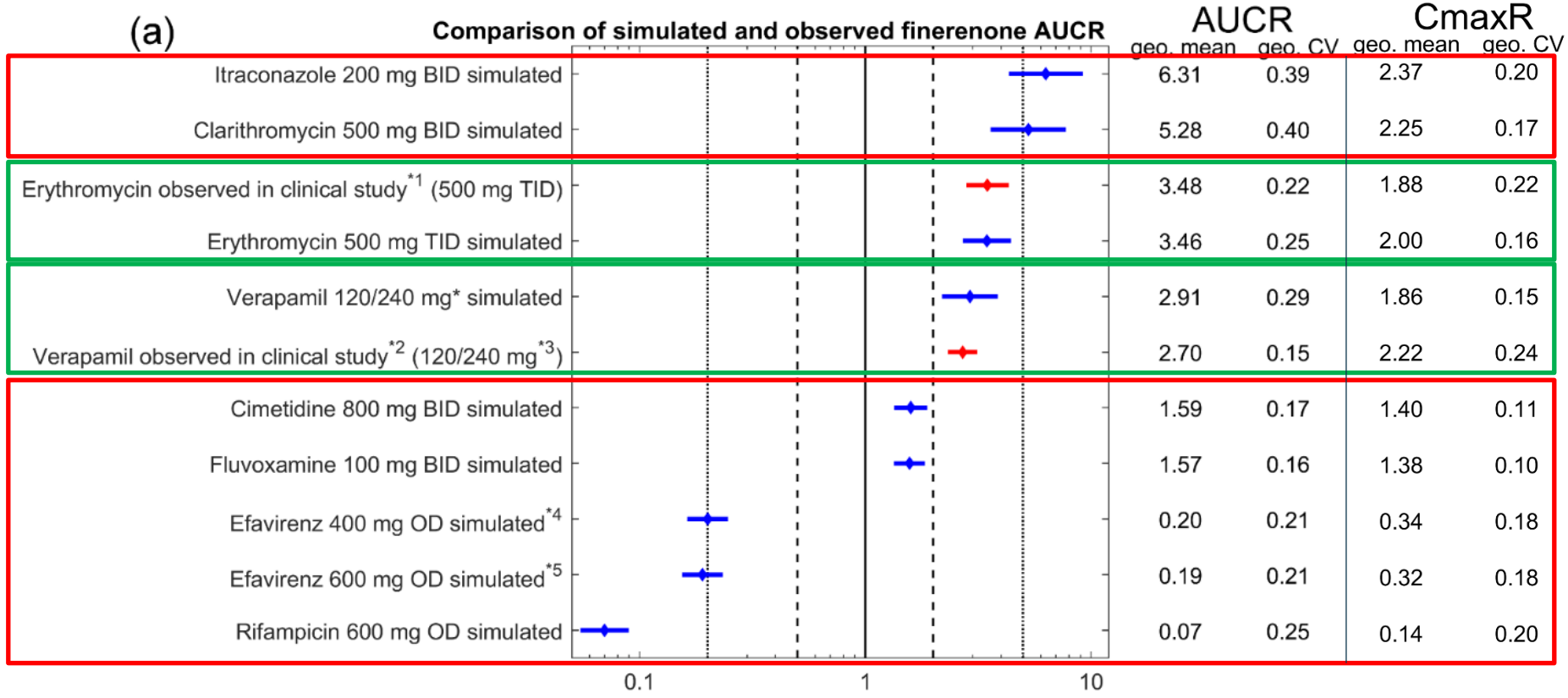
Approved July 2021 in US, Feb 2022 in EU

1. **Verify** finerenone PBPK model as a victim of CYP3A4 DDI
2. **Predict** untested drug interactions



Wendl *et. al*. CPT Pharmacometrics Syst Pharmacol. 2022 Feb;11(2):199-211

Assess uncertainty

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A: Uncertainty of the **investigational drug product model, i.e finerenone:** Sensitivity analysis on $f_{m,CYP3A4}$ proposed by FDA

Reference Scenario	Scenario 1	Scenario 2
CYP3A4 liver 90% CYP2C8 liver 10%	**CYP3A4 liver 85% CYP2C8 liver 15%**	**CYP3A4 liver 95% CYP2C8 liver 5%**

