Received: 30 December 2020 | Revised: 8 March 2021 | Accepted: 1 April 2021

DOI: 10.1002/psp4.12636

ARTICLE

A generic framework for the physiologically-based pharmacokinetic platform qualification of PK-Sim and its application to predicting cytochrome P450 3A4–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]

[1]Pharmacometrics/Modeling & Simulation, Research & Development, Pharmaceuticals, Bayer AG, Leverkusen, Germany

[2]Clinical Pharmacy, Saarland University, Saarbrücken, Germany

Correspondence
Sebastian Frechen, Pharmaceuticals, Systems Pharmacology & Medicine, Research & Development, Bayer AG, Building B106, 51368 Leverkusen, Germany.
Email: sebastian.frechen@bayer.com

Funding information
This work is part of the Horizon 2020 INSPIRATION (Qualified Open Systems Pharmacology Modeling Network of Drug-Drug-Gene-Interactions) project. The INSPIRATION project (FKZ 031L0241) is supported by the German Federal Ministry of Education and Research under the framework of ERACoSysMed3.

Abstract

The success of applications of physiologically-based pharmacokinetic (PBPK) modeling in drug development and drug labeling has triggered regulatory agencies to demand rigorous demonstration of the predictive capability of the specific PBPK platform for a particular intended application purpose. The effort needed to comply with such qualification requirements exceeds the costs for any individual PBPK application. Because changes or updates of a PBPK platform would require (re-)qualification, a reliable and efficient generic qualification framework is needed. We describe the development and implementation of an agile and sustainable technical framework for automatic PBPK platform (re-)qualification of PK-Sim® embedded in the open source and open science GitHub landscape of Open Systems Pharmacology. The qualification approach enables the efficient assessment of all aspects relevant to the qualification of a particular purpose and provides transparency and traceability for all stakeholders. As a showcase example for the power and versatility of the qualification framework, we present the qualification of PK-Sim® for the intended purpose of predicting cytochrome P450 3A4 (CYP3A4)–mediated drug–drug interactions (DDIs). Several perpetrator PBPK models featuring various degrees of CYP3A4 modulation and different types of mechanisms (competitive inhibition, mechanism-based inactivation, and induction) were coupled with a set of PBPK models of sensitive CYP3A4 victim drugs. Simulations were compared to a comprehensive data set of 135 observations from published clinical DDI studies. The platform's overall predictive performance showed reasonable accuracy and precision (geometric mean fold error of 1.4 for both area under the plasma concentration-time curve ratios and peak plasma concentration ratios with/without perpetrator) and suggests that PK-Sim® can be applied to quantitatively assess CYP3A4-mediated DDI in clinically untested scenarios.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Applications of physiologically-based pharmacokinetic (PBPK) modeling are gaining relevance as an independent evidence source in drug development, and regulatory agencies have specified qualification requirements for a specific PBPK application in dedicated PBPK guidances.

WHAT QUESTION DID THIS STUDY ADDRESS?

This study addresses how to design and implement a technical framework for automated (re-)qualification of the PBPK platform PK-Sim® for an intended purpose and demonstrates the power and versatility of the framework by its application to the prediction of cytochrome P450 3A4 (CYP3A4)–mediated drug–drug interactions as a lighthouse example.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

An agile and sustainable framework for automated PBPK platform (re-)qualification is provided as an embedded functionality of the Open Systems Pharmacology GitHub platform. PK-Sim® is qualified (in its current version) to assess CYP3A4-mediated DDI in clinically untested scenarios.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?

The presented qualification framework enables efficient assessment of the PBPK platform (re-)qualifications for all stakeholders and agile (and open) development of qualification applications. This facilitates the use of PBPK modeling during drug development with transparent levels of confidence.

INTRODUCTION

Physiologically-based pharmacokinetic (PBPK) modeling, integrating various drug properties and system-specific organism properties, is a powerful tool that is increasingly used in numerous application areas to guide decision making during drug development and evaluate clinically untested scenarios for the support of prescription drug labeling.[1–5] Many applications have been accepted by several health authorities, especially for the assessment of quantitatively exploring drug–drug interactions (DDIs). Regulatory agencies now even recommend the use of PBPK under certain conditions to evaluate the DDI risk for new investigational drugs both as victim or as perpetrator.[6,7] Therefore, it is no surprise that DDI predictions account for the majority of submitted PBPK analyses to the US Food and Drug Administration (FDA).[2]

However, within this rapid story of success, regulatory agencies have also now increasingly demanded that sponsors of PBPK studies need to explicitly demonstrate the predictive capability of the PBPK platform for a particular context of use. Specifically, the European Medicines Agency (EMA) requests in its current guideline on PBPK reporting a version-specific PBPK platform qualification for the intended purpose.[8] Similarly, the FDA asks in its current guidance on PBPK reporting for a rigorous demonstration of the level of confidence in PBPK analyses for their intended uses.[9]

Although several reports demonstrated good predictive performance for different PBPK platforms in various application areas,[10–14] all of these potential "qualifications" reflect just a snapshot in time in terms of a temporary qualification of the current version of the respective PBPK platform. Even if a use case from such a publication was considered "qualified," changes and updates in the PBPK platform (e.g., adjusted model structure, changes in model parameterization) with new software version releases would require (re-)qualification. The effort needed to comply with qualification requirements thus may exceed the costs for any individual PBPK application. Consequently, a reliable and efficient generic qualification framework is needed.

Thus, the first objective in this article was to report on the implementation of a technical framework for qualification of the PK-Sim® PBPK platform (as part of the Open Systems Pharmacology [OSP] Suite) for particular intended purposes (qualification scenarios) with the following properties:

- Generate comprehensive standardized reports to facilitate efficient review
- Enable efficient (re-)qualification (e.g., for upcoming new PK-Sim® versions) via an automated workflow
- Enable agile and versatile development of qualification scenarios (extensions, tailoring, etc.)
- Provide full transparency and traceability
- Allow collaborative development of (publicly available) qualification scenarios

The second objective was to qualify PK-Sim® in its current version for the intended purpose of the prediction of cytochrome P450 3A4 (CYP3A4)–mediated DDIs as an important showcase example for the power and versatility of the developed qualification framework.

MATERIAL AND METHODS

OSP platform

OSP offers the professional open access and open source PBPK software platform PK-Sim®.[15] The OSP community (governed by the OSP management team) develops, qualifies, and shares the software tools and models in a collaborative, open science way.[16] OSP uses GitHub as its source control platform for proper release management.[16] The platform also serves for collaboration and exchange.[15] Although the core software PK-Sim® includes any functionality for the full range of PBPK applications, the OSP platform in a broader sense on GitHub provides a dynamic landscape of repositories for models, libraries, data, and qualifications.

We first describe in the Automatic (Re-) Qualification Framework section the core features of a newly developed generic technical framework to generate platform qualification reports for a specific intended purpose, for example, prediction of CYP3A4-mediated DDI, translating pharmacokinetics (PK) to a pediatric population for drugs cleared mainly via glomerular filtration, and so on via an automated workflow. We then elaborate in the OSP Repository Landscape section on the underlying organization of repositories of the OSP platform on GitHub to enable an efficient embedment of the qualification framework.

