CERTARA

Simcyp™ PBPK for Drug-Drug Interactions (DDI)

Inform, Reduce, Eliminate Clinical Studies

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OVERVIEW

The past two decades have witnessed transformative changes in our approach to using modeling & simulation to assess and manage 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 new guidance documents from the US FDA and the International Committee on Harmonization (ICH). [2,3,4] In this paper, we focus on how modeling & simulation, specifically physiologically based pharmacokinetic (PBPK) modeling has grown to become an accepted (and encouraged) approach to inform, reduce and/or waive DDI studies.

Simcyp PBPK is the gold standard for use on assessment of DDIs, as evidenced by >100 marketed drugs for which the Simcyp Simulator was used in lieu of clinical studies to achieve 325+ individual label claims for prescribing the drug to patients (*Figure 1*).

ONCOLOGY	Agios — Tibsovo *(ivosidenib)*	Genentech — Cotellic *(cobimetinib)*	Novartis — Vijoice *(alpelisib)*
	Amgen — Blincyto *(blinatumomab)*	Genentech — Polivy *(polatuzumab vedotin-piiq)*	Novartis — Rydapt *(midostaurin)*
	Amgen — Lumakras *(sotorasib)*	Genentech — Rozlytrek *(entrectinib)*	Novartis — Tabrecta *(capmatinib)*
	Ariad — Alunbrig *(brigatinib)*	Incyte — Pemazyre *(pemigatinib)*	Novartis — Zykadia *(ceritinib)*
	Ariad (Takeda) — Iclusig *(ponatinib)*	Janssen — Balversa *(erdafitinib)*	Novartis — Jakavi *(ruxolitinib)*
	AstraZeneca — Calquence *(acalabrutinib)*	Janssen — Erleada *(apalutamide)*	Pfizer — Bosulif *(bosutinib)*
	AstraZeneca — Lynparza *(olaparib)*	Lilly — Retevmo *(selpercatinib)*	Pfizer — Lorbrena *(lorlatinib)*
	AstraZeneca — Tagrisso *(osimertinib)*	Lilly — Verzenio *(abemaciclib)*	Pharmacyclics — Imbruvica *(ibrutinib)*
	Beigene — Brukinsa *(zanubrutinib)*	Loxo — Jaypirca *(pirtobrutinib)*	Sanofi — Jevtana *(cabazitaxel)*
	BluePrint Medicines — Ayvakit *(avapritinib)*	Loxo Oncology — Vitrakvi *(larotrectinib)*	Seattle Genetics — Tukysa *(tucatinib)*
	Celgene — Inrebic *(fedratinib hydrochloride)*	Menarini/Stemline — Orserdu *(elacestranto)*	Spectrum — Beleodaq *(belinostat)*
	Daiichi Sankyo — Turalio *(pexidartinib)*	Mirati — Krazati *(adagrasib)*	Takeda — Exkivity *(mobocertinib)*
	Daiichi Sankyo — Ezharmia *(valmetostat tosilate)*	Novartis — Farydak *(panobinostat)*	Taiho — Lytgobi *(futibatinib)*
	Eisai — Lenvima *(lenvatinib)*	Novartis — Kisqali *(ribociclib succinate)*	Verastem — Copiktra *(duvelisib)*
	EMD Serono — Tepmetko *(tepotinib hydrochloride)*	Novartis — Scemblix *(asciminib)*	
	Genentech — Alecensa *(alectinib)*	Novartis — Odomzo *(sonidegib)*	
RARE DISEASE	Agios — Pyrukynd *(mitapivat)*	Intercept — Ocaliva *(obeticholic acid)*	PTC Therapeutics — Emflaza *(deflazacort)*
	AkaRx (Eisai) — Doptelet *(avatrombopag maleate)*	Kadmon — Rezurock *(belumosudil)*	Reata — Skyclarys *(omaveloxolene)*
	AstraZeneca — Koselugo *(selumetinib)*	Merck — Welireg *(belzutifan)*	Sanofi Genzyme — Cerdelga *(eliglustat tartrate)*
	Aurinia — Lupkynis *(voclosporin)*	Mirum — Livmarli *(maralixibat)*	Travere — Filspari *(sparsentan)*
	Genentech — Enspryng *(satralizumab)*	Mitsubishi Tanabe — Dysval *(Valbenazine)*	Vertex — Symdeko *(tezacaftor/ivacaftor)*
	Genentech — Evrysdi *(risdiplam)*	Novartis — Isturisa *(osilodrostat)*	Vertex — Trikafta *(elexacaftor/ivacaftor/tezacaftor)*
	Global Blood Therapeutics — Oxbryta *(voxelotor)*	Peloton/Merck — Welireg *(belzutifan)*	
CENTRAL NERVOUS SYSTEM	AbbVie — Rinvoq *(upadacitinib)*	Eisai — Dayvigo *(lemborexant)*	Lilly — Reyvow *(lasmiditan succinate)*
	AbbVie — Qulipta *(atogepant)*	Idorsia — Quviviq *(daridorexant)*	Novartis — Mayzent *(siponimod fumaric acid)*
	Alkermes — Aristada *(aripiprazole lauroxil)*	Janssen — Ponvory *(ponesimod)*	Pfizer — Zavzpret *(zavegepant)*
	Alkermes — Lybalvi *(olanzapine/samidorphan)*	Kyowa Kirin — Nourianz *(istradefylline)*	UCB — Briviact *(brivaracetam)*
INFECTIOUS DISEASE	Gilead — Veklury *(remdesivir)*	Merck — Prevymis *(letermovir)*	Tibotec — Edurant *(rilpivirine)*
	Janssen — Olysio *(simeprevir)*	Nabriva — Xenleta *(lefamulin acetate)*	ViiV — Cabenuva Kit *(cabotegravir/rilpivirine)*
	Merck — Pifeltro *(doravirine)*	Novartis — Egaten *(triclabendazole)*	
GASTROENTEROLOGY	AstraZeneca — Movantik *(naloxegol)*	Phathom — Voquezna TriplePak (*vonoprazan/amoxicillin/clarithromycin*)	Shire — Motegrity *(prucalopride)*
	Helsinn — Akynzeo *(fosnetupitant/palonosetron)*	Shionogi — Symproic *(naldemedine)*	
CARDIOVASCULAR	Actelion (J & J) — Opsumit *(macitentan)*	BMS — Camzyos *(mavacamten)*	Pfizer — Revatio *(sildenafil)*
	Bayer (and Merck) — Verquvo *(vericiguat)*	Johnson & JohnsonXarelto *(rivaroxaban)*	
ENDOCRINE	AbbVie — Orilissa *(elagolix)*	Lilly — Olumiant *(baricitinib)*	Merck — Steglatro *(ertugliflozin)*
	Janssen — Invokana *(canagliflozin)*	Lilly — Mounjaro *(tirzepatide)*	
OTHER	Galderma — Aklief *(trifarotene)*	Takeda — Livtencity *(maribavir)*	

Updated July. 2023

Figure 1: >100 Novel Drugs and 325+ label claims, approved by global regulators using the Simcyp Simulator in lieu of clinical studies.