Modulator	Scenario	AUCR geo. mean	AUCR geo. CV	$C_{max}R$ geo. mean	$C_{max}R$ geo. CV
Erythromycin	Observed in clinical study	3.48	0.22	1.88	0.22
	Simulated reference scenario	3.46	0.25	2.00	0.16
	Simulated scenario #1	3.19	0.25	1.93	0.16
	Simulated scenario #2	3.74	0.25	2.07	0.17
Verapamil	Observed in clinical study	2.70	0.15	2.22	0.24
	Simulated reference scenario	2.91	0.29	1.86	0.15
	Simulated scenario #1	2.73	0.28	1.80	0.15
	Simulated scenario #2	3.09	0.30	1.91	0.16
Gemfibrozil	Observed in clinical study	1.10	0.18	1.16	0.31
	Simulated reference scenario	1.11	0.08	1.06	0.04
	Simulated scenario #1	1.19	0.11	1.09	0.06
	Simulated scenario #2	1.06	0.04	1.03	0.02
Itraconazole	Simulated reference scenario	6.31	0.39	2.37	0.20
	Simulated scenario #1	5.23	0.39	2.24	0.19
	Simulated scenario #2	7.76	0.40	2.50	0.20
Clarithromycin	Simulated reference scenario	5.28	0.40	2.25	0.17
	Simulated scenario #1	4.52	0.38	2.14	0.16
	Simulated scenario #2	6.27	0.45	2.36	0.17

B: Uncertainty of the **interaction partner substance model network**

→ Determine geometric mean fold error (GMFE) i.e. for the whole CYP3A4 interaction network:

GMFE (AUCR) = 1.38
GMFE (CmaxR) = 1.33

→ discuss implications on predictions.

Regulatory feedback

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FDA label
(US prescribing information)

Drug Interaction Studies

Clinical Studies and Model-Informed Approaches ← **PBPK modeling!**

Strong CYP3A Inhibitors: Concomitant use of itraconazole (strong CYP3A4 inhibitor) increased finerenone AUC by >400%.

Moderate CYP3A Inhibitors: Concomitant use of erythromycin (moderate CYP3A4 inhibitor) increased finerenone mean AUC and C_{max} by 248% and 88%, respectively.

Weak CYP3A Inhibitors: Concomitant use of amiodarone (weak CYP3A4 inhibitor) increased finerenone AUC by 21%.

Strong or Moderate CYP3A Inducers: Concomitant use of efavirenz (moderate CYP3A4 inducer) and rifampicin (strong CYP3A4 inducer) decreased finerenone AUC by 80% and 90%, respectively.

Switzerland
(part of ACCESS consortium)
Swissmedic Fachinformation

Simulationen zeigen, dass die gleichzeitige Anwendung von **Kerendia mit Itraconazol** (…) die Finerenon-Exposition erhöht (geometrisches mittleres Verhältnis (GMR) und 90% Populationsintervall für **AUC und C_{max}: 6.31 [3.36-11.41]** und **2.37 [1.76-3.31])**. **Clarithromycin** (…) führt ebenfalls zum erwartungsgemässen Anstieg der Finerenon-Exposition (GMR und 90% PI für **AUC und C_{max}: 5.28 [2.88-10.48] und 2.25 [1.76-2.98])**

