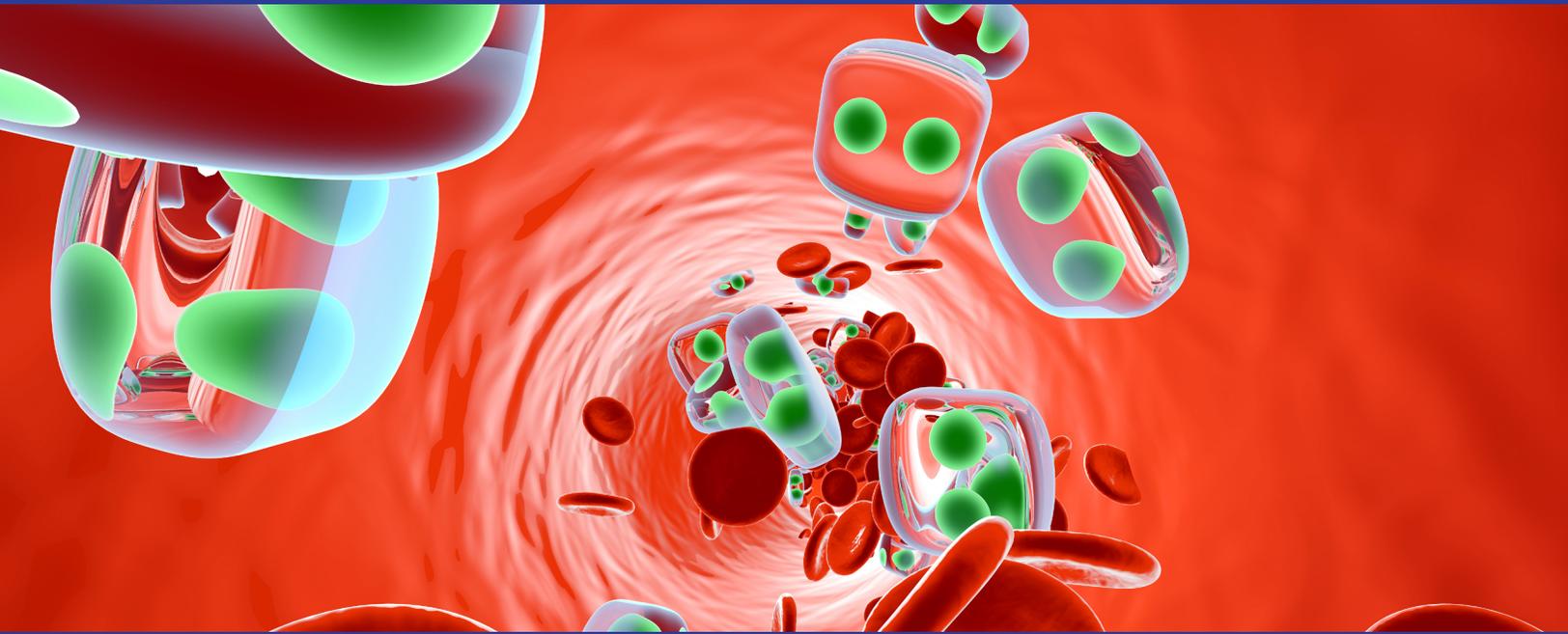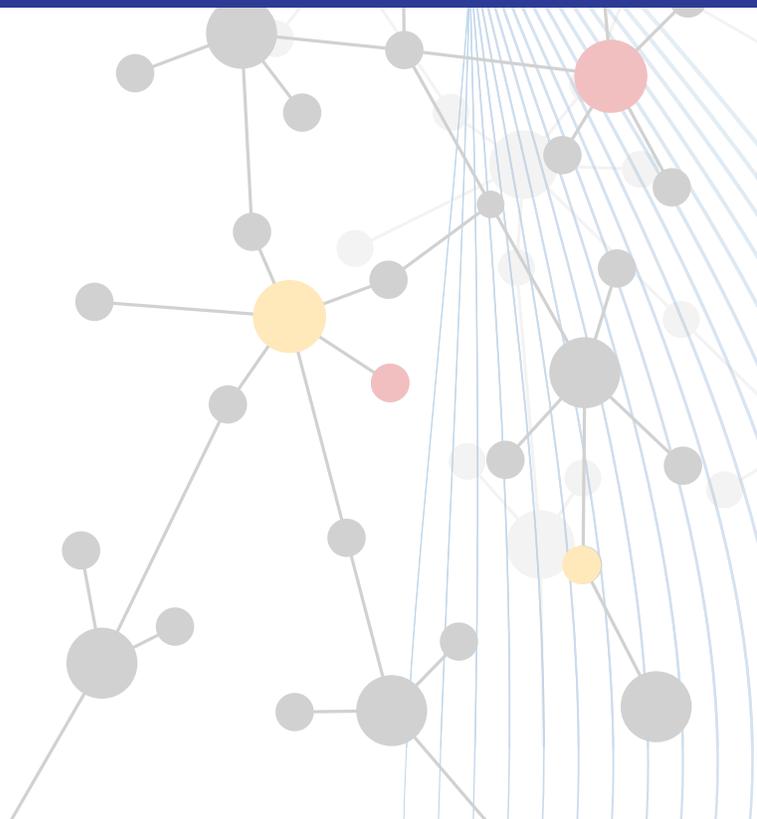# CERTARA