Automatic (re-) qualification framework

A technical framework to assess platform qualification (and re-qualification) for an intended application purpose has been developed. We present an automated workflow that generates comprehensive qualification reports based on prespecified dedicated qualification plans. A qualification report is a document structured in chapters, beginning with a short description of the scientific background of the qualification scenario, followed by a brief methodological description (e.g., modeling strategy, available data) and the presentation of the results.

A qualification plan represents a technical document (text file in JavaScript object notation [JSON] format[17]) and contains all information to generate such a qualification report. It is developed, maintained, and released within a dedicated qualification repository. The plan defines how static text-module content and dynamic simulation-based content will be combined. Although static text modules will be taken as is and inserted into the report, dynamic content is newly produced with every execution of the qualification workflow and may change between OSP versions in case of differences between the previous and new model structures/parameterizations. A qualification plan consists of the following main sections:

- *Projects*: defines references to all project repositories of PBPK substance model snapshots (file in JSON format) and potential dependencies with inheritance of certain building blocks between projects. A model snapshot contains only the minimal amount of information required to set up the compound's PBPK model file including simulations from scratch in (a new version of) PK-Sim®; this includes in particular primary substance-specific input parameters (e.g., molecular weight, lipophilicity).
- *ObservedDataSets*: reference to required observed PK data.
- *Sections*: defines the chapter structure of the report and links to respective static text modules.
- *Plots*: defines desired figures, tables and qualification measures. Various predefined plot types are available, such as concentration-time profile plots, goodness of fit plots, and so on.

The dedicated OSP software tool *Qualification Runner* then processes the qualification plan, that is, all project parts are exported and prepared for the *Reporting Engine*. The reporting engine provides an environment (implemented in MATLAB®, a transfer to R is in development) for model execution and generates the final qualification report in *Markdown* format.[18] The presented workflow may be triggered for (re-)qualification, for example, if new data, changes in model structure or parameterization, or new OSP suite releases arise.

The presented workflow cannot only be used to generate qualification reports for entire qualification scenarios but also to generate model evaluation reports for single PBPK substance models that document the particular modeling strategy, model development, input parameters, model features, and model performance (regarding the description of the respective compound's PK). Similar to a qualification plan, an evaluation plan comprises all information needed to

generate the evaluation report, that is, it links dynamic output from simulations with observed data and static text modules and defines desired figures and tables.

OSP repository landscape

Although the presented qualification framework per se can be executed in any (local) environment, we additionally focused on its embedment in the dynamic landscape of OSP (featuring fully traceable version control of GitHub) for officially released platform qualifications and models. Various types of (input) repositories on the OSP GitHub platform were defined:

- Model repositories for single PBPK substance models: *<Substance>-Model*. The repository contains the PBPK substance model in form of its snapshot along with its evaluation plan (and static text modules) and serves for their development, maintenance, and releases. A new version here would be released in case of changes in the model snapshot and/or the evaluation plan.
- (Dependent intermediate) model repositories needed for specific qualification scenarios, for example, model snapshot files containing DDI simulations of two interacting compounds (*<Substance1>-<Substance2>-DDI*) or pediatric simulations (*<Substance>-Pediatric*). A new version here would be released in case of changes in the snapshot file (e.g., due to the addition of particular simulations).
- Qualification repositories for specific qualification purposes: *Qualification-<intended purpose>*. The repository contains the qualification plan (and static text modules) and serves for its development, maintenance, and releases. A new version here would be released in case of changes in the qualification plan.
- The OSP database for observed PK data: *Database-for-observed-data*.[19] It contains PK data from publicly available sources for the use in PBPK simulations. The database integrates information from published clinical studies about study designs, statistics of PK parameters (area under the plasma concentration-time curve [AUC], peak plasma concentration [C_{max}], etc.), digitized concentration-time profiles and DDI records (AUC ratios [AUCR] and C_{max} ratios [$C_{max}R$]). Respective data can easily be integrated into PK-Sim® or used in the context of qualifications.

The following two additional (output) container repositories are provided:

- The *OSP-PBPK-Model-Library*[20] constitutes a special repository comprising the officially released PBPK substance models for use in PK-Sim®. These models are published along with a respective model evaluation report. Every model file and its evaluation report is (re-)generated in the automized workflow (see the Automatic ReQualification Framework section) and re-released with every new OSP version within this repository based on the current release of the specific PK-Sim® PBPK model snapshot and the respective evaluation plan.
- The *OSP-Qualification-Reports*[21] constitutes another special repository that contains the officially released qualifications of the PK-Sim® platform (as qualification reports) for specific intended purposes. A respective qualification report is (re-)generated in the automized workflow (see the Automatic ReQualification Framework section) and re-released with every new OSP version within this repository based on the current release of its qualification plan.

Figure 1 gives an overview of the implemented OSP landscape. PBPK models and qualifications to be included in the latter repositories are identified within the release management of the OSP software.[16]

The showcase example: prediction of CYP3A4-mediated DDI

The development of the described qualification framework was accompanied with the development of a prototypical use case, namely, the qualification of PK-Sim® for the intended purpose to simulate CYP3A4-mediated DDI. A set of PBPK substance models of index perpetrators, covering the range from strong CYP3A4 induction to strong inhibition, and respective CYP3A4 DDI victim drugs was specified to set up a DDI modeling network. Within this network, each model was mutually evaluated to verify the perpetrator's and victim's properties with regard to CYP3A4 modulation and metabolism, respectively, by comparing simulations against observations of a comprehensive qualification data set of published clinical DDI studies and hereby to assess the platform's overall predictive performance for this intended purpose.

For the current set of compounds of the network, the six prototypical inhibitors itraconazole, clarithromycin, erythromycin, verapamil, fluvoxamine, and cimetidine, the two prototypical inducers rifampicin and efavirenz, and the four sensitive CYP3A4 substrates midazolam, triazolam, alprazolam, and alfentanil were chosen (Figure 2). This initial selection of the network was mainly based on the prototypical character toward CYP3A4 DDI (i.e., “index” perpetrator/victim), well-established PK characterization (toward CYP3A4 properties), and abundant availability of public data.