THE IMPORTANCE OF DDIs IN DRUG DISCOVERY AND DEVELOPMENT

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, and 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, included in drug labeling and monitored on an ongoing basis.

Per FDA's final guidance on the topic, "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."

> *"DDIs are a critical factor in a drug's overall benefit-risk profile. Understanding how to safely manage a DDI can allow approval of a drug that would otherwise have an unacceptable level of risk."*
>
> *- US FDA*

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.[5]

DDIs, PBPK AND REGULATORY GUIDANCE

In 1997, the US FDA published its first draft guidance on DDIs, which was updated numerous times over the past 20+ years. In 2020, the FDA published two final guidance documents; *in vitro*, and clinical cytochrome P450 enzyme- and transporter-mediated drug interactions.

Both guidance documents identify PBPK as a relevant and growing technology for predicting clinical DDIs, as evidenced by this introductory statement to the *in vitro* guidance:

> *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.*

> *"PBPK models can predict the DDI potential of an investigational drug/ and or metabolite as an enzyme substrate or enzyme perpetrator"*
>
> *- US FDA*

Among the many PBPK citations in the aforementioned clinical guidance document, we share:

> *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.*
>
> *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."*

In addition to the above seminal documents, the US FDA has published several other relevant guidances:

- DDI and therapeutic proteins. Draft guidance published in August, 2020 states:
  The application of PBPK modeling in the evaluation of the DDI potential of a TP is an emerging 212 area. PBPK modeling has a potential role in understanding the underlying mechanism of a DDI. 213 Sponsors are encouraged to contact the FDA when proposing to use PBPK modeling to evaluate 214 the DDI potential of TPs.[6]
- Patients with impaired renal function. Draft guidance published in September, 2020 states:
  Early characterization can be based on data obtained from phase 1 and/or phase 2 studies. Alternatively, this information can be obtained by utilizing modeling and simulation strategies, for example, physiologically based pharmacokinetic modeling and simulation.[7]
- Assessing the effects of food on drugs. Guidance published in June, 2020 states:
  In conjunction with FE data in subjects, PBPK analyses can sometimes be used to further assess the effects of food on a drug. For example, PBPK models can guide *in vitro* experimental designs to generate data that can be used to further support PBPK model development, and to identify and optimize parameters that are important to understanding and predicting food-drug interactions in conjunction with FE data. PBPK approaches can also be useful to guide clinical study design.[8]
- Gastric pH-dependent DDI with acid-reducing agents. Guidance published in March, 2023 states:
  In conjunction with the assessment framework outlined in Figure 1, PBPK simulations can sometimes be used to further assess the potential for pH-dependent DDIs. PBPK approaches can also be useful to inform clinical study designs.[9]

As the application of PBPK in drug development is continually evolving, the US FDA notes "that PBPK modeling is still evolving, and new applications of PBPK simulation are continuously being evaluated by the FDA. Sponsors are encouraged to consult the appropriate review division regarding the suitability of the PBPK approach."

Other global regulatory agencies have written guidance on the topic of DDI, as well as other uses for PBPK in drug development. Agencies from Europe, Japan, Canada, Australia, and the UK for example, all have case studies using Simcyp in lieu of clinical studies.

Finally, the ICH M12 guidance document, published in 2022 identifies PBPK for predicting DDI throughout the document.

As an innovator in the field of PBPK, we are continually developing new and expanded uses for the Simcyp Simulator in drug development and regulatory acceptance. To that end, we share these advances with global regulators via workshops, training events, and individual meetings with regulators alongside our biopharma partners. That progression and future perspective is evidenced in this paper.

THE SIMCYP SIMULATOR IS BEING APPLIED ACROSS INCREASINGLY COMPLEX SCENARIOS

The case studies presented in this paper demonstrate how the Simcyp Simulator has been applied to increasingly complex drugs and regulatory approaches (Figure 2). Beginning with Imbruvica, which is considered the 'poster child' for use of PBPK in DDIs, we outline two pathways of expansion. The first is the application and acceptance of PBPK in lieu of clinical studies for increasingly complex scenarios; the second focuses on PBPK for DDI and dose prediction in special populations.