Simcyp PBPK for Drug-Drug Interactions (DDIs):

A Regulatory Imperative

By Dr. Karen Yeo, Sr. VP of Client and Regulatory Strategy

Simcyp PBPK for DDIs: A Regulatory Imperative

OVERVIEW

The past two decades have witnessed transformative changes in our approach to using modeling & simulation to assess and manage drug–drug interactions (DDIs). Multidisciplinary innovations in mechanistic assessment of absorption, distribution, metabolism, and excretion (ADME), population pharmacology and pharmacogenetics, physiologically based modeling, and regulatory science have enabled a profound shift in mindset from risk aversion to informative prescribing guidance for optimal risk management[1]. These advances have resulted in a sea change in how we study and regulate DDIs, as documented in two newly published FDA guidance documents [2,3].

In this paper, we focus on how modeling & simulation, specifically physiologically based pharmacokinetics (PBPK) has grown to become an accepted (and encouraged) approach to inform and/or waive DDI studies.

Simcyp PBPK is the gold standard for use on DDIs, as evidenced by >70 marketed drugs where the Simcyp Simulator was used in labelling per the drug's final FDA approval documentation (*figure 1*). Most important, the acceptance of PBPK in lieu of clinical DDI studies by the FDA has been evolving, where initially both inducer and inhibitor studies were used to verify the model, we have now demonstrated examples where only one study was conducted, and more recently, where there were no clinical DDI studies with the drug as a victim conducted.

	Oncology		CNS	Infectious Disease		Cardiovascular	Gastroenterology		Other
Agios	Tibsovo (*Ivosidenib*)	Daiichi	Sankyo (*Turalio Pexidartinib*)		Pfizer		Bosulif (Bosutinib)		
AstraZeneca	Calquence (*Acalabrutinib*)	Genentech	Polivay (*Polatuzumab Vedotin-PIIQ*)		Pfizer		Lorbrena (*Lorlatinib*)		
Celgene	Inrebic (*Fedratinib Hydrochloride*)	Janssen	Balversa (*Erdafitinib*)		Spectrum		Beleodaq (*Belinostat*)		
Lilly	Verzenio (*Abemaciclib*)	Novartis	Zykadia (*Certinib*)		Ariad		Alunbrig (*Brigatinib*)		
Genentech	Cotellic (*Cobimetinib*)	Novartis	Piqray (*Alpelisib*)		Ariad (Takeda)		Iclusig (*Ponatinib*)		
Loxo Oncology	Vitrakvi (*Larotrectinib*)	Novartis	Odomzo (*Sonidegib*)		AstraZeneca		Tagrisso (*Osimertinib*)		
Amgen	Blincyto (*Blinatumomab*)	Novartis	Kisqali (*Ribociclib succinate*)		Eisai		Lenvima (*Lenvatinib*)		
AstraZeneca	Lynparza (*Olaparib*)	Novartis	Farydak (*Panobinostat*)		Genentech		Alecensa (*Alectinib*)		
Verastem	Copiktra (*Duvelisib*)	Novartis	Rydapt (*Midostaurin*)		Janssen		Erleada (*Apalutamide*)		
Sanofi	Jevtana (*Cabazitaxel*)								

	Rare Disease								
Akarx	Doptelet (*Avatrombopag maleate*)	Global Blood Therapeutics	Oxbryta (*Voxelotor*)		Vertex		Symdeko (*Tezacaftor/ivacaftor*)		
PTC Therapeutics	Emflaza (*Deflazacort*)	Sanofi Genzyme	Cerdelga (*Eliglustat Tartrate*)		Vertex		Trikafta (ELEXACAFTOR, IVACAFTOR, TEZACAFTOR; IVACAFTOR)		
Intercept	Oclavia (*Obeticholic acid*)								

			CNS						
Alkermes	Aristada (*Aripiprazole*)	GW Research	Epidiolex (*Cannabidiol*)		Kyowa Kirin		Nourianz (*Istradefylline*)		
Eisai	Dayvigo (*Lemborexant*)	Novartis	Mayzent (*Siponimod Fumaric Acid*)		UCB		Briviact (*Brivaracetam*)		
Lilly	Rayvow (*Lasmiditan Succinate*)								

			Infectious Disease						
GSK	Dectora (*Zanamivir*)	Janssen	Olysio (*Simeprevir*)		Novartis		Egaten (TRICLABENDAZOLE)		
Merck	Prevymis (*Letermovir*)	Nabriva	Zenita (*Lefamulin Acetate*)		Tibotec		Edurant (*Rilpivirine*)		
Merck	Pifeltro (*Doravirine*)								

	Cardiovascular								
Johnson & Johnson	Xarelto (*Rivaroxaban*)	Actelion (J & J)	Opsumit (*Macitentan*)		Actelion (J & J)		Uptravi (*Selexipeg*)		
Pfizer	Revatio (*Sildenafi*)								

Shionogi	Symproic (*Naldemedine*)	AstraZeneca	Movantik (*Naloxegol*)		Helsinn		Akynzeo (*fosnetupitant/palonosetron*)		
Shire	Motegrity (*Prucalopride*)								

								Other	
Galderma	Aklief (*Trifarotene*)	Lilly	Olumiant (*Baricitinib*)		Pfizer		Revatio (*Sildenafil*)		
Janssen	Invokana (*Canagliflozin*)	Merck	Steglatro (*Ertugliflozin*)		AbbVie		Orilissa (*Elagolix*)		

Figure 1: Drug labels informed by Simcyp PBPK (DDI indications and other label claims)

WHAT ARE DRUG-DRUG INTERACTIONS (DDIs)?