PBPK models for each compound were either built from scratch or adopted from previous publications and released as snapshots in respective repositories (e.g., Midazolam-Model). An evaluation plan was written for each substance model to enable generation of an automated model evaluation

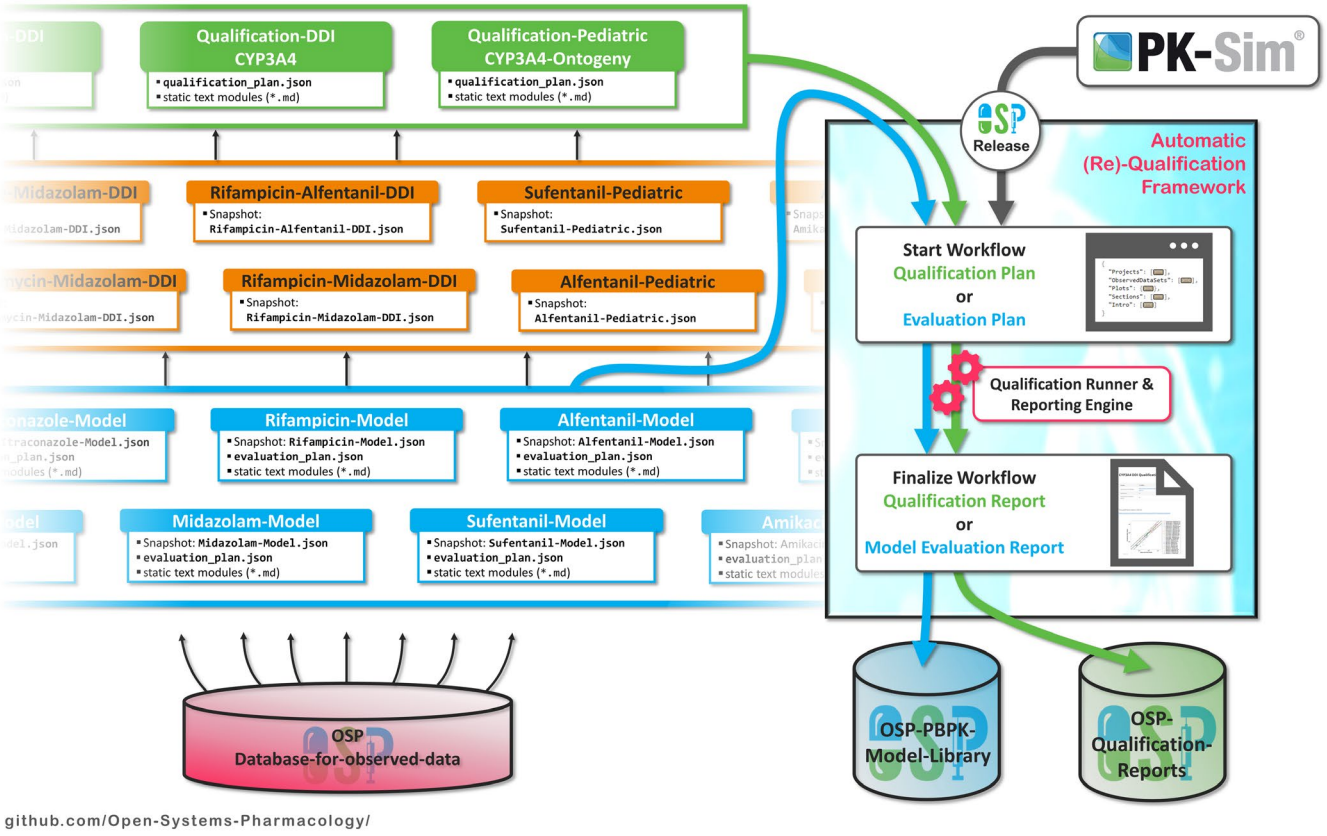

FIGURE 1 OSP qualification landscape on GitHub. Schematic representation of an excerpt of the repository landscape with the embedded automated (re-) qualification framework. The left area shows the various input repositories: blue boxes represent the model repositories for single PBPK substance models (including in particular a snapshot file and an evaluation plan), orange boxes represent the dependent (intermediate) model repositories needed for specific qualification scenarios (including a snapshot file for a specific simulation set-up), green boxes represent qualification repositories for specific qualification purposes, the pink container represents the OSP database for observed PK data repository, and black arrows show the direction of inheritance during workflow execution. The right area shows the execution of the automated workflow of the qualification framework that is triggered with the new PK-Sim® version within a release of the OSP software. The workflow processes the qualification plans (green arrow) and evaluation plans (blue arrow) and generates qualification reports and model evaluation reports, respectively. The report documents are then released in the official OSP container repositories OSP-Qualification-Reports and OSP-PBPK-Model-Library. CYP3A4, cytochrome P450 3A4; DDI, drug–drug interaction; OSP, Open Systems Pharmacology; PBPK, physiologically-based pharmacokinetic

report documenting the model-building process and evaluating the model's performance (in particular via goodness-of-fit plots and the comparison of concentration-time profiles). Respective PK data were taken from the scientific literature and integrated into the OSP PK database.

An extensive literature search (mainly via PubMed®, the University of Washington Drug Interaction Database (DIDB),[22] Google Scholar, and references within articles) was conducted to compile in the OSP PK database a comprehensive data set of clinical DDI studies between the compounds of the network. The focus was set on classic DDI studies (mainly in healthy volunteers) reporting study design and respective exposure ratios of the victim drugs. Obviously, we cannot make a claim for completeness, but integration of further data would always be possible. Currently, 135 different observations (i.e., study arms, etc.) from clinical studies were integrated in this qualification data set (Table 1). Simulations for these 135 studies were set up and released as snapshots in respective dedicated (dependent) repositories (e.g., Clarithromycin-Midazolam-DDI).

The metric to assess the predictive performance of the platform was the $R_{\text{simulated/observed}}$ value ($R_{\text{simulated/observed}}$ = [simulated mean exposure ratio]/[observed mean exposure ratio]), with the exposure ratio defined as the victim's AUCR and $C_{max}R$ ([AUC or C_{max} in the presence of CYP3A4 modulation]/[AUC or C_{max} in the absence of CYP3A4 modulation]). Simulated mean exposure ratios were calculated based on the simulation for a typical/representative (healthy) individual; observed mean exposure ratios were usually represented as reported means, geometric means, or medians from the published available data. The $R_{\text{simulated/observed}}$ values were challenged by the twofold criterion and the more stringent criterion proposed by Guest et al.,[23] which sets a boundary narrower than twofold in particular for mild DDIs. Overall precision and accuracy of the DDI simulations were evaluated using a geometric mean fold error (GMFE) for $R_{\text{simulated/observed}}$. In addition, the performance

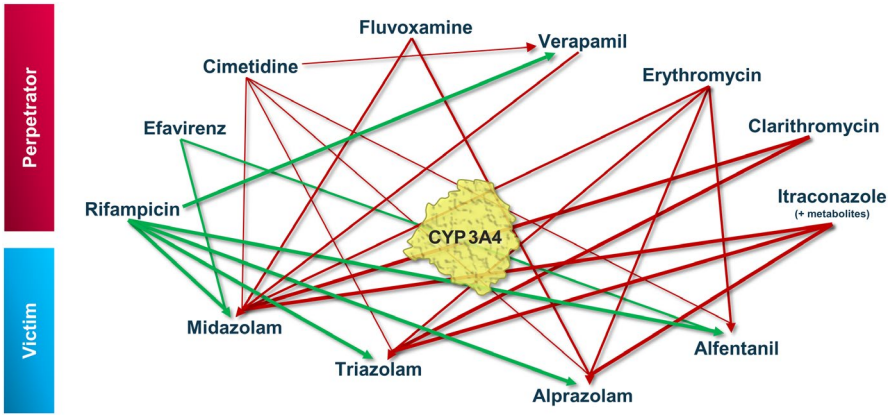

FIGURE 2 Physiologically-based pharmacokinetic model network for CYP3A4-mediated DDI simulations. Schematic illustration of the drug–drug interaction modeling network of interacting perpetrator and victim drugs for the Open Systems Pharmacology suite qualification of simulating CYP3A4-mediated DDI. The upper row shows the typical (index) CYP3A4 perpetrators, and the lower row shows sensitive CYP3A4 substrates. The arrows indicate where at least one clinical drug–drug interaction study between the two connected substances was available and included in the model network. Red indicates inhibition and green indicates induction as the primary type of interaction. Thin arrows indicate weak, mid-thick arrows moderate, and thick arrows strong CYP3A4 modulation by the perpetrator. CYP3A4, cytochrome P450 3A4

of the network was evaluated visually by comparison of simulated versus observed victim drug plasma concentration-time profiles with and without coadministration of the perpetrators.