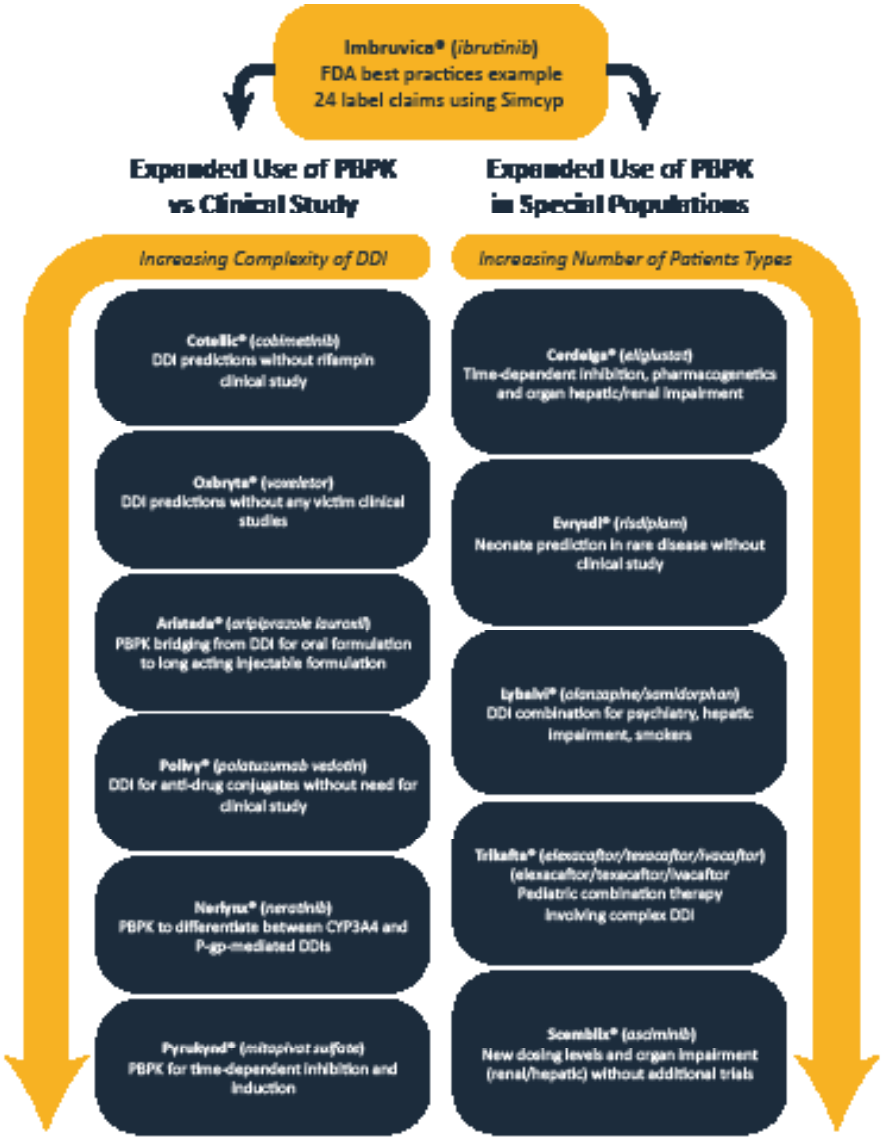

Figure 2: Predicting DDI, waiving clinical studies and attaining additional label claims with the Simcyp Simulator has evolved significantly in the past decade.

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 Imbruvica®, was recently approved by the US FDA for its 12th 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 ibrutinib as a 'best practice' as depicted in Figure 3.

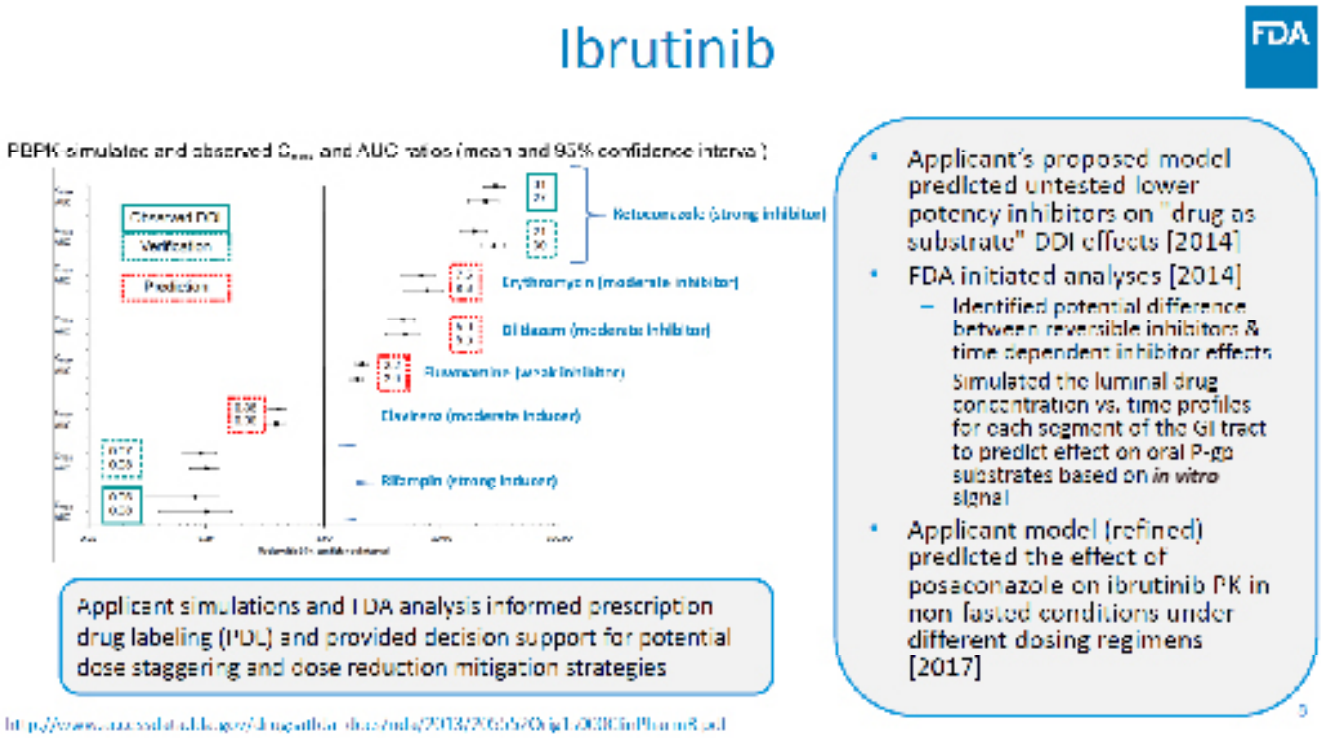

Figure 3: FDA refers to the use of PBPK for DDI labeling and dose projection on ibrutinib as a 'best practice.'

CASE STUDY 2: COBIMETINIB - DDI PREDICTIONS WITHOUT REQUIRING 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 4 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 C_{max} (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 4: Label language for Cobimetinib clearly indicates approved claims based on simulations (PBPK with Simcyp) alone.

CASE STUDY 3: VOXELOTOR – DDI PREDICTIONS 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, 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."[10]

As drug types become more complex, we are using PBPK to answer difficult development questions, such as in the case of voxelotor, which 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 analysis 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 5.

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 5: DDI and dose predictions for voxelotor (Oxybryta) on drug label attained via Simcyp PBPK simulations alone.

CASE STUDY 4: ARIPIPRAZOLE LAUROXIL – DDIs WITH NEW AND COMBINATION FORMULATIONS USING PBPK

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 (LAI) formulation that was developed to address compliance issues associated with the oral formulation since schizophrenic patients often have difficulty with medication adherence. Clinical DDI studies had been conducted with the oral formulation but not with the LAI.