DDIs occur when two or more drugs interact with each other. These interactions of drug combinations can result in pharmacological or clinical response that differs from the response of each drug independently. DDIs can decrease, delay or enhance absorption or the metabolism of either drug, can increase or decrease the action of either or both drugs, or can cause adverse events. DDIs are a critical factor in a drug's overall benefit-risk profile, therefore clinically relevant DDIs should be identified during drug development, known at the time of approval, included in labeling and monitored on an ongoing basis.

Per FDA final guidance, "The concomitant use of more than one medication in a patient is common. Unanticipated, unrecognized, or mismanaged DDIs are an important cause of morbidity and mortality associated with prescription drug use and have occasionally been the basis for withdrawal of approved drugs from the market. In some instances, understanding how to safely manage a DDI can allow approval of a drug that would otherwise have an unacceptable level of risk[2]."

Although the common approach and attitude to deal with DDIs are to avoid the interacting combinations by choosing alternative drugs, these choices may not always be an option. Therefore, alterations in dose, treatment (sequence and scheduling), or additional monitoring to maintain therapeutic effect or to prevent adverse outcomes may be required. There are certain characteristics that make drugs susceptible to clinically significant DDIs including a narrow therapeutic index, nonlinear pharmacokinetics, steep dose response curves, and enzyme- or transporter-inhibiting or-inducing properties[4].

> "
> *Together, the two final guidances describe a systematic risk-based approach to evaluation and communication of DDIs.*
> *- US FDA*
> "

DDI REGULATORY GUIDANCE

The US FDA issued its first *in vitro* DDI guidance document in 1997 and *in vivo* in 1999. Since that time, the agency has published draft updates in 2006, 2012, 2017, culminating in two final guidance documents in 2020 (one on *in vitro* and one on clinical). This final guidance addresses cyctochrome P450 (CYP) and transporter DDIs; it does not address therapeutic protein, gastric pH change-dependent, protein displacement-mediated, and phase 2 enzyme-mediated or pharmacodynamic DDIs. However, CYP 450 enzymes contribute to about 70% of the overall metabolism of marketed drugs, with CYP3A alone accounting for 30% and the family of CYP3A, CYP2D6 and CYP2C at 55-60%.
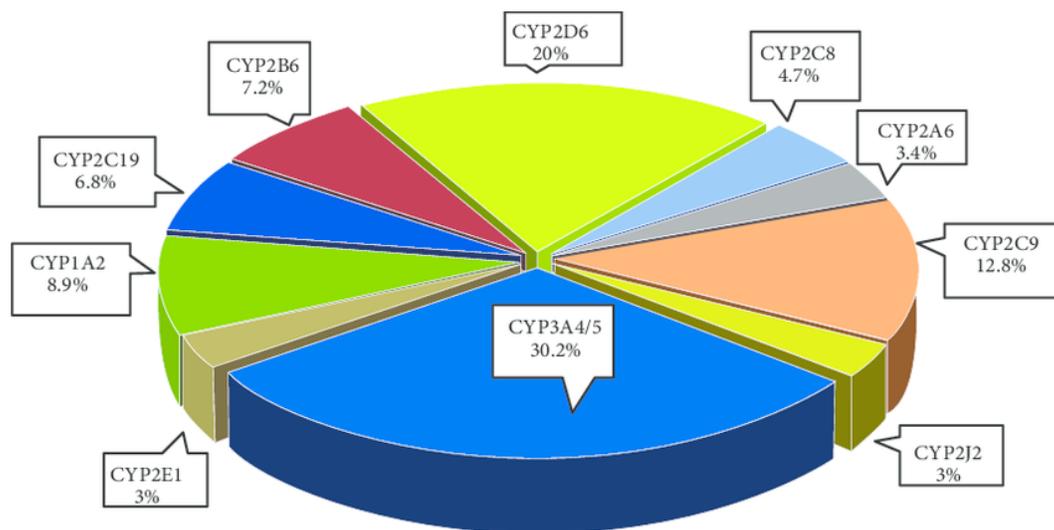
Figure 2: Prevalence of CYP enzymes

Per FDA, clinically relevant DDIs between an investigational drug and other drugs should be defined during drug development as part of the sponsor's assessment of the investigational drug's benefits and risks, understood via nonclinical and clinical assessment at the time of the investigational drug's approval, monitored after approval, and communicated in the labeling. The goals of studies that investigate CYP enzyme- and transporter-mediated DDIs are to:

- Determine whether the investigational drug alters the pharmacokinetics of other drugs;
- Determine whether other drugs alter the pharmacokinetics of the investigational drug;
- Determine the magnitude of changes in pharmacokinetic parameters;
- Determine the clinical significance of the observed or expected DDIs;
- Inform the appropriate management and prevention strategies for clinically significant DDIs.

Other regulatory agencies follow similar pathways to FDA on DDI guidance. Presently under rewrite, the current EMA DDI guidance was published in 2012, addressing the DDI potential for the investigational drug on the PK of other drugs (perpetrator) and for the effects of other drugs on the PK of the investigational drug (victim). Since 2012, there have been other documents updating this guidance, including a concept paper in 2017 and a guideline on the use of PBPK for this purpose. The Japanese regulators (PMDA) published its DDI guidance in 2018.