RESULTS

(Re-) Qualification framework

We developed a technical framework with an efficient automated workflow generating platform qualification reports based on qualification plans for a specific intended simulation purpose. The respective software around this framework is developed, released, and freely available on the OSP GitHub platform.[24] A detailed technical how-to of the whole workflow can be found in the OSP documentation.[25]

The OSP database for observed PK data has been released and already contains in its current version 1.1 more than 1000 concentration-time profiles from more than 300 publications.[19]

Qualifying CYP3A4-mediated DDI simulations

PBPK substance model network

All presented PBPK models represent whole-body PBPK models, which allow dynamic DDI simulations in organs expressing CYP3A4. Although the PBPK models for the competitive inhibitors itraconazole (including its three sequential metabolites hydroxy-itraconazole, keto-itraconazole, and N-desalkyl-itraconazole), fluvoxamine, and cimetidine, the mechanism-based inactivator clarithromycin, the inducer rifampicin, and the substrate alfentanil are based on published models with minor revisions,[13,26–28] the PBPK models for the mechanism-based inactivators erythromycin and verapamil, the inducer efavirenz, and the victim models midazolam, triazolam, and alprazolam have been newly developed. All models have been released along with detailed model evaluation reports with the current OSP version 9.1 and are freely accessible.[29]

Qualification summary

Using the established qualification framework, the PK-Sim® platform was qualified for the intended purpose of simulating CYP3A4-mediated DDIs. The current underlying qualification plan has been released as version 1.1[30]; the qualification report was created for the current OSP version 9.1 and has been released as the corresponding version 1.1-OSP9.1.[31]

With the application of the described network approach, simulations were compared against 135 observations of the qualification data set of published clinical DDI studies. Detailed information on the respective study designs is outlined in the released qualification report. In total, 118 of 135 (87%) simulated AUCR of the CYP3A4 interaction network were simulated within a twofold range and 99 (73%) within the Guest et al. criterion; 80 of 88 (91%) $C_{max}R$ were simulated within a twofold range and 49 (56%) within the Guest et al. criterion. The overall GMFE for AUCR and $C_{max}R$ was 1.39 and 1.37, respectively. An overview about the quality of this CYP3A4 interaction network is displayed in Figure 3, where predicted AUCR and $C_{max}R$ are compared to the corresponding observed values. More detailed subanalyses categorized by type of mechanism (competitive inhibition,

TABLE 1 Number of observations from clinical DDI studies in the qualification data set

DDI combination	No. of observations*
Cimetidine–alfentanil	1
Cimetidine–alprazolam	2
Cimetidine–midazolam	6
Cimetidine–triazolam	4
Cimetidine–verapamil	2
Clarithromycin–midazolam	10
Clarithromycin–triazolam	1
Efavirenz–alfentanil	2
Efavirenz–midazolam	11
Erythromycin–alfentanil	2
Erythromycin–alprazolam	1
Erythromycin–midazolam	9
Erythromycin–triazolam	2
Fluvoxamine–alprazolam	2
Fluvoxamine–midazolam	2
Itraconazole–alprazolam	1
Itraconazole–midazolam	12
Itraconazole–triazolam	5
Rifampicin–alfentanil	16
Rifampicin–alprazolam	3
Rifampicin–midazolam	35
Rifampicin–triazolam	1
Rifampicin–verapamil	2
Verapamil–midazolam	3

Abbreviation: DDI, drug–drug interaction.

*Observation is defined as a distinct study arm/study phase resulting in an observation of a potential DDI effect in the victim's pharmacokinetics.

mechanism-based inactivation, and induction) and by compound of the network are presented in the released qualification report. Selected exemplary victim concentration-time profile plots in the presence and absence of coadministered perpetrators are shown in Figure 4. The full set for every study is available in the released qualification report along with a table displaying all simulated and observed AUCR and $C_{max}R$.

DISCUSSION

OSP develops the formerly commercial software tools PK-Sim® and MoBi® freely available as OSP Suite under the GPLv2 License, where all source code and content are public.[15] In 2017, OSP transitioned into an open source project to further broaden and accelerate the development of systems pharmacology modeling (with a focus on PBPK) and leverage its application in drug development and pharmaceutical research.[16] To address the rising demands for rigorous PBPK platform qualifications and demonstrations of the level of confidence for intended regulatory purposes by health authorities,[8,9] OSP has recently set goals to (1) develop an open source technical qualification framework for the OSP suite and (2) provide open science, community-developed platform qualifications covering widely used PBPK applications.[16,32]

The core of the herein presented established qualification framework represents an automated workflow that generates comprehensive qualification reports based on predefined qualification plans with prespecified qualification measures and charts assessing the predictive performance to demonstrate the platform's overall capability for the particular use case. Although similarly comprehensive reports have been published in the past with other PBPK platforms, such as Simcyp™ for use cases such as "Prediction of drug-drug interactions using PBPK models of CYP450 modulators,"[10] "PBPK Modeling of Drugs Extensively Metabolized by Major Cytochrome P450 s in Children,"[11] or "PBPK models of Renally Cleared Drugs in Children"[12] or with PK-Sim® for the use cases "CYP3A4 and P-gp DDI Prediction"[13] and "Prediction of CYP1A2 and CYP2C19 Drug-Drug-Gene Interactions,"[14] all of these high-quality reports just reflect a snapshot in time being only applicable for the current version of the used PBPK platform. Contrary to this, the framework presented here focused on sustainability and was designed to easily recreate the qualification report and thus requalify the use case with every upcoming version of PK-Sim®. In addition, the framework enables agile and continuous development of qualification plans, for example, extensions by new data and new models, to update evidence on the platform's capability of the use case. Finally, the framework allows a well-defined and coherent organization of all required input files together with the outputs. This facilitates an easy orientation for users because data and files relevant to the qualification and its execution are not distributed over various locations and times (e.g., several publications).