The sponsor needed to understand the DDI potential of the LAI. 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 6.

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 6: Dosing guidance for Aristada injectable formulation, as predicted by Simcyp.

CASE STUDY #5: POLATUZUMAB VEDOTIN - DDI FOR ANTIBODY-DRUG CONJUGATES (ADC) WITHOUT NEED FOR CLINICAL STUDY

Antibody-Drug Conjugates (ADCs) are highly potent biological drugs built by attaching a small molecule drug to an antibody via a linker. The benefit for ADC is in cancer treatment. The antibody selectively targets tumor cells, releases the cytotoxic drug at the tumor site with no adverse events in healthy tissues. The Simcyp Simulator model for ADCs can support the first-in-human dose selection, predict drug-drug interaction (DDI) between the small molecule payload and other co-medication, and understand the disposition of an ADC in special populations.

As recently published, Genentech developed a PBPK model-based approach to assess CYP3A-mediated DDI risk for polatuzumab vedotin (Polivy®), an anti-CD79b-vc-monomethyl auristatin E (MMAE) ADC10. As shown in the Figure 7, the model was developed and verified using data from the existing clinical DDI study for a similar compound, brentuximab vedotin. While the DDI risk for the antibody is low, the unconjugated MMAE formed from the catabolism of polatuzumab vedotin can behave like a small molecule, which could be metabolized and cleared via CYPs and transporters. Concomitant medications that are inhibitors or inducers of the same metabolic enzymes and/or transporters could alter the pharmacokinetics of unconjugated MMAE, affecting clinical outcomes. The Simcyp PBPK model was able to demonstrate that the two compounds (brentsuximab vedotin) and Polivy were analogous from a DDI perspective, negating the need for any DDI clinical studies. This was the first case of its kind.

The novelty of the Simcyp PBPK model for ADCs is to model the antibody and the small molecule drug simultaneously. As many ADCs share the same payload and linker, we believe that this approach can support additional DDI predictions for achieving BLA approval without the need for dedicated clinical studies.

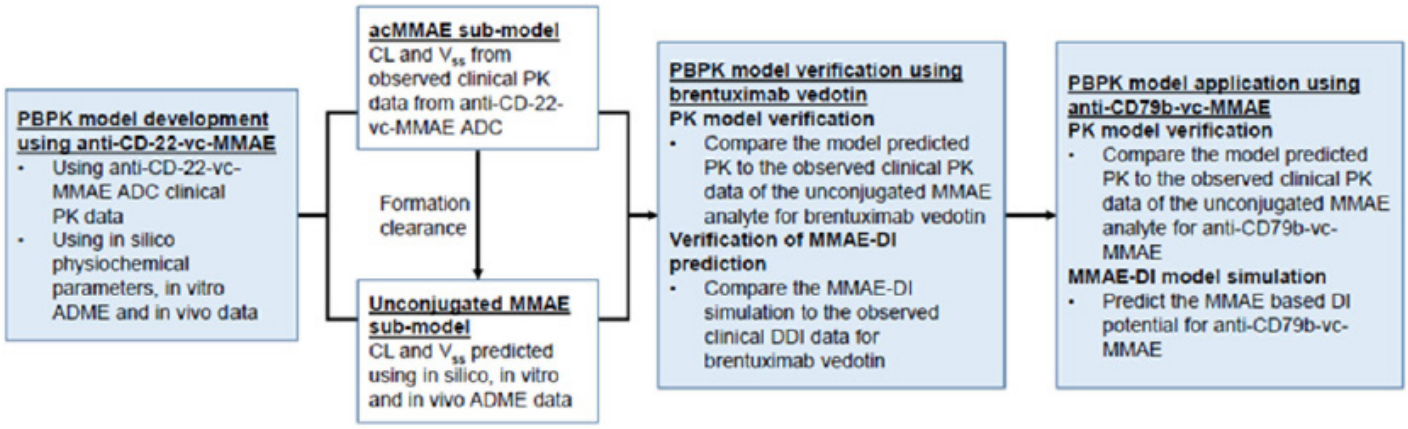

Figure 7: Simcyp used to predict performance of ADC drugs.

CASE STUDY #6: NERATINIB - PBPK AND MASS BALANCE STUDY (TOTALITY OF EVIDENCE) TO ADDRESS TRANSPORTER DDIs

Initially approved by the US FDA in 2017 for extended adjuvant treatment of adult patients with early stage HER2-overexpressed/amplified breast cancer, neratinib (Nerlynx™) was required to conduct a PBPK study as a post-marketing requirement (PMR). That study was to evaluate the effect of repeat doses of a moderate CYP3A4 inhibitor on the single dose pharmacokinetics of neratinib and its active metabolites to assess the magnitude of increased drug exposure and to address the potential for excessive drug toxicity.

A PBPK model for neratinib was developed in Simcyp based on both *in vitro* and *in vivo* data. Mass balance data were used to refine the model to ensure that plasma concentrations and faecal excretion of neratinib and M3 and M6 metabolites after a single oral dose matched the observed data. Recent FDA-authored papers, along with ICH and FDA guidance address the many benefits of this study such as providing information on which metabolite(s) should be structurally characterized and which metabolite(s) would be subject to nonclinical safety assessment. In addition, metabolism and excretion information obtained from the human mass balance studies can inform the need to further evaluate the impact of renal and/or hepatic impairment as well as DDI studies during drug development.[11]

The PBPK model was further developed in response to a second PMR to simulate repeat doses of a moderate CYP3A4 inducer on the single dose pharmacokinetics of neratinib and its active metabolites to assess the magnitude of decreased drug exposure and to determine appropriate dosing recommendations.

Regulatory (FDA and EMA) approval was obtained to use this model to support drug label statements (five claims) for the predicted DDI scenarios: strong and moderate CYP3A4 inhibitors, moderate CYP3A4 and P-gP dual inhibitors, and strong and moderate CYP3A4 inducers. This work also supported a label expansion for a new indication of neratinib in combination with capecitabine, for the treatment of adult patients with advanced or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2 based regimens in the metastatic setting.