PBPK FOR DDIs: FROM THE REGULATORY SEAT

FDA's 2020 *In Vitro* DDI Guidance provides >20 citations for use of PBPK, including this introductory statement:

Various modeling approaches can help translate in vitro observations into in vivo predictions of potential clinical DDIs. For example, when evaluating the drug as a perpetrator of a metabolism-mediated DDI, basic models, static mechanistic models, or dynamic mechanistic models including PBPK models. PBPK models can predict the DDI potential of an investigational drug and/or a metabolite as an enzyme substrate or an enzyme perpetrator.

Per FDA's 2020 Final Clinical DDI Guidance:

PBPK models can be used in lieu of some prospective DDI studies. For example, PBPK models have predicted the impact of weak and moderate inhibitors on the substrates of some CYP isoforms (e.g., CYP2D6, CYP3A) as well as the impact of weak and moderate inducers on CYP3A substrates. These predictions were made after prospective clinical trials showed a significant DDI between the investigational drug and strong index inhibitors or inducers. Before using a PBPK modeling approach to predict the effects of moderate or weak perpetrator drugs on the exposure of an investigational drug, the sponsor should verify the models using human pharmacokinetic data and information from DDI studies that used strong index perpetrators.

- Because of evolving science, new uses of *in silico* methods to predict DDIs in lieu of clinical DDI studies are continuously being considered by the FDA. We encourage sponsors to discuss issues and considerations related to the use of *in silico* models with the FDA.

- PBPK models verified for the mechanism of dose-dependent pharmacokinetics of the substrate can be used to support dose selection.

- The effect of the additional inhibitors and inducers can be evaluated in a clinical interaction study or through modeling and simulation approaches, such as PBPK modeling with a verified perpetrator (inhibitor or inducer) and substrate models.

- When there are multiple factors that affect the absorption and disposition of an investigational drug as well as multiple mechanisms of DDIs (e.g., multiple CYP enzymes and/or transporters), the sponsor should evaluate the investigational drug's DDI potential by integrating knowledge from multiple *in vitro* and clinical studies. PBPK models may be useful to integrate the information from multiple studies, determine whether a clinical study is appropriate and inform the design of clinical studies.

> *Because of evolving science, new uses of in silico methods to predict DDIs in lieu of clinical DDI studies are continuously being considered by the FDA. Simcyp is actively working with industry to deliver case studies to the FDA that expand the use of PBPK in regulatory decision-making.*
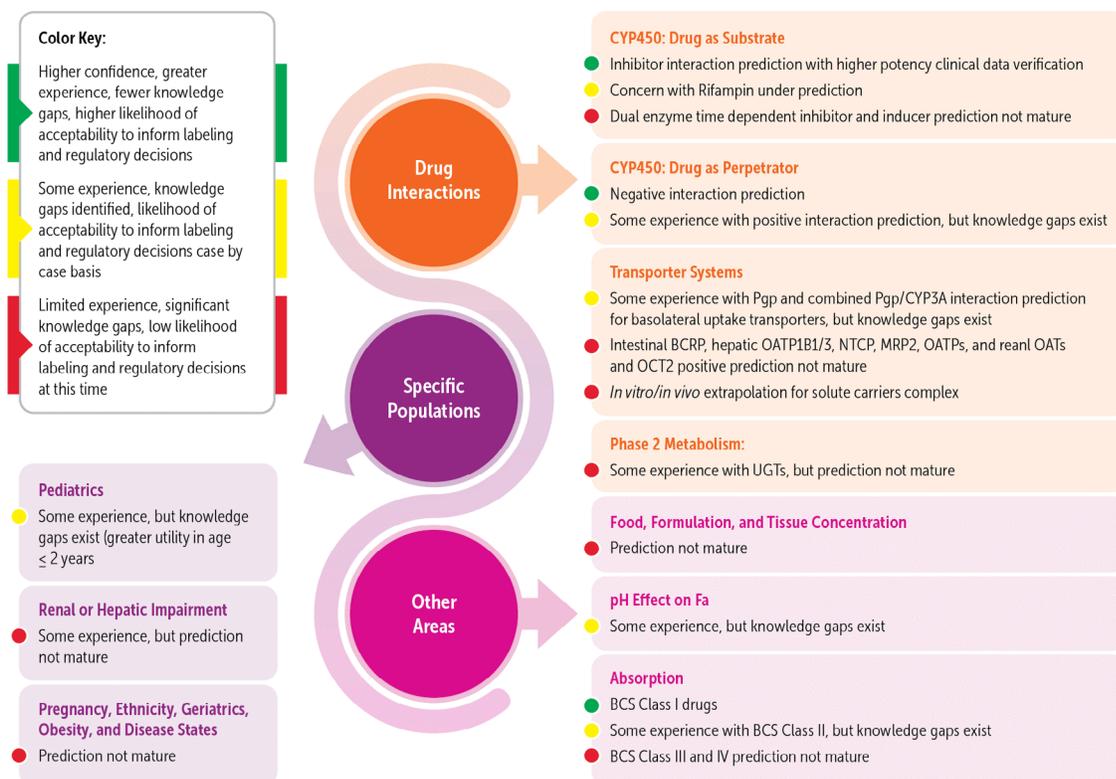
> *PBPK models can predict the DDI potential of an investigational drug/ and or metabolite as an enzyme substrate or enzyme perpetrator*
>
> *- US FDA*