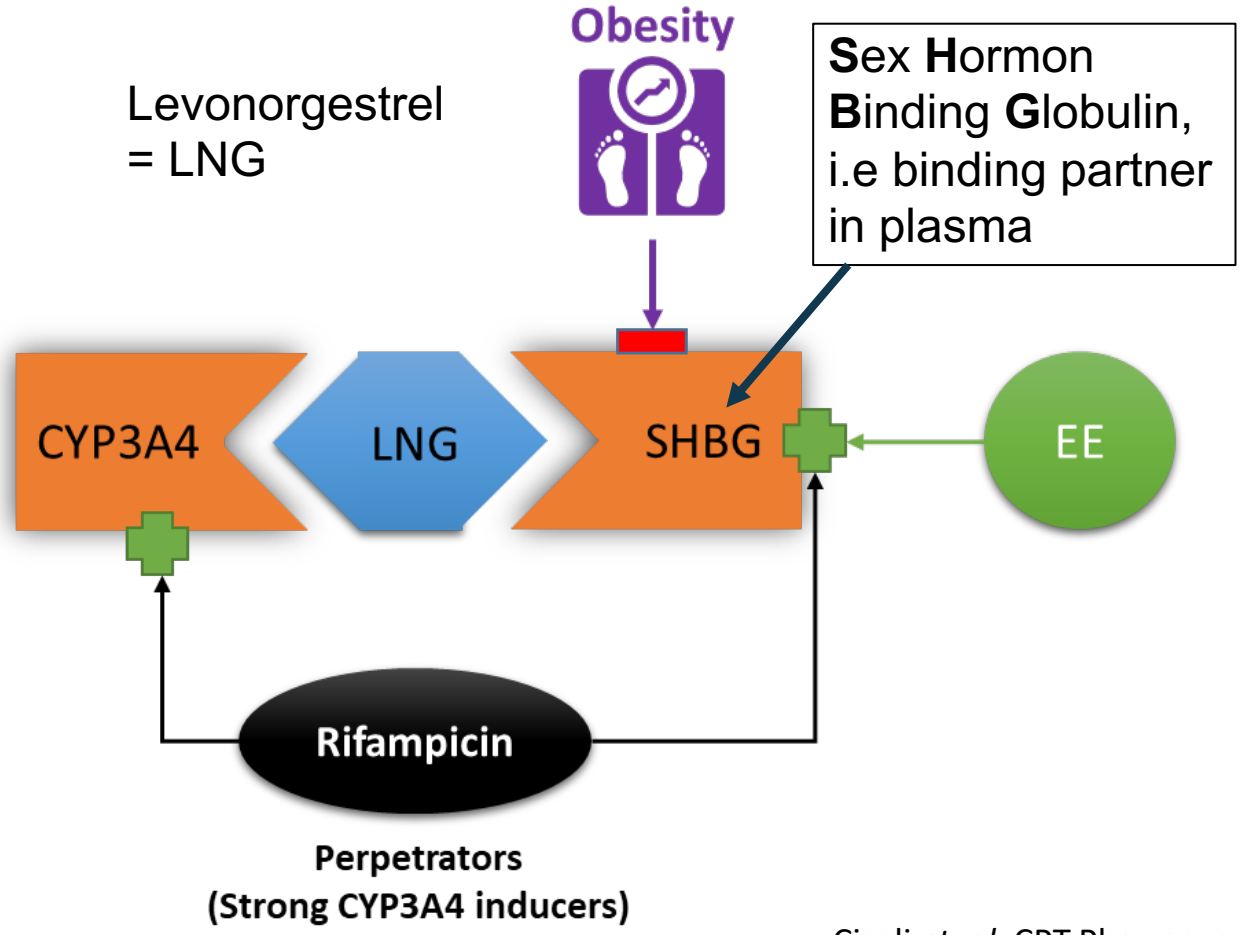
took over exact numbers of PBPK DDI simulations!!

…

EMA
(Assessment report)

Agrees with qualitative, but not quantitative information:
(…) the **number of selected compounds** was considered **insufficient to qualify** the PBPK platform for the intended purpose, (… i.e. CYP3A4 interaction prediction)
→ **PBPK predicted numerical values** (…) were **considered unreliable**

Academic collaborations: Example of complex DDIs



Verification of CYP3A4 contribution in LNG PBPK model

Formulation	Observed AUCR	Predicted AUCR	pred/obs
CBZ + LNG + EE	0.65	0.66	**1.01**
EFA + LNG	0.42	0.46	**1.09**
RFP + LNG	0.43	0.42	**1.02**

