Physiologically Based Pharmacokinetic Modeling & Simulation in OCP Submissions: Case Studies

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Development of Best Practices in Physiologically Based Pharmacokinetic Modeling to Support Clinical Pharmacology Regulatory Decision-Making

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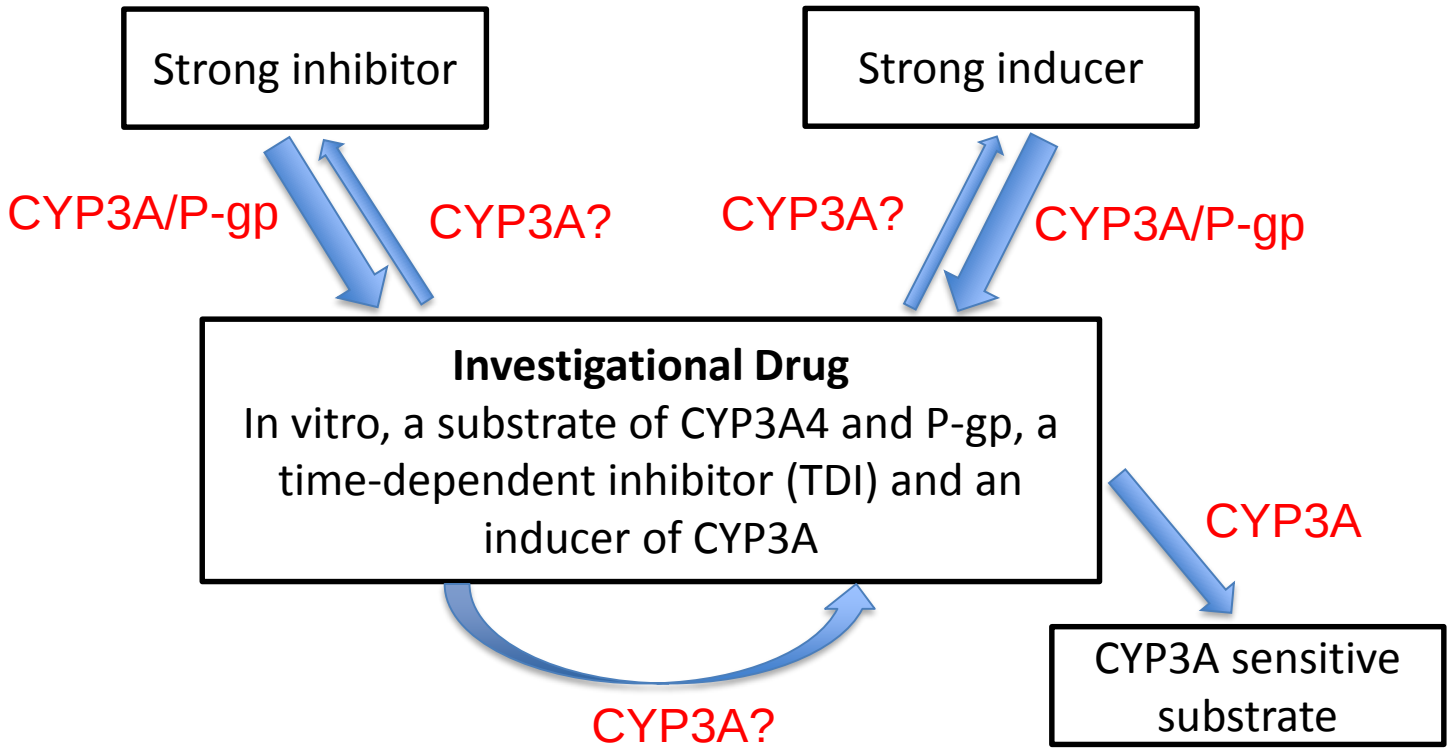
Outline

- Complex CYP3A-mediated DDIs
- Mystery about induction
- Forgotten metabolite
- All about specific populations
- Where are we with transporters?

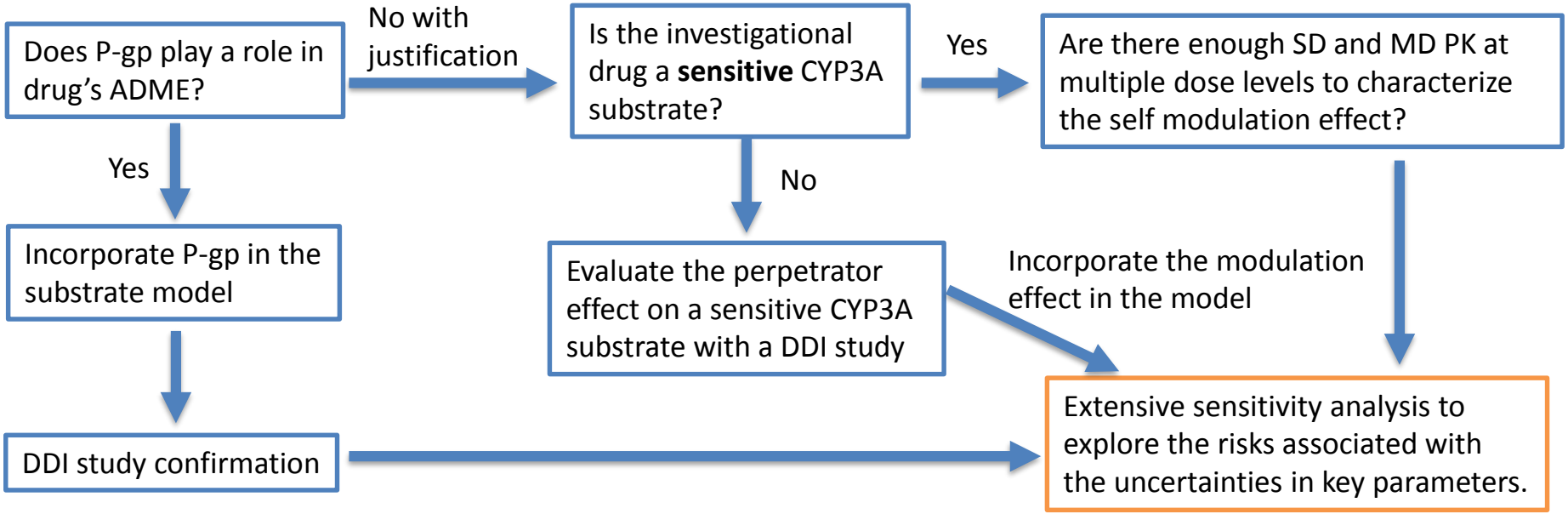
Disclaimer: Examples for each case are not all inclusive but only for illustrative purpose.

Case 1: Complex CYP3A-mediated DDIs



Case 1: Complex CYP3A-mediated DDIs – How?

In vitro, the investigational drug is a CYP3A substrate, P-gp substrate, CYP3A TDI and inducer.



SD: single dose; MD: multiple dose

Case 1: Complex CYP3A-mediated DDIs – examples

Investigational drug is a CYP3A substrate and modulator

Drugs	fmCYP3A	Effect on MDZ AUC	PBPK model assessment for enzyme-mediated DDIs
Duvelisib	~0.7	↑ 4.3	Accepted: Model can describe SD, MD, DDIs
Ribociclib	~0.7	↑ 3.8	Accepted: Model can describe SD, MD, DDIs
Fedratinib	~0.7	↑ 3.8	Partially accepted: Model can describe SD, MD, DDIs (single pathway); uncertainty in induction prediction (PMR/PMC)
Erdafitinib	~0.2	N.A.	Partially accepted: Need MDZ DDI to characterize TDI (PMR/PMC)
Apalutamide	0.13	↓ 92%	Accepted: Model can describe SD, MD, DDIs

Investigational drug is a CYP3A/P-gp substrate

Drugs	fmCYP3A	PBPK model assessment
Naloxegol	~1	DDI study with quinidine, P-gp was incorporated into the model in response to an IR

SD: single dose; MD: multiple dose; MDZ: midazolam; TDI: time-dependent inhibition; IR: information request; PMR/PMC: post marketing requirement/commitment

Case 2: Mystery about induction

In submissions: Rifampin DDIs were often under-predicted.

Drug	fmCYP3A	Observed		Predicted	
		CmaxR	AUCR	CmaxR	AUCR
Abemaciclib	~0.9	0.08	0.05	0.14	0.07
Doravirine	~0.9	0.43	0.12	0.71	0.26
21-desDeflazacort	~0.9	0.06	0.08	0.22	0.15
Lorlatinib	auto-induction, dose dependent	0.24	0.14	0.63	0.30

Drugs@FDA. CmaxR and AUCR are the ratios of substrate's Cmax and AUC in the presence vs. absence of rifampin

Literature reports: Rifampin CYP3A maximum induction potential (Indmax) continues to be refined to match the observed DDI studies.

Almond LM et al. 2016 DMD

Case 2: Mystery about induction – what does the study with a strong inducer inform the model?

- The strong inducer DDI study alone provides limited information about labeling for both strong and moderate inducers.
- Effects of moderate inducers may be more relevant when the drug is a sensitive substrate.
- Thoughts on dose modification when co-administrated with an inducer
  - Absorption may be limited when dose is increased.
  - Efficacy and safety profiles of major metabolite(s)

Case 3: Forgotten metabolite – When should I include metabolite(s) in the model?

Investigational drug / metabolite as substrates

Investigational drug / metabolite as perpetrators

Follow in vitro DDI guidance to determine if further investigation is needed

Additional considerations:

1. Metabolite accumulation
2. DDI - does the change in exposure to major metabolite(s) cause safety concerns?
3. DDI - does the change in exposure to active metabolite(s) cause safety and efficacy concerns from a dose adjustment perspective?

Build the metabolite(s) model

Case 3: Forgotten metabolite – examples

Drug	Issues	Actions
Investigational drug / metabolite as substrates		
Entrectinib	The active metabolite (M5) accumulates at steady state and contributes significantly to efficacy.	M5 was incorporated during the review cycle for DDI evaluation in response to FDA's IR.
Doravirine	The inactive metabolite M9 exposure increases when co-administered with an inducer.	M9 was incorporated during the review cycle for risk assessment in response to FDA's IR.
Investigational drug / metabolite as perpetrators		
Cannabidiol	In vitro DDI assessments for the major metabolites were ongoing.	Pending in vitro DDI assessments for the major metabolites to be incorporated into the model.

IR: information request

Case 4: Specific populations – every patient matters, but conducting studies can be difficult…

Currently, PK data are needed for model validation

Population	Current status in submissions	Examples
Pediatrics	Incorporation of variability in ontogeny, mechanistic absorption models	deflazacort, entrectinib
Geriatrics	Matching ages	prucalopride
Diseases	Incorporation of parameter changes in disease populations, such as protein levels	duvelisib, fedratinib, erdafitinib
Hepatic impairment	Incorporation of parameter changes, such as liver volume, enzyme abundance, fup, and fa	duvelisib
Renal impairment	Incorporation of parameter changes, such as GFR	deflazacort

GFR: glomerular filtration rate

Case 4: Specific populations – moving forward

- Step-by-step approach
  - Combing modeling approach with limited studies
- Quantitative approach to measure system parameters
  - Similar compounds
  - Similar populations

Case 5: Where are we with transporters?

- Focus on substrate models
  - Do we have accumulated enough knowledge to characterize the substrate models relevant to the transporters of interest?
  - Can the model describe all available PK and DDI studies?
- Focus on the perpetrator models
  - Qualitative or quantitative prediction?

Case 5: Where are we with transporters – examples

Investigational drug as a substrate

Transporter	Drugs	PBPK assessment
OATP1B1/3	simeprevir, letermovir	Exploratory

Investigational drug is a perpetrator

Transporter	Drugs	PBPK assessment
OCT2/MATEs	apalutamide	Substrate model (metformin) cannot capture all reported DDIs.
P-gp	erdafitinib	Model is qualitative and not quantitative.
OATP1B1/3	fedratinib	Substrate model (rosuvastatin) cannot capture all reported DDIs.

Summary

- PBPK analyses become routine in drug development and submissions.
- PBPK analyses can be complex and challenging.
- Collaborative efforts (applicants/sponsors, regulators, independent researchers, platform developers) are needed to achieve the goals of successful PBPK analyses.

Acknowledgement

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