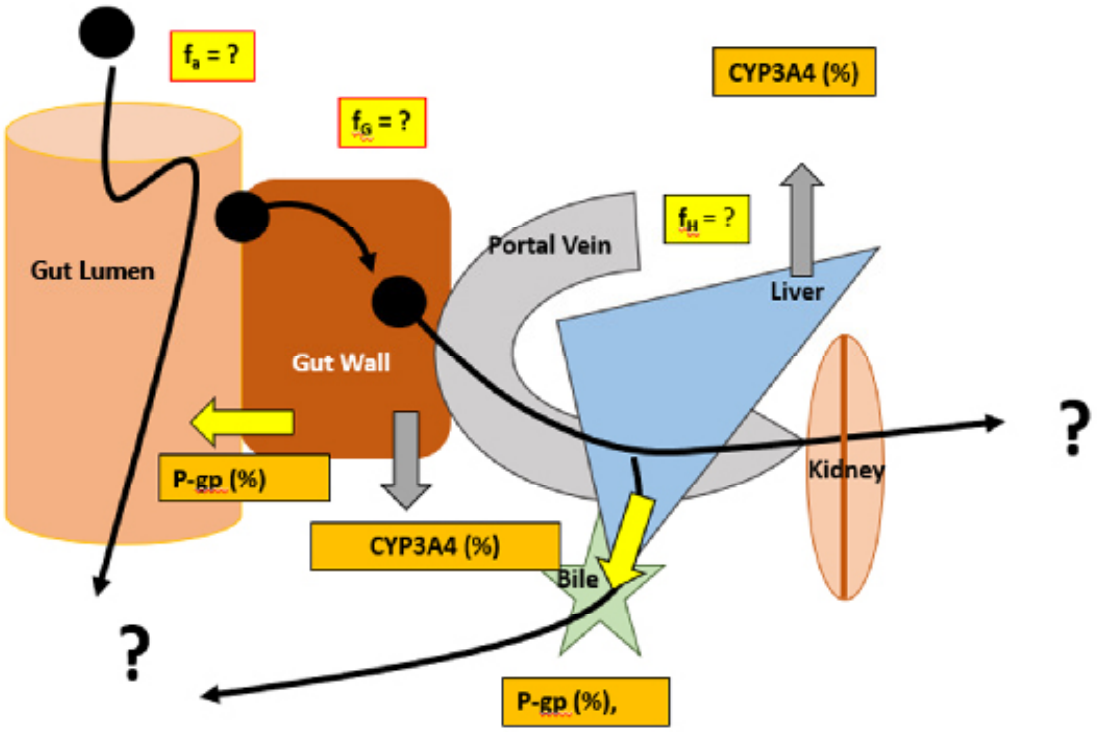

Figure 8: Neratinib is a substrate of CYP3A4 and P-gp (Simcyp leveraged for CYPs and enzymes).

CASE STUDY #7: MITAPIVAT SULFATE - PBPK FOR TIME-DEPENDENT INHIBITION AND INDUCTION

Mitapivat sulfate (Pyrukynd®), approved by US FDA in February, 2022 is a weak base compound that has higher solubility in lower pH conditions and has lower solubility in higher pH conditions. It is used to treat hemolytic anemia, a rare and inherited disease in which red blood cells are destroyed faster than they can be made, in adults with pyruvate kinase deficiency.

Mitapivat was determined to be both a time-dependent inhibitor and inducer of CYP3A and a sensitive substrate of CYP3A. Because mitapivat has the potential to induce CYP3A4/5 and itraconazole is metabolized via CYP3A4/5, the study was designed as a single-dose with a prospective plan to use those results to simulate multiple-dose scenarios by PBPK modeling. DDI simulations were then conducted to predict the effect of strong and moderate CYP3A inhibitors or inducers on the pharmacokinetics of mitapivat following multiple doses at 5, 20, and 50 mg BID. The PBPK analysis was also leveraged to assess the DDI potential of mitapivat with methotrexate, a substrate of the renal uptake transporter OAT3.

Proton pump inhibitors (PPIs) are the most commonly used anti-acid drugs worldwide and are often prescribed along with other treatments. However, drug-drug interactions between PPIs and other agents may lead to decreased drug absorption with possible reduced therapeutic benefit, or even increased toxicity. The ADAM-PBPK model in Simcyp was applied to assess the impact of simulating an increase in gastric pH on the pharmacokinetics and fraction absorbed of mitapivat, enabling the sponsor to avoid the need for a clinical study, allowing the dosing recommendations to remain unchanged.