Color Key:

Higher confidence, greater experience, fewer knowledge gaps, higher likelihood of acceptability to inform labeling and regulatory decisions

Some experience, knowledge gaps identified, likelihood of acceptability to inform labeling and regulatory decisions case by case basis

Limited experience, significant knowledge gaps, low likelihood of acceptability to inform labeling and regulatory decisions at this time

Drug Interactions

CYP450: Drug as Substrate
- Inhibitor interaction prediction with higher potency clinical data verification
- Concern with Rifampin under prediction
- Dual enzyme time dependent inhibitor and inducer prediction not mature

CYP450: Drug as Perpetrator
- Negative interaction prediction
- Some experience with positive interaction prediction, but knowledge gaps exist

Transporter Systems
- Some experience with Pgp and combined Pgp/CYP3A interaction prediction for basolateral uptake transporters, but knowledge gaps exist
- Intestinal BCRP, hepatic OATP1B1/3, NTCP, MRP2, OATPs, and reanl OATs and OCT2 positive prediction not mature
- *In vitro/in vivo* extrapolation for solute carriers complex

Specific Populations

Phase 2 Metabolism:
- Some experience with UGTs, but prediction not mature

Food, Formulation, and Tissue Concentration
- Prediction not mature

Pediatrics
- Some experience, but knowledge gaps exist (greater utility in age ≤ 2 years

Renal or Hepatic Impairment
- Some experience, but prediction not mature

Other Areas

pH Effect on Fa
- Some experience, but knowledge gaps exist

Pregnancy, Ethnicity, Geriatrics, Obesity, and Disease States
- Prediction not mature

Absorption
- BCS Class I drugs
- Some experience with BCS Class II, but knowledge gaps exist
- BCS Class III and IV prediction not mature

Figure 3: FDA roadmap regulatory application and prediction performance guidelines
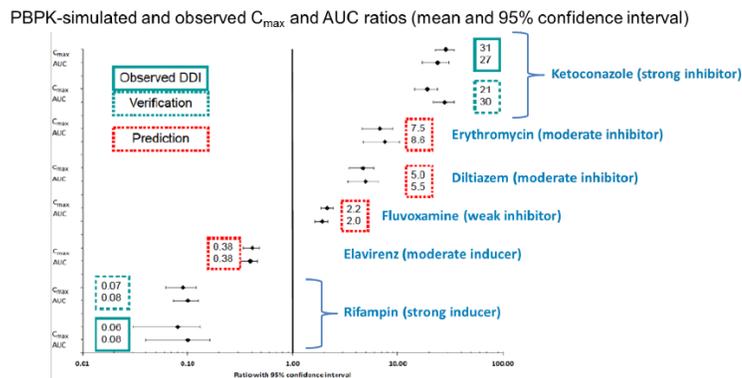
CASE STUDY #1: IBRUTINIB – DDI REGULATORY POSTER CHILD

Initially approved by the US FDA in 2013 for mantle cell lymphoma as a breakthrough therapy, ibrutinib, marketed as Imbrivica®, was recently approved by the US FDA for its 11th indication. The drug has treated almost 200,000 oncology patients in 100 countries.

Ibrutinib is susceptible to interactions with a strong inhibitor and inducer of CYP3A4 enzymes. Models built in the Simcyp Simulator using *in vitro* data were validated using clinical data on the observed effects of both a strong CYP3A4 inhibitor and a strong inducer on ibrutinib exposure. Simulations then predicted the effects of a moderate CYP3A4 inducer and other CYP3A4 inhibitors (strong, moderate and weak) on ibrutinib exposure, as well as investigating the impact of dose staggering and dose adjustment. The final drug label included 24 individual claims for untested DDI scenarios (without the need for clinical trials) and provided a dose optimization strategy aligned to individuals with different metabolic profiles.

While in 2013 the use of PBPK to predict DDIs, inform drug labels and eliminate the need for in vivo trials was quite novel, it is now an 'expected' or 'encouraged' approach. As outlined in the new guidance and shown in this case study, the extrapolation from itraconazole and rifampin studies provide dosing guidance on intermediate scenarios using PBPK. In fact, the regulators cite the use of PBPK for this Ibrutinib as a 'best practice' as depicted in figure 4.

Ibrutinib

PBPK-simulated and observed C_{max} and AUC ratios (mean and 95% confidence interval)

- Applicant's proposed model predicted untested lower potency inhibitors on "drug as substrate" DDI effects [2014]
- FDA initiated analyses [2014]
  - Identified potential difference between reversible inhibitors & time dependent inhibitor effects
  - Simulated the luminal drug concentration vs. time profiles for each segment of the GI tract to predict effect on oral P-gp substrates based on in vitro signal
- Applicant model (refined) predicted the effect of posaconazole on ibrutinib PK in non-fasted conditions under different dosing regimens [2017]

Applicant simulations and FDA analysis informed prescription drug labeling (PDL) and provided decision support for potential dose staggering and dose reduction mitigation strategies

http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/205552Orig1s000ClinPharmR.pdf

Figure 4: FDA refers to the use of PBPK for DDI labeling and dose projection on Ibrutinib as a 'best practice'

CASE STUDY #2: ELUGISTAT – QUANTIFYING THE IMPACT OF PHARMACOGENETIC STATUS ON DDIs

Gaucher's disease is an inherited disorder that affects many of the body's organs and tissues. According to the National Gaucher Foundation, the incidence of Gaucher's disease is about one in 20,000. In 2014, Eliglustat (Cerdelga®) was approved by the FDA as the first long-term treatment for adults with type 1 Gaucher's disease.

