Physiologically Based Pharmacokinetic Modeling in Regulatory Decision-Making at the European Medicines Agency

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Physiologically based pharmacokinetic (PBPK) modeling is a valuable tool in drug development and regulatory assessment, as it offers the opportunity to simulate the pharmacokinetics of a compound, with a mechanistic understanding, in a variety of populations and situations. This work reviews the use and impact of such modeling in selected regulatory procedures submitted to the European Medicines Agency (EMA) before the end of 2015, together with its subsequent reflection in public documents relating to the assessment of these procedures. It is apparent that the reference to PBPK modeling in regulatory public documents underrepresents its use. A positive trend over time of the number of PBPK models submitted is shown, and in a number of cases the results of these may impact the decision-making process or lead to recommendations in the product labeling. These results confirm the need for regulatory guidance in this field, which is currently under development by the EMA.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ PBPK is a cutting-edge technology that is increasingly being applied to drug development to address various aspects related to clinical pharmacology. Previous works by the FDA acknowledge its use in regulatory submissions in the