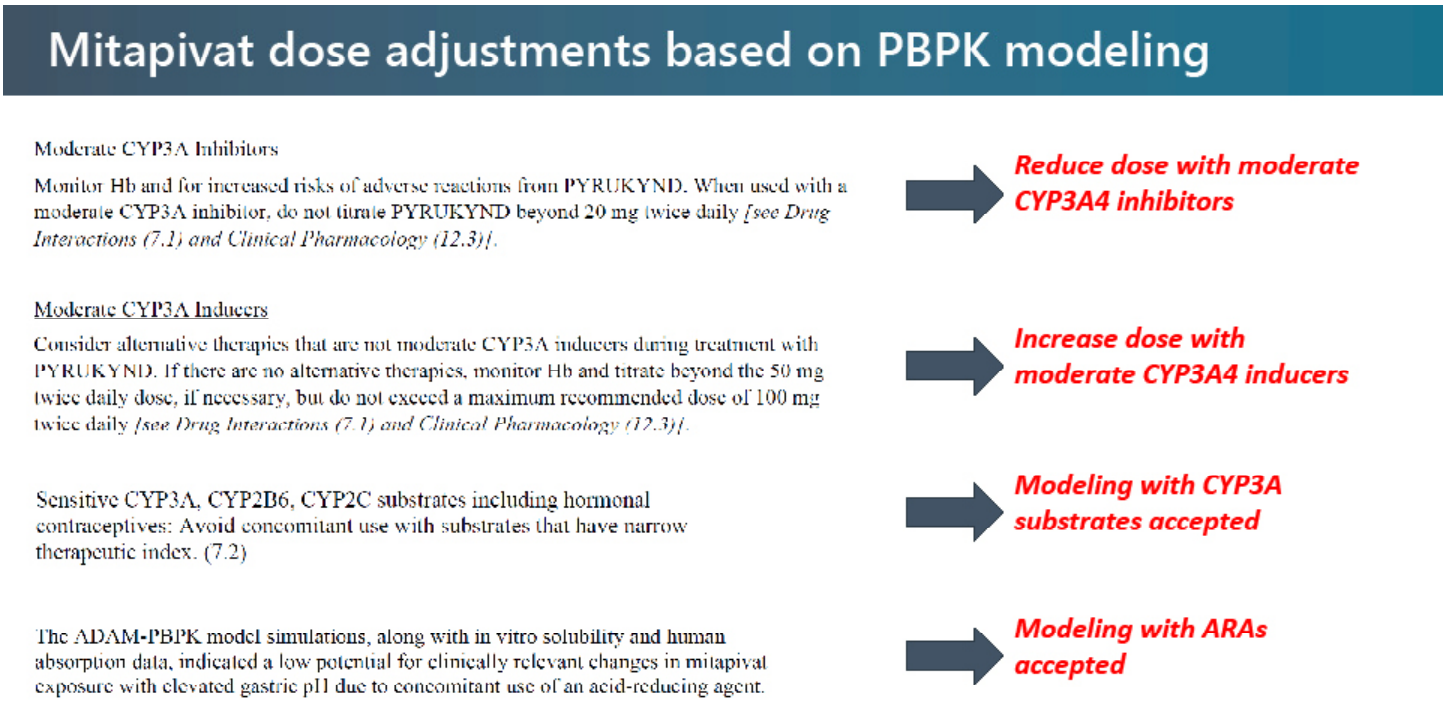

Figure 9: FDA drug label does not differentiate between observed and simulated data.

CASE STUDY #8: ELIGLUSTAT – QUANTIFYING THE IMPACT OF PHARMACOGENETICS ON DDI AND PREDICTING DDI FOR ORGAN IMPAIRED PATIENTS

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 (Figure 10).

The initial label did not include recommendations for patients with hepatic or renal impairment due to insufficient data. Subsequently, phase one trials on both renal and hepatic impairment subjects were conducted, and an extension of the PBPK model was used to predict untested scenarios in subjects with hepatic impairment. Based on those predictions, the label for eliglustat was expanded.[12]

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 10.

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 10: Label language depicting use of PBPK for dosing recommendations of different phenotypical patients of Gaucher's disease.

CASE STUDY #9: RISDIPLAM – DDI EXTRAPOLATION FOR NEONATES IN RARE DISEASE

Spinal muscular atrophy (SMA) is a genetic disease that progressively destroys motor neurons—nerve cells in the brain stem and spinal cord that control essential skeletal muscle activity such as speaking, walking, breathing, and swallowing, leading to muscle weakness and atrophy. It typically begins in infancy or childhood and affects about 1 in 11,000 babies.

Risdiplam (Evrysdi®) was approved by the US FDA in 2020 as the first orally administered drug for SMA treatment for patients ≥2 months old, followed by the European Medicine Agency. Risdiplam addresses the underlying cause of SMA: a reduced amount of survival motor neuron (SMN) protein.

As Risdiplam exhibits time-dependent inhibition of CYP3A *in vitro*, DDI were a concern, but a clinical study in pediatric patients with SMA was not feasible. Therefore, a novel PBPK strategy using the Simcyp Simulator was used to extrapolate DDI risk from healthy adults to children with SMA. As shown in Figure 11, model-based prediction of *in vivo* CYP3A inhibition of risdiplam using PBPK models for healthy adults and patients with SMA including pediatric populations were conducted.[13]

Validation of the risdiplam and midazolam PBPK model for healthy adults using the observations of the clinical DDI study followed, included refinement of the *in vivo* data, facilitating the extrapolation and DDI risk assessments using the pediatric risdiplam PBPK model. Different ontogeny functions of CYP3A enzyme predicted different susceptibility to CYP3A modulations in children and thus various functions were considered. The risdiplam PBPK model was validated with independent data for each population. The PBPK-predicted risdiplam CYP3A inhibition risk in pediatric patients with SMA aged 2 months–18 years was negligible and included in the prescribing information.

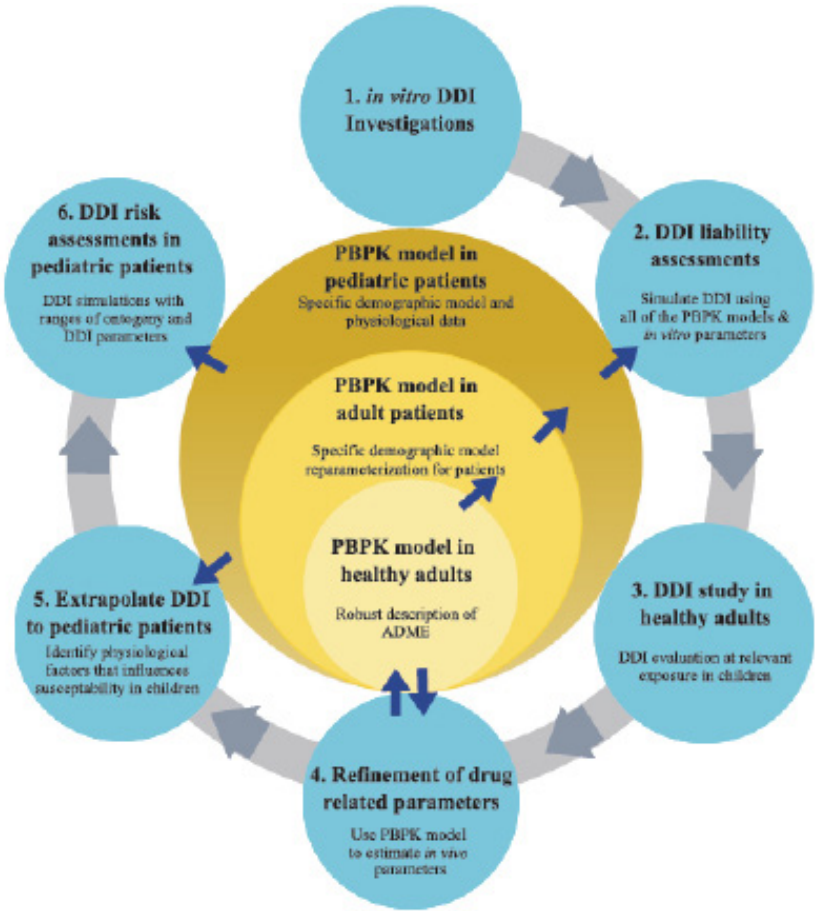

Figure 11: Process for developing PBPK model for prediction of clinical outcomes in pediatrics.