Metabolized primarily by CYP2D6, and to a lesser extent by CYP3A4, eliglustat is also an inhibitor of CYP2D6 and is both a substrate and inhibitor of P-gp. A high clearance drug, the model needed to consider both the CYP2D6 phenotypes and genotypes, as well as the time-dependency of CYP2D6 inhibition. We used PBPK modeling extensively to understand and quantify the impact of metabolizer status and concomitant medication on eliglustat exposure—as well as the effect that eliglustat has on other drugs—and guide the specific dose adjustment recommendations and labeling language.

Another example of a best practices case study shared by FDA, the impact of the PBPK model for eliglustat was huge because of the number of clinical studies that would have to be informed to assess all of the DDI scenarios. The DDI is dependent on both the dose: the CYP2D6 changes with the dose, therefore affecting DDI liability, as well as the CYP2D6 phenotype

The result is represented in the labeling for 12 DDIs and dosing recommendations from PBPK simulations, as shown in figure 5.
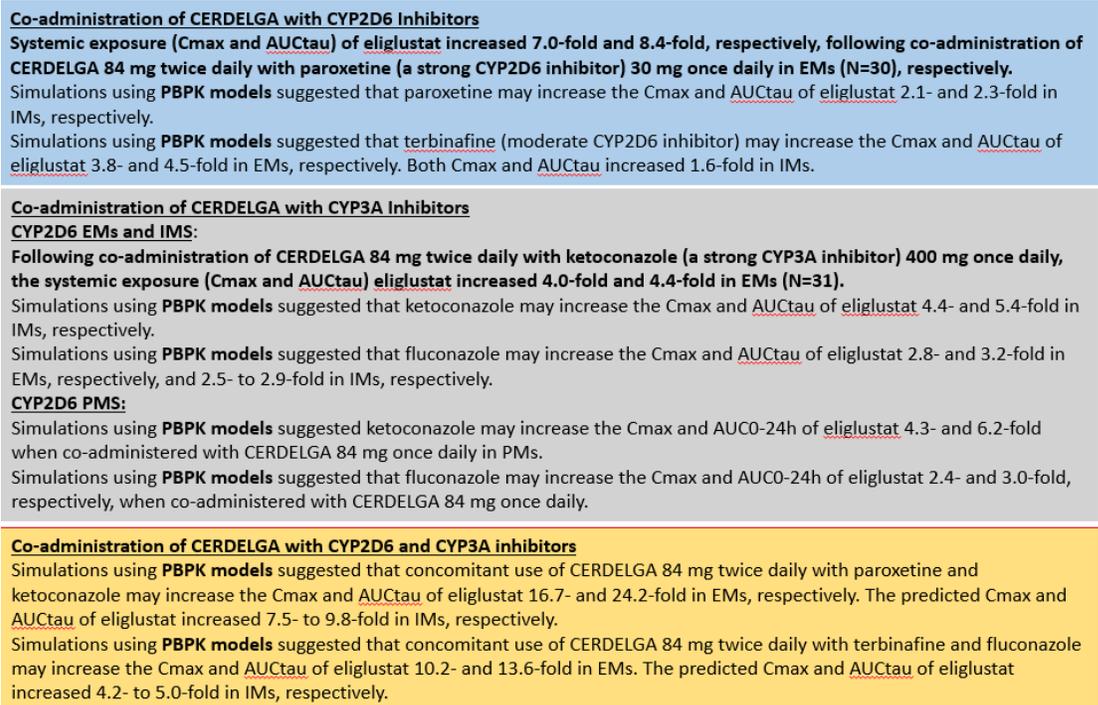
Co-administration of CERDELGA with CYP2D6 Inhibitors
Systemic exposure (Cmax and AUCtau) of eliglustat increased 7.0-fold and 8.4-fold, respectively, following co-administration of CERDELGA 84 mg twice daily with paroxetine (a strong CYP2D6 inhibitor) 30 mg once daily in EMs (N=30), respectively.
Simulations using **PBPK models** suggested that paroxetine may increase the Cmax and AUCtau of eliglustat 2.1- and 2.3-fold in IMs, respectively.
Simulations using **PBPK models** suggested that terbinafine (moderate CYP2D6 inhibitor) may increase the Cmax and AUCtau of eliglustat 3.8- and 4.5-fold in EMs, respectively. Both Cmax and AUCtau increased 1.6-fold in IMs.