Although each sponsor of PBPK studies is empowered to use the qualification framework along with PK-Sim® for its own use during regulatory interactions (e.g., due to data confidentiality reasons of the potential qualification data set), the OSP GitHub landscape of models and data was set up in a way that (1) embeds the presented framework for openly developed/maintained platform qualifications of common PBPK applications based on publicly available clinical data and thus (2) provides the respective qualifications along with an underlying global OSP database for observed PK data freely and fully accessible for the entire community. Thus, all individual stakeholders in the PBPK field (industry, academics, consultancy firms, software providers, and regulatory agencies) find transparent, traceable (with full version

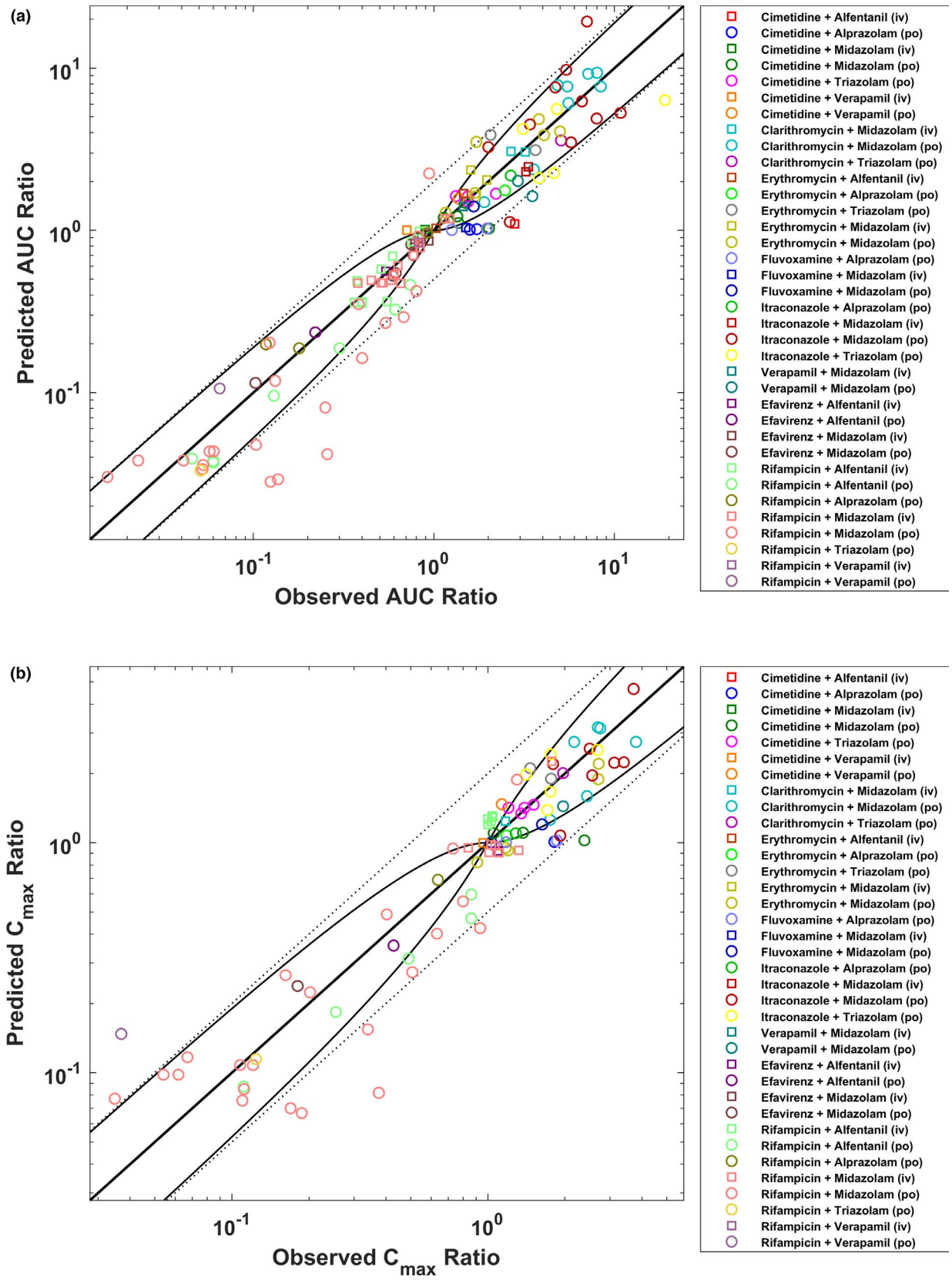

FIGURE 3 Correlation of predicted versus observed exposure ratios for all combinations of drug–drug interactions in the established cytochrome P450 3A4 network. (a) Predicted versus observed AUC ratio. (b) Predicted versus observed C_{max} ratio. Every symbol represents a data set of an interaction study. Details of the clinical trials can be found in the qualification report version.[31] The dotted line represents twofold deviation from identity. The thick solid line represents the line of identity, and the thin solid line represents the criterion developed by Guest et al.[23]AUC, area under the plasma concentration-time curve; C_{max}, peak plasma concentration