This case study demonstrates that pediatric PBPK modeling performed iteratively with well-designed clinical study in adults enables prospective DDI risk assessments in children. Further, proper selection of intestinal and hepatic ontogeny models based on sensitivity to enzyme modulation facilitates the DDI extrapolation to children.

CASE STUDY #10: OLANZAPINE/SAMIDORPHAN - DDI COMBINATION FOR PSYCHIATRIC PATIENTS, HEPATIC IMPAIRMENT, SMOKERS

The antipsychotic drug olanzapine is very effective for the treatment of schizophrenia, but causes side effects such as weight gain, which can cause patients to become less adherent. Samidorphan is a relatively new opioid antagonist that has been found to reduce weight gain induced by olanzapine. Alkermes developed a combination therapy of olanzapine and samidorphan (OLZ/SAM), called Lybalvi®, approved by the US FDA in June, 2021 for the treatment of both schizophrenia and bipolar I disorder.

A PBPK model in Simcyp was developed and validated with clinical data to evaluate the DDI impact of CYP1A2 and CYP3A4, the major enzymes involved in metabolism of OLZ/ SAM8. Patients with schizophrenia tend to have additional comorbidities, requiring additional medicines, exposing them to additional DDI risk. Additionally, there is a high correlation of smoking amongst this population, which alter plasma drug levels and affect the efficacy or safety of psychiatric medications. The model showed no DDI between olanzapine and samidorphan when administered in combination. CYP3A4 inhibition was predicted to have a weak effect on samidorphan exposure and negligible effect on olanzapine exposure. The model predicted CYP3A4 induction as reducing both samidorphan and olanzapine exposure and CYP1A2 inhibition or induction as increasing or decreasing, respectively, olanzapine exposure only.[14] These DDI label claims were accepted without the need for clinical studies.

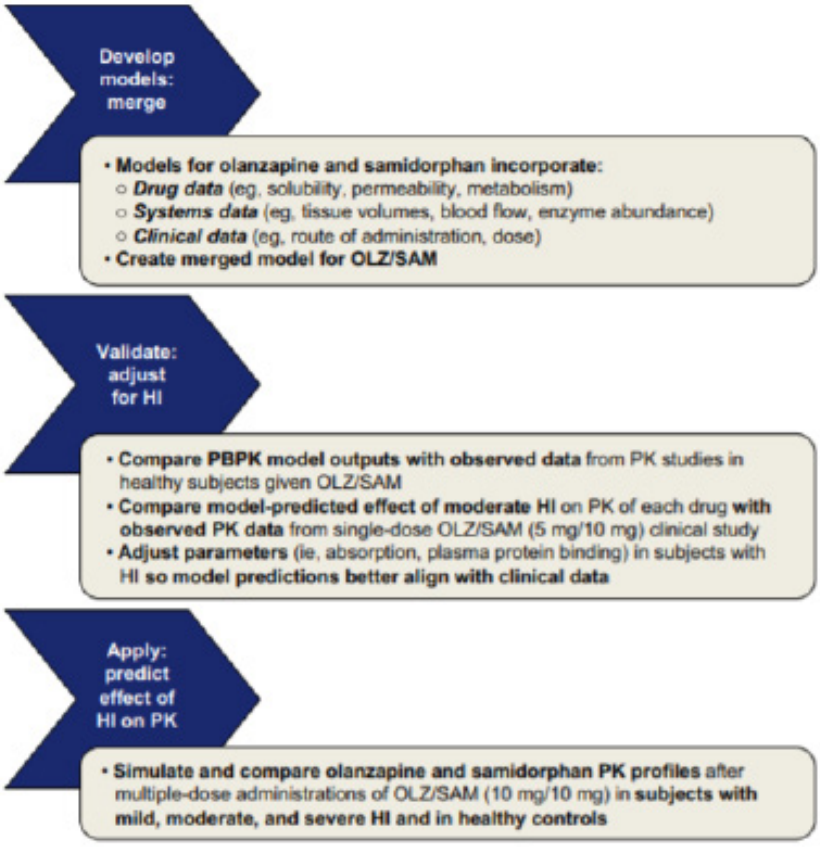

Figure 12: Process for developing PBPK model for prediction of combination therapy and hepatic impaired patients.

Hepatic metabolism plays a major role in both olanzapine and samidorphan clearance, thus the risk that impairment in hepatic function could affect the PKs of both compounds. To assess this risk, the aforementioned PBPK model was further refined to predict changes in olanzapine and samidorphan PKs after multiple once-daily doses of OLZ/SAM in subjects with mild, moderate, and severe hepatic impairment. To evaluate the PK changes in subjects with moderate hepatic impairment, model parameters such as absorption rate constant and fraction unbound to plasma protein were modified. The PBPK modeling indicated that mild hepatic impairment would have minimal impact on steady-state exposures of olanzapine and samidorphan, and moderate to severe hepatic impairment would result in up to 1.6-fold and 2.3-fold increases in total exposure (AUC) of olanzapine and samidorphan, respectively. PBPK modeling allowed for prediction of untested clinical scenarios of varying degrees of hepatic impairment in lieu of additional clinical studies.

CASE STUDY #11: TRIKAFTA – TRIPLE COMBINATION THERAPY FOR PEDIATRIC PATIENTS

Cystic fibrosis is an inherited condition that causes sticky mucus to build up in the lungs and digestive system. This causes lung infections and problems with digesting food. Symptoms usually start in early childhood and vary from child to child, but the condition gets slowly worse over time, with the lungs and digestive system becoming increasingly damaged. In 2012, FDA approved ivacaftor (Kalydeco®) for treatment of the underlying cause of CF in a small subset of the patient population. In 2015, a combination treatment of ivacaftor and lumacaftor (Orkambi®), followed by a combination of ivacaftor and texacaftor (Symdeko®) in 2018. In 2019, the first triple combination of elexacaftor/texacaftor/ivacaftor (Trikafta®) for patients 12 and up, accounting for about 90% of patients with CF was approved.