Co-administration of CERDELGA with CYP3A Inhibitors
CYP2D6 EMs and IMS:
Following co-administration of CERDELGA 84 mg twice daily with ketoconazole (a strong CYP3A inhibitor) 400 mg once daily, the systemic exposure (Cmax and AUCtau) eliglustat increased 4.0-fold and 4.4-fold in EMs (N=31).
Simulations using **PBPK models** suggested that ketoconazole may increase the Cmax and AUCtau of eliglustat 4.4- and 5.4-fold in IMs, respectively.
Simulations using **PBPK models** suggested that fluconazole may increase the Cmax and AUCtau of eliglustat 2.8- and 3.2-fold in EMs, respectively, and 2.5- to 2.9-fold in IMs, respectively.
CYP2D6 PMS:
Simulations using **PBPK models** suggested ketoconazole may increase the Cmax and AUC0-24h of eliglustat 4.3- and 6.2-fold when co-administered with CERDELGA 84 mg once daily in PMs.
Simulations using **PBPK models** suggested that fluconazole may increase the Cmax and AUC0-24h of eliglustat 2.4- and 3.0-fold, respectively, when co-administered with CERDELGA 84 mg once daily.

Co-administration of CERDELGA with CYP2D6 and CYP3A inhibitors
Simulations using **PBPK models** suggested that concomitant use of CERDELGA 84 mg twice daily with paroxetine and ketoconazole may increase the Cmax and AUCtau of eliglustat 16.7- and 24.2-fold in EMs, respectively. The predicted Cmax and AUCtau of eliglustat increased 7.5- to 9.8-fold in IMs, respectively.
Simulations using **PBPK models** suggested that concomitant use of CERDELGA 84 mg twice daily with terbinafine and fluconazole may increase the Cmax and AUCtau of eliglustat 10.2- and 13.6-fold in EMs. The predicted Cmax and AUCtau of eliglustat increased 4.2- to 5.0-fold in IMs, respectively.

Figure 5: Label language depicting use of PBPK for dosing recommendations of different phenotypical patients of Gaucher's Disease

CASE STUDY #3: COBIMETINIB – DDI PREDICTION WITHOUT A RIFAMPIN STUDY

Cobimetinib (Cotellic®), approved by the US FDA in 2015, is a kinase inhibitor for the treatment of advanced melanoma. As in the best practice case of Ibrutinib, we generally perform PBPK simulations with model verification based on CYP3A4 strong inhibitor and inducer clinical data. However, with cobimetinib, which is a CYP3A4/ UGT2B7 drug, the sponsor had only conducted a study with itraconazole. There was no rifampin data available to verify the effect of inducers.

To build the model, the one itraconazole study, along with mass balance, human PK and *in vitro* data was used to predict the effects of those inducers and inform the final drug label. By leveraging the Simcyp Simulator and its oncology population file, the effects of CYP3A4 modulators on Cobimetinib PK in healthy and cancer patients were predicted, with only one clinical study. The label language in figure 6 clearly indicates that the final label was informed by simulations alone.

Effect of Strong and Moderate CYP3A Inhibitors on Cobimetinib:

In vitro studies show that cobimetinib is a substrate of CYP3A. Coadministration of itraconazole (a strong CYP3A inhibitor) 200 mg once daily for 14 days with a single 10 mg cobimetinib dose increased mean cobimetinib AUC (90% CI) by 6.7-fold (5.6, 8.0) and mean Cmax (90% CI) by 3.2-fold (2.7, 3.7) in 15 healthy subjects. Simulations showed that predicted steady-state concentrations of cobimetinib at a reduced dose of 20 mg administered concurrently with short-term (less than 14 days) treatment of a moderate CYP3A inhibitor were similar to observed steady-state concentrations of cobimetinib at the 60 mg dose alone.

Effect of Strong and Moderate CYP3A Inducers on Cobimetinib:

Based on simulations, cobimetinib exposures would decrease by 83% when coadministered with a strong CYP3A inducer and by 73% when coadministered with a moderate CYP3A inducer.

Figure 6: Label language for Cobimetinib clearly indicates approved claims based on simulations (PBPK with Simcyp) alone.

CASE STUDY #4: VOXELOTOR – DDI PREDICTION WITHOUT ANY CLINICAL STUDIES

Sickle Cell Disease (SCD) is a group of inherited red blood cell disorders. The most common genetic disease in the world, approximately 250 million people worldwide carry the gene responsible for sickle cell disease and other hemoglobin diseases. Until recently, the only cure for SCD was a bone marrow or stem cell transplant.

In November, 2019, the US FDA granted accelerated approval for Oxbryta™ tablets for the treatment of SCD in adults and children 12 years of age and older. Voxelotor is an oral therapy taken once daily, is the first approved treatment that directly inhibits sickle hemoglobin polymerization, the root cause of SCD. Per FDA, "Today's approval provides additional hope to the 100,000 people in the U.S., and the more than 20 million globally, who live with this debilitating blood disorder[5]."

As drug types become more complex, we are using PBPK to answer difficult development questions, such as in the case of voxelotor. Voxelotor was developed under FDA's accelerated review and orphan designations. Delivered via multiple pathways, our initial goal was to determine dose projections for children aged 9 months to 12 years. This required us to develop a model using the in vitro and clinical data in healthy volunteers, verify with independent clinical data sets, create a new population file for SCD, and verify with adults and adolescents with the disease in order to predict exposure in children.

We were then asked to predict DDI with CYP3A4 enzymes, but there were no clinical DDI studies using the drug as a victim for us to use in building the model. To address this issue, we leveraged the model we built for dose prediction in healthy and SCD patients along with in vitro data to create the DDI predictions. We then performed a sensitivity analyses under multiple scenarios and were able to inform the final label without need for any clinical studies. Further, there was no post-marketing requirement covering DDI. DDI and dosing recommendations are shown in figure 7.