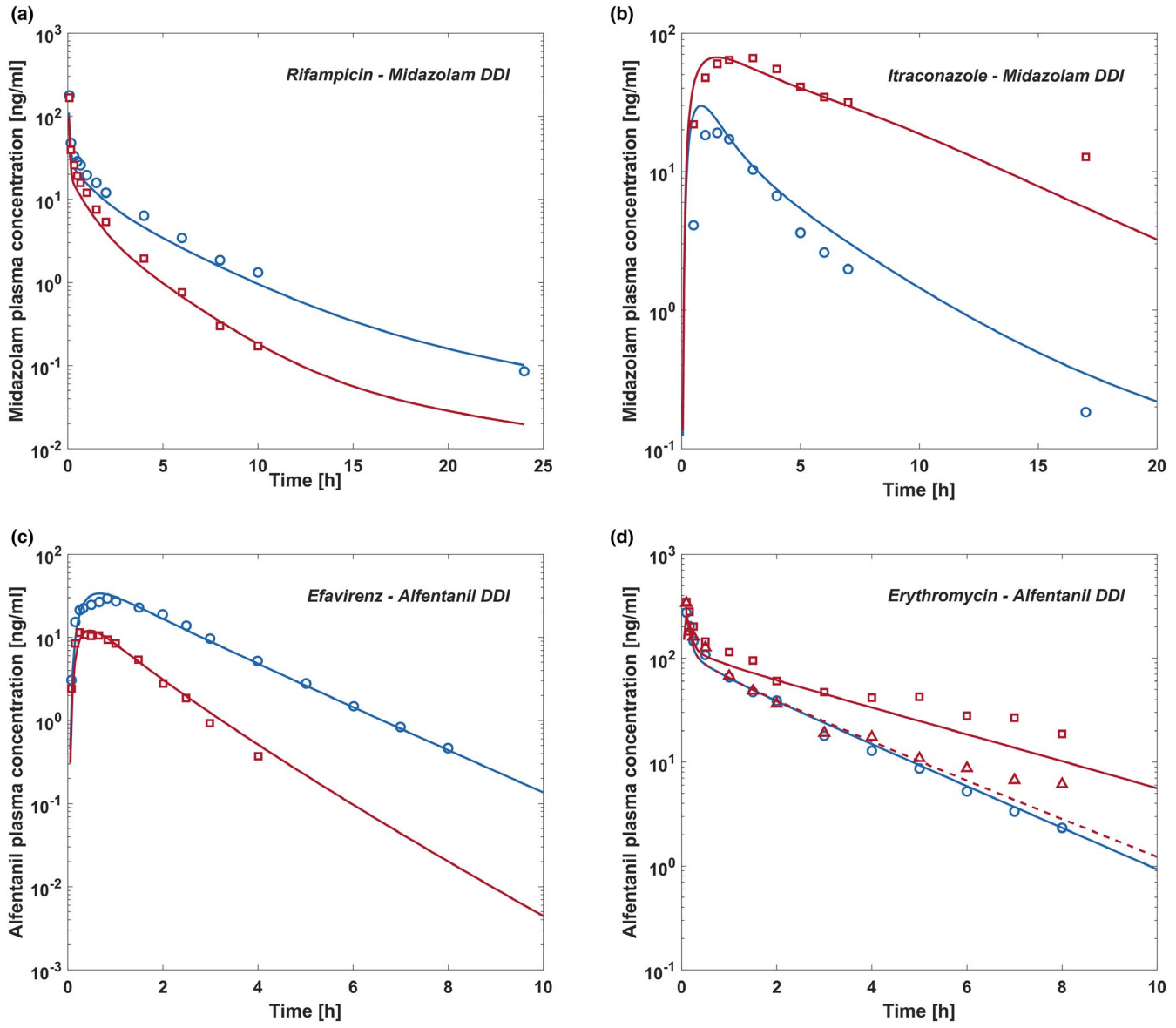

FIGURE 4 Selected exemplary concentration-time profile plots. Plasma concentration profiles against time after dose for selected victim drugs in the absence (blue) and presence (red) of selected perpetrators. Lines indicate simulations. Symbols indicate observations from clinical DDI studies. (a) Midazolam 2 mg intravenous single dose 24 h after six once-daily doses of 600 mg rifampicin[37]; (b) midazolam 7.5 mg oral single dose 1 hour after four once-daily doses of 200 mg itraconazole[43]; (c) alfentanil 43 µg/kg oral single dose 0.5 hours after 15 doses once-daily of 600 mg efavirenz dose[44]; (d) alfentanil 0.05 mg/kg intravenous single dose 1.5 hours after a first dose of erythromycin (dashed line and triangles) and 13 twice-daily doses of 500 mg erythromycin (solid line and squares).[45] DDI, drug–drug interaction

control), and anytime reproducible qualifications on the OSP GitHub platform.[15] All of this also applies for particular PBPK substance models and their model evaluation reports. It is noted that OSP supports via GitHub collaboration and discussion on features and issues.

We here present a generic technical framework for platform qualification. The approach is applicable to a broad spectrum of intended use cases requiring qualification. Whether a successful qualification is possible will depend on the specifics of the intended use, data quality and availability, and the resulting breadth and depth of simulations for qualification, model quality, and prior knowledge about the relevant processes. The assessment of the qualification status for any particular potential platform qualification will finally require an expert assessment. Likewise, it will be subject to an expert assessment whether an intended use pursued by a sponsor's PBPK study is sufficiently covered by the scope of an existing qualification, for example, with respect to properties of the drug of interest (absorption, distribution, metabolism, and excretion and formulation characteristics, administration route, etc.) and the (patient) population.

The qualification of PK-Sim® for simulating CYP3A4-mediated DDIs was developed and released as a lighthouse example and proof of concept for the qualification

framework. The predictive performance of the platform to predict CYP3A4-mediated DDIs was assessed via a network approach. Here, various perpetrator PBPK models featuring various degrees of CYP3A4 modulation and different types of mechanisms (competitive inhibition, mechanism-based inactivation, and induction) were coupled with various PBPK models of sensitive index CYP3A4 victim drugs. Simulations were compared to a comprehensive data set from published clinical DDI studies and showed reasonable accuracy and precision over the whole range (GMFE approximately 1.4 for both AUCR and C_{max}R). Notably, both simulated AUCR and C_{max}R showed good agreement with observed data irrespective of whether the victim drug was administered orally or intravenously, highlighting that the different major sites of interaction (i.e., liver and gut wall) are well reflected in the simulations.

The overall prediction accuracy in terms of CYP3A4-mediated DDIs is comparable with recent reports in literature. Marsousi et al. assessed the prediction success of DDIs involving several CYP450 modulators (including in particular the CYP3A4 modulators ketoconazole, itraconazole, clarithromycin, rifampicin) using Simcyp™ software.[10] The authors analyzed 74 CYP3A4-mediated DDI studies with a GMFE for AUCR of approximately 1.5. A recently published summary of the current drug interaction guidance from the EMA contained an example of a platform qualification with the purpose to predict time-dependent inhibition (i.e., mechanism-based inactivation) of CYP3A4, which was finally accepted by the EMA.[33] This analysis included 22 studies of the inhibitors diltiazem, erythromycin, fluoxetine, and ritonavir and showed a GMFE for AUCR of approximately 1.4.

Although our analysis demonstrates an overall successful performance of PK-Sim® to simulate CYP3A4-mediated DDIs for all perpetrator–victim combinations, a closer look reveals that the observed results of a small subset of clinical studies could not be well recovered (17 $R_{predicted/observed}$ for AUCR outside the twofold criterion). Outliers are predominantly found for midazolam in combination with rifampicin (9 of 17) and itraconazole (3 of 17). For the rifampicin–midazolam combination, 35 studies were simulated and compared to observations. Although the majority (26 of 35 studies) can be described very well, the cause of the deviation for the nine outliers is unclear. It might simply be attributed to unexplained interstudy variability in a way that similar study designs with comparable patient populations result in different AUCR; for example, Chung et al.,[34] Gorski et al.,[35] Kharasch et al.,[36] and Link et al.[37] all used once-daily doses of 600 mg rifampicin over 6 to 9 days before oral administration of midazolam. The reported AUCR varied up to approximately eightfold: Link et al. reported an AUCR of 0.015, Kharasch et al. reported 0.052, Gorski et al. reported 0.103 and Chung et al. reported 0.124. Obviously, not all of these point estimates can be captured by the model as similar study set-ups obviously result in similar simulated point estimates of AUCR. For the itraconazole–midazolam combination with three outliers, 12 scenarios were simulated and compared with observations. Three of these scenarios are outside of a twofold range. In the study by Prueksaritanont et al.,[38] midazolam micro-doses were used in a cocktail of substrates with potential PK interferences. In a study by Backman et al.,[39] a large time window of 4 days between perpetrator and victim dosing was used, and the PBPK model underpredicted the inhibitory effect. Although the itraconazole PBPK model includes three inhibitory sequential metabolites resulting in a prolonged inhibitory effect, still the observed prolonged inhibition cannot be fully explained. In other PBPK studies using different PBPK platforms, for example, Prieto García et al.[40] and Chen et al.,[41] a general trend of the applied itraconazole PBPK models to underpredict this DDI became obvious as well. There might be a general knowledge gap in understanding this prolonged inhibitory effect of itraconazole mechanistically. Another prominent outlier represents the reported study on alfentanil kinetics under the coadministration of cimetidine by Kienlen et al.[42] Comparing the observed data of alfentanil alone and alfentanil under coadministration suggests an exposure increase by almost threefold, whereas PBPK simulations yield an increase of only 1.1-fold. A closer look at the clinical trial reveals that the design was not a cross-over but a parallel group design, thus, the data from the two groups may not really be comparable given the low number of subjects and considering alfentanil PK variability. Actually, the model-based obtained low increase of alfentanil exposure is even more plausible in the overall picture of observed effects in cimetidine clinical DDI studies.