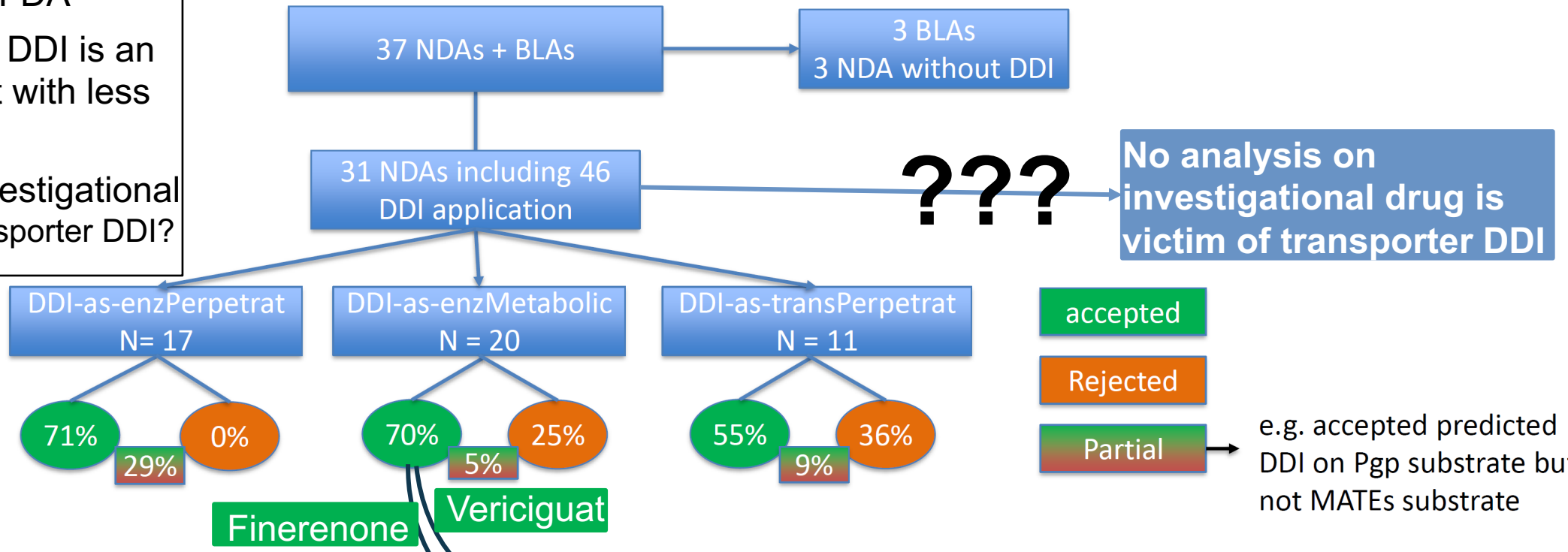
Cicali *et. al*. CPT:Pharmacometrics Syst Pharmacol. 10, 48-58

Summary I

Slide at Marbach DDI workshop 2024 by Yuching Yang, FDA

- OSP PBPK DDI submissions (finerenone and vericiguat) were accepted by FDA
- Transporter PBPK DDI is an emerging field, but with less confidence
- No analysis on investigational drug is victim of transporter DDI?

Adequacy of PBPK analysis breakdown 2020-2022



Reference: NDA-212608 ;NDA-212801 ;NDA-213756 ;NDA-213411 ;NDA-213736 ;NDA-213591 ;NDA-213246 ;NDA-210730 ;NDA-213535 ;BLA-761149 ;NDA-213721 ;NDA-214787 ;NDA-214377 ;NDA-212888 ;NDA-213716 ;NDA-214096 ;NDA-213176 ;NDA-213498 ;NDA-213378 ;NDA-214665 ;NDA-215341 ;NDA-214783 ;NDA-215383 ;NDA-215310 ;NDA-215206 ;NDA-214662 ;NDA-215358 ;NDA-215596 ;NDA-214985 ;NDA-216196 ;NDA-208712 ;NDA-214998 ;NDA-215152 ;NDA-215866 ;BLA-761261 ;NDA-214801 ;BLA-761291; NDA 210730

PBPK analyses in novel drug approvals between 2020 and 2022; no formal QC

Summary II

OSP offers a lot of features to simulate DDIs:

- Library of PBPK models verified for the intended use of modelling CYP3A4, CYP1A2, CYP2C19 and UGTs interactions
- Documentation of all models incl. full written model evaluation reports
- Documented CYP3A4 qualification package (also exists for CYP1A2, CYP2C19 and UGTs)
- Requalification framework

Things to consider!

- Not only a technical exercise, every PBPK DDI submission is still a scientific challenge!
- Structural uncertainties in the models, „unknown unknowns“, e.g. binding partner might be also induced by rifampicin as in LNG example
- What is **not covered** by qualification and verification steps and the model?

Thank you!!! It‘s a community effort!

Open Systems Pharmacology

Bayer:

Sebastian Frechen (now working in medical practice)

Juri Solodenko

Thomas Eißing

André Dallmann

Annika Schneider

Ibrahim Ince (now: Boehringer Ingelheim)

Rolf Burghaus

Jörg Lippert

Roland Heinig

Michael Gerisch (now: Janssen)

etc.

University of Saarland (Thorsten Lehr group):

Thorsten Lehr

Nina Hanke (now: Boehringer Ingelheim)

Daniel Moj

Hannah Britz

Denise Feick (now: Sanofi)

etc.

University of Florida:

Stephan Schmidt

Rodrigo Christofoletti

Brian Cicali

etc.