Many CF patients that take modulator regimens of the above dual combinations will need to transition to the triple combination. An assessment of whether adequate exposures to achieve clinical efficacy are maintained during this transition was needed, as this has not been directly addressed in clinical trials. PBPK modeling using Simcyp was used for this analysis, specifically to understand the CYP3A4 during the cystic fibrosis transmembrane conductance regulator process. Individual models for each drug were developed, followed by simulations of various combination to assess exposure.

The PBPK modeling demonstrated that immediate transfer from the three dual combinations to the triple combination resulted in sustained CFTR in patients 12 years and older. In June, 2021 the label was expanded to children 6 years and older.

Co-administered drug	Effect on PK	$AUC_{inf}R$	$C_{max}R$	Dosing recommendation
Strong CYP3A inhibitor: itraconazole	↑ TEZ	4.51	1.48	Two tablets of ELX/TEZ/IVA twice a week, taken approximately 3 to 4 days apart. The evening dose of ivacaftor 150 mg should not be taken. This is consistent with the labeling of SYMDEKO (TEZ/IVA).
	↑ ELX	2.83	1.05	
Moderate CYP3A inhibitor	ELX	1.9-2.3*	1.07-1.08*	Dose adjustment based on PBPK. Overall, dose is reduced by half for ELX/TEZ/IVA. This is consistent with the labeling of SYMDEKO (TEZ/IVA).
CYP3A inducer: rifampin	ELX (expected ↓)	NA	NA	Co-administration not recommended. This is consistent with the labeling of SYMDEKO (TEZ/IVA).
DDI studies conducted previously and reviewed under NDA 210491 and NDA 203188				
Strong CYP3A inhibitor: itraconazole	↑ TEZ	4.02	2.83	One tablet of TEZ 100 mg/IVA 150 mg twice a week, taken approximately 3 to 4 days apart. The evening dose of ivacaftor 150 mg should not be taken. Overall, TEZ dose is reduced to 1/3.5, and IVA dose is reduced to 1/7 for SYMDEKO.
	↑ IVA	15.6	8.60	
Moderate CYP3A inhibitor: fluconazole	TEZ	2.1**	1.7**	Dose adjustment based on PBPK. Overall, dose is reduced by half for TEZ and IVA.
	↑ IVA	2.95	2.47	
	↔ TEZ	1.08	1.05	No dose adjustment for TEZ and IVA.

Figure 13: Impact of Other Drugs on Systemic Exposure of Elexacaftor, Tezacaftor and/or Ivacaftor (from FDA drug label package).

CASE STUDY #12: ASCIMINIB – PBPK-LED STRATEGIC PROGRAM RESULTING IN 10+ CLINICAL STUDIES WAIVED AND NEW DOSING LEVELS DETERMINED WITHOUT ADDITIONAL TRIALS

In November, 2021 the US FDA granted accelerated approval for asciminib (Scemblix®) with a novel mechanism of action for two indications of chronic myeloid leukemia. Asciminib is a BCS class II weak base formulated as a HCl salt. The FDA nod was followed by EMA and PMDA approvals in 2022.

Simcyp PBPK played a key role in the development and approval of asciminib, beginning in early development for trial design, early DDI assessment and formulation support. The Simcyp model was refined for use in PK characterization, expanded DDI simulations, to assess food effect, and to support organ impairment studies. Prior to the NDA filing, the model was further refined to evaluate issues of PK nonlinearity, assess the impact of multiple dosing regimens, and to simulate untested scenarios.

In a unique approach, the sponsor proposed to use model-informed drug development (MIDD) to bridge efficacy and safety between dosing regimens, including leveraging PBPK modeling to bridge DDI clinical assessments at one dose to other doses not studied clinically. PBPK was used to inform the drug label, its predictions accepted in lieu of >10 clinical pharmacology studies, as shown in Figure 14.

Simcyp's ADAM-PBPK model simulations suggested that changes on gastric pH do not significantly affect asciminib exposure due to its high solubility in bile salts attributed to supersaturation, which override the pH effect. The label concludes that the predicted effect of elevated gastric pH on asciminib PK following a single dose of 200 mg is unlikely to be clinically meaningful.

PBPK addressed several (FDA) agency information requests and helped to avoid further PMR, including additional clinical studies. Simcyp model predictions on the effect of asciminib on the exposure of P-gp substrates were accepted, after the model established IVIVE. PMR for additional protein pump inhibitor (PPI) trials was lifted, as the PBPK modeling with mechanistic absorption was deemed to be predictive of the effect of PPI in the exposure at 80 mg and 200 mg. MIDD, including PBPK and PKPD were accepted in lieu of PMR studies for assessment of hepatically impaired populations at the 80 and 200 mg doses. Additionally, except for victim DDI with a strong CYP3A inducer at the 200 mg dose, there was no need for any other clinical pharmacology studies at the 80 or 200 mg dose.

In summary, PBPK simulations replaced more than 10 clinical pharmacology studies and played an instrumental role in the approval of two additional doses by the US FDA, with no additional studies required in PMR.

----------DRUG INTERACTIONS----------

- Strong CYP3A4 Inhibitors: Closely monitor for adverse reactions during concomitant use of SCEMBLIX at 200 mg twice daily. (7.1)
- Itraconazole Oral Solution Containing Hydroxypropyl-β-cyclodextrin: Avoid concomitant use of SCEMBLIX at all recommended doses. (7.1)
- Certain Substrates of CYP3A4: Closely monitor for adverse reactions during concomitant use of SCEMBLIX at 80 mg total daily dose. Avoid use of SCEMBLIX at 200 mg twice daily. (7.2)
- Substrates of CYP2C9: Avoid concomitant use of SCEMBLIX at all recommended doses.
  - 80 mg total daily dose: If unavoidable, reduce the CYP2C9 substrate dosage as necessary. (7.2)
  - 200 mg twice daily: If unavoidable, consider alternative therapy with non-CYP2C9 substrate. (7.2)
- Certain P-gp Substrates: Closely monitor for adverse reactions during concomitant use of SCEMBLIX at all recommended doses. (7.2)

Figure 14: Portion of drug label for asciminib (Scemblix) determined using Simcyp, at multiple doses.

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 global regulators have continually delivered guidance on this topic to drug developers.

One of the most profound advancements in those guidance documents 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, supporting, and avoiding clinical trials.

Each year we update this white paper to include new case studies that highlight how advances in PBPK are being used to inform drug labels and expand the prescribing of important and lifesaving drugs to patients around the world.

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