A limitation of the depicted qualification for simulations of CYP3A4-mediated DDIs is that population predictions are not included in the qualification process, and thus currently no conclusions with regard to capturing population variability can be inferred as only typical and/or mean values are compared. It is planned that the qualification framework will be extended to cover population simulations for such use cases as well in future. However, it must be noted that the computational burden would highly increase. Although the current execution of the workflow to generate the herein presented qualification report on CYP3A4-mediated DDIs takes about a few hours on a single computer, a similar set-up with population simulations for each study probably would require cluster computing and would at least complicate a reproducibility by any user at any time.

In summary, our qualification package demonstrates that sponsors can use PK-Sim®—more specifically PK-Sim® version 9.1—to successfully evaluate CYP3A4-mediated DDIs in clinically untested scenarios for new investigational drugs either as enzyme substrates or perpetrators within the presented compound network. The presented qualification package

currently consists of data for a limited number of compounds. With the future addition of further drugs and drug combinations with even more diverse properties (i.e., different general PK properties, different types of interactions, different contributions of sites of interaction, etc.) to the DDI network, the generic applicability and confidence in the predictive power will also grow further. Finally, sponsors will always need to address the specific verification/validation of the PBPK model of a new investigational drug following the general recommendations in current health authority guidances.[7,8]

CONCLUSION

An agile and sustainable technical framework for automatic PBPK platform (re-)qualification of PK-Sim® has been developed and embedded in the open source and open science GitHub landscape of OSP. The presented approach enables an efficient assessment of the current predictive performance of the platform for all kinds of intended purposes (e.g., DDI applications, pediatric translations) and provides full transparency and traceability for all stakeholders, including regulatory agencies.

To demonstrate the power and versatility of the qualification framework, the qualification of PK-Sim® for simulating CYP3A4-mediated DDIs was successfully developed and released as a showcase example for future platform qualifications of various intended purposes.

CONFLICTS OF INTEREST

All authors use Open Systems Pharmacology software, tools, or models in their professional roles. S.F. is a member of the Open Systems Pharmacology Sounding Board. J.S., T.L., J.L., and R.B. are members of the Open Systems Pharmacology Management Team.

AUTHOR CONTRIBUTIONS

S.F. wrote the manuscript. S.F., J.S., I.I., T.L., J.L., and R.B. designed research. S.F., J.S., T.W., and A.D. performed the research. S.F., J.S., T.W., and A.D. analyzed the data.

ORCID

André Dallmann https://orcid.org/0000-0003-1108-5719
Jörg Lippert https://orcid.org/0000-0002-0683-2874

REFERENCES

1. Grimstein M, Yang Y, Zhang X, et al. Physiologically based pharmacokinetic modeling in regulatory science: an update from the U.S. Food and Drug Administration's Office of Clinical Pharmacology. *J Pharm Sci*. 2019;108(1):21-25.
2. Zhang X, Yang Y, Grimstein M, et al. Application of PBPK modeling and simulation for regulatory decision making and its impact on US prescribing information: an update on the 2018–2019 submissions to the US FDA's office of clinical pharmacology. *J Clin Pharmacol*. 2020;60(suppl 1):S160-S178.
3. Luzon E, Blake K, Cole S, Nordmark A, Versantvoort C, Berglund EG. Physiologically based pharmacokinetic modeling in regulatory decision-making at the European Medicines Agency. *Clin Pharmacol Ther*. 2017;102(1):98-105.
4. Workgroup EM, Marshall SF, Burghaus R, et al. Good practices in model-informed drug discovery and development: practice, application, and documentation. *CPT Pharmacomet Syst Pharmacol*. 2016;5(3):93-122.
5. Kuemmel C, Yang Y, Zhang X, et al. Consideration of a credibility assessment framework in model-informed drug development: potential application to physiologically-based pharmacokinetic modeling and simulation. *CPT Pharmacomet Syst Pharmacol*. 2020;9(1):21-28.
6. European Medicines Agency. Guideline on the investigation of drug interactions. https://www.ema.europa.eu/en/investigation-drug-interactions. Accessed December 18, 2020.
7. US Food and Drug Administration. In Vitro Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions Guidance for Industry. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/vitro-drug-interaction-studies-cytochrome-p450-enzyme-and-transporter-mediated-drug-interactions. Accessed December 18, 2020.
8. European Medicines Agency. Reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation. https://www.ema.europa.eu/en/reporting-physiologically-based-pharmacokinetic-pbpk-modelling-simulation. Accessed December 18, 2020.
9. US Food and Drug Administration. Physiologically Based Pharmacokinetic Analyses — Format and Content Guidance for Industry. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/physiologically-based-pharmacokinetic-analyses-format-and-content-guidance-industry. Accessed December 18, 2020.
10. Marsousi N, Desmeules JA, Rudaz S, Daali Y. Prediction of drug-drug interactions using physiologically-based pharmacokinetic models of CYP450 modulators included in Simcyp software. *Biopharm Drug Dispos*. 2018;39(1):3-17.
11. Zhou W, Johnson TN, Bui KH, et al. Predictive performance of physiologically based pharmacokinetic (PBPK) modeling of drugs extensively metabolized by major cytochrome P450s in children. *Clin Pharmacol Ther*. 2018;104(1):188-200.
12. Zhou W, Johnson TN, Xu H, et al. Predictive performance of physiologically based pharmacokinetic and population pharmacokinetic modeling of renally cleared drugs in children. *CPT Pharmacomet Syst Pharmacol*. 2016;5(9):475-483.
13. Hanke N, Frechen S, Moj D, et al. PBPK models for CYP3A4 and P-gp DDI prediction: a modeling network of rifampicin, itraconazole, clarithromycin, midazolam, alfentanil, and digoxin. *CPT Pharmacomet Syst Pharmacol*. 2018;7(10):647-659.
14. Kanacher T, Lindauer A, Mezzalana E, et al. A physiologically-based pharmacokinetic (PBPK) model network for the prediction of CYP1A2 and CYP2C19 drug-drug-gene interactions with fluvoxamine, omeprazole, S-mephenytoin, moclobemide, tizanidine, mexiletine, ethinylestradiol, and caffeine. *Pharmaceutics*. 2020;12(12):1191.
15. Open Systems Pharmacology. OSP platform on GitHub. https://github.com/Open-Systems-Pharmacology. Accessed December 18, 2020.
16. Lippert J, Burghaus R, Edginton A, et al. Open systems pharmacology community-an open access, open source, open science

approach to modeling and simulation in pharmaceutical sciences. *CPT Pharmacomet Syst Pharmacol*. 2019;8(12):878-882.
17. Ecma International. Standard ECMA-404: The JSON Data Interchange Syntax. http://www.ecma-international.org/publications/files/ECMA-ST/ECMA-404.pdf. Accessed December 18, 2020.
18. GitHub. GitHub Flavored Markdown Spec. https://github.github.com/gfm/. Accessed December 18, 2020.
19. Open Systems Pharmacology. OSP Database for observed data repository. https://github.com/Open-Systems-Pharmacology/Database-for-observed-data. Accessed December 18, 2020.
20. Open Systems Pharmacology. OSP PBPK Model Library repository. https://github.com/Open-Systems-Pharmacology/OSP-PBPK-Model-Library. Accessed December 18, 2020.
21. Open Systems Pharmacology. OSP Qualification Reports repository. https://github.com/Open-Systems-Pharmacology/OSP-Qualification-Reports. Accessed December 18, 2020.
22. University of Washington. DIDB – The Drug Interaction Database. https://www.druginteractionsolutions.org/solutions/drug-interaction-database/. Accessed December 18, 2020.
23. Guest EJ, Aarons L, Houston JB, Rostami-Hodjegan A, Galetin A. Critique of the two-fold measure of prediction success for ratios: application for the assessment of drug-drug interactions. *Drug Metab Disposit*. 2011;39(2):170-173.
24. Open Systems Pharmacology. Release of OSP Qualification Framework. https://github.com/Open-Systems-Pharmacology/QualificationPlan/releases. Accessed December 18, 2020.
25. Open Systems Pharmacology. How-to documentation of OSP Qualification Framework. https://docs.open-systems-pharmacology.org/shared-tools-and-example-workflows/qualification. Accessed December 18, 2020.
26. Britz H, Hanke N, Volz AK, et al. Physiologically-based pharmacokinetic models for CYP1A2 drug-drug interaction prediction: a modeling network of fluvoxamine, theophylline. Caffeine, rifampicin, and midazolam. *CPT Pharmacomet Syst Pharmacol*. 2019;8(5):296-307.
27. Turk D, Hanke N, Wolf S, et al. Physiologically based pharmacokinetic models for prediction of complex CYP2C8 and OATP1B1 (SLCO1B1) drug-drug-gene interactions: a modeling network of gemfibrozil, repaglinide, pioglitazone, rifampicin, clarithromycin and itraconazole. *Clin Pharmacokinet*. 2019;58(12):1595-1607.
28. Hanke N, Turk D, Selzer D, et al. A comprehensive whole-body physiologically based pharmacokinetic drug-drug-gene interaction model of metformin and cimetidine in healthy adults and renally impaired individuals. *Clin Pharmacokinet*. 2020;59(11):1419-1431.
29. Open Systems Pharmacology. Release 9.1.1 of OSP PBPK Model Library. https://github.com/Open-Systems-Pharmacology/OSP-PBPK-Model-Library/releases/tag/v9.1.1. Accessed December 18, 2020.
30. Open Systems Pharmacology. Release 1.1 of Qualification Plan for CYP3A4 DDI. https://github.com/Open-Systems-Pharmacology/Qualification-DDI-CYP3A4/releases/tag/v1.1. Accessed December 18, 2020.
31. Open Systems Pharmacology. Release 1.1-OSP9.1 of Qualification Report for CYP3A4 DDI. https://github.com/Open-Systems-Pharmacology/OSP-Qualification-Reports/tree/v9.1.1/DDI_Qualification_CYP3A4. Accessed December 18, 2020.
32. Ince I, Solodenko J, Frechen S, et al. Predictive pediatric modeling and simulation using ontogeny information. *J Clin Pharmacol*. 2019;59(Suppl 1):S95-S103.
33. Cole S, Kerwash E, Andersson A. A summary of the current drug interaction guidance from the European Medicines Agency and considerations of future updates. *Drug Metab Pharmacokinet*. 2020;35(1):2-11.
34. Chung E, Nafziger AN, Kazierad DJ, Bertino JS Jr. Comparison of midazolam and simvastatin as cytochrome P450 3A probes. *Clin Pharmacol Ther*. 2006;79(4):350-361.
35. Gorski JC, Vannaprasaht S, Hamman MA, et al. The effect of age, sex, and rifampin administration on intestinal and hepatic cytochrome P450 3A activity. *Clin Pharmacol Ther*. 2003;74(3):275-287.
36. Kharasch ED, Francis A, London A, Frey K, Kim T, Blood J. Sensitivity of intravenous and oral alfentanil and pupillary miosis as minimal and noninvasive probes for hepatic and first-pass CYP3A induction. *Clin Pharmacol Ther*. 2011;90(1):100-108.
37. Link B, Haschke M, Grignaschi N, et al. Pharmacokinetics of intravenous and oral midazolam in plasma and saliva in humans: usefulness of saliva as matrix for CYP3A phenotyping. *Br J Clin Pharmacol*. 2008;66(4):473-484.
38. Prueksaritanont T, Tatosian DA, Chu X, et al. Validation of a microdose probe drug cocktail for clinical drug interaction assessments for drug transporters and CYP3A. *Clin Pharmacol Ther*. 2017;101(4):519-530.
39. Backman JT, Kivisto KT, Olkkola KT, Neuvonen PJ. The area under the plasma concentration-time curve for oral midazolam is 400-fold larger during treatment with itraconazole than with rifampicin. *Eur J Clin Pharmacol*. 1998;54(1):53-58.
40. PrietoGarcía L, Janzen D, Kanebratt KP, Ericsson H, Lennernas H, Lundahl A. Physiologically based pharmacokinetic model of itraconazole and two of its metabolites to improve the predictions and the mechanistic understanding of CYP3A4 drug-drug interactions. *Drug Metab Disposit*. 2018;46(10):1420-1433.
41. Chen Y, Cabalu TD, Callegari E, et al. Recommendations for the design of clinical drug-drug interaction studies with itraconazole using a mechanistic physiologically-based pharmacokinetic model. *CPT Pharmacomet Syst Pharmacol*. 2019;8(9):685-695.
42. Kienlen J, Levron J-C, Aubas S, Roustan J-P, du Cailar J. Pharmacokinetics of alfentanil in patients treated with either cimetidine or ranitidine. *Drug Investigation*. 1993;6(5):257-262.
43. Olkkola KT, Backman JT, Neuvonen PJ. Midazolam should be avoided in patients receiving the systemic antimycotics ketoconazole or itraconazole. *Clin Pharmacol Ther*. 1994;55(5):481-485.
44. Kharasch ED, Whittington D, Ensign D, et al. Mechanism of efavirenz influence on methadone pharmacokinetics and pharmacodynamics. *Clin Pharmacol Ther*. 2012;91(4):673-684.
45. Bartkowski RR, Goldberg ME, Larijani GE, Boerner T. Inhibition of alfentanil metabolism by erythromycin. *Clin Pharmacol Ther*. 1989;46(1):99-102.

How to cite this article: Frechen S, Solodenko J, Wendl T, et al. A generic framework for the physiologically-based pharmacokinetic platform qualification of PK-Sim and its application to predicting cytochrome P450 3A4–mediated drug–drug interactions. *CPT Pharmacometrics Syst. Pharmacol.* 2021;10:633–644. https://doi.org/10.1002/psp4.12636