2.3 Recommended Dosage of OXBRYTA When Used with Concomitant Moderate or Strong Inducers, Strong Inhibitors of CYP3A4, or Fluconazole

Avoid concomitant use of strong or moderate CYP3A4 inducers, strong CYP3A4 inhibitors, or fluconazole with OXBRYTA [see *Drug Interactions (7.1)* and *Clinical Pharmacology (12.3)*]. If concomitant use of strong or moderate CYP3A4 inducers, strong CYP3A4 inhibitors, or fluconazole is unavoidable, adjust the OXBRYTA dosage as recommended in Table 1.

Table 1: OXBRYTA Recommended Dosage for Concomitant Medications

Concomitant Medication	Recommended OXBRYTA Dosage
Strong CYP3A4 inhibitors or fluconazole	1,000 mg once daily
Strong or moderate CYP3A4 inducers	2,500 mg once daily

Figure 7: DDI and dose predictions for voxelotor (Oxbryta) on drug label attained via Simcyp PBPK simulations alone

CASE STUDY #5: ARIPIPRAZOLE LAUROXIL – DDIs WITH NEW AND COMBINED FORMULATIONS

Aripiprazole lauroxil (Aristada®) was approved by the FDA for the treatment of schizophrenia in October 2015 at monthly and 6-week dosing options. Although aripiprazole was not a new drug, Aristada was a new, long-acting injectable formulation to combat this challenging disease.

The sponsor needed to understand the impact of different dosing scenarios for this new injectable antipsychotic drug, including missing doses, since schizophrenia patients often have difficulty with medication adherence. We built a model using the Simcyp whole body PBPK Simulator for the evaluation of oral metabolism, combined with the Simulator's MechDermA model for evaluation of the new intramuscular injection route of administration. The PBPK model was used to inform the label for the intramuscular injection formulation and assess the combination of the oral and intramuscular formulation.

That same PBPK model was leveraged to evaluate the impact of concomitant administration of strong CYP3A4 inhibitors and inducers and strong CYP2D6 inhibitors on the drug's pharmacokinetics (PK). Since patients that are CYP2D6 poor

metabolizers have a reduced ability to eliminate CYP2D6 substrates, they also wanted to know if these patients would require dose adjustments. The effects of CYP3A and CYP2D6 modulators on different CYP2D6 phenotype groups (efficient, intermediate and poor metabolizers) were provided via Simcyp PBPK modeling and simulation as shared in the label in figure 8.

Concomitant Medicine	Dose Change for AL*
Strong CYP3A4 Inhibitor	Reduce the dose of AL to the next lower strength. No dosage adjustment is necessary in patients taking 441 mg AL, if tolerated. *For patients known to be poor metabolizers of CYP2D6*: Reduce dose to 441 mg from 662 mg or 882 mg. No dosage adjustment is necessary in patients taking 441 mg AL, if tolerated.
Strong CYP2D6 Inhibitor	Reduce the dose of AL to the next lower strength. No dosage adjustment is necessary in patients taking 441 mg AL, if tolerated. *For patients known to be poor metabolizers of CYP2D6*: No dose adjustment required.
Both Strong CYP3A4 Inhibitor and Strong CYP2D6 Inhibitor	Avoid use for patients at 662 mg or 882 mg dose. No dosage adjustment is necessary in patients taking 441 mg AL, if tolerated.
CYP3A4 Inducers	No dose adjustment for 662 mg and 882 mg dose, increase the 441 mg dose to 662 mg.

Figure 8: Dosing guidance for Aristada injectable formulation

SUMMARY

DDIs are an important factor to determining risk in developing and delivering medicines. As we know, patients frequently use more than one medication at a time so unanticipated, unrecognized, or mismanaged DDIs can result in an unacceptable level of risk. As an industry, we have learned a great deal about how to measure and manage DDIs, which is why the regulators have continually delivered guidance on this topic to drug developers.

Perhaps the most profound advancement in that guidance has been the evolution of modeling and simulation for informing DDIs, specifically PBPK. This article has shown the ubiquitous potential of PBPK for studying this subject and the regulatory roadmap toward informing and/or avoiding unnecessary DDI studies.

CERTARA

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Dr Karen Rowland Yeo is Senior Vice-President, Client & Regulatory Strategy at Certara UK Limited's Simcyp Division. Prior to this, she was the Head of PBPK Consultancy Services at Simcyp where she led a team of scientists engaged in Consultancy projects relating to the application of physiologically based pharmacokinetic (PBPK) modeling in the drug development process. This involved putting a framework in place for developing models used for both internal decision-making and regulatory submissions. Her work ranged across most therapeutic areas and included the development of models used for dosing of special populations, including organ impairment. She has worked directly with global regulators to gain acceptance of PBPK models, increasingly raising the bar in innovation and quality.

She received her BSc Honours degree in Physics at the University of Natal in South Africa in 1989 and her PhD in Drug Metabolism from the University of Sheffield in 1995. This was followed by a two-year position as a Postdoctoral Leukaemia Research Fund Fellow in the area of Childhood Acute Lymphoblastoid Leukaemia and then a 5-year lectureship in the Department of Clinical Pharmacology & Therapeutics at the University of Sheffield. Karen has been the author/co-author of more than 80 peer-reviewed articles, and is a frequently called as an invited speaker and session organiser/moderator at many international meetings in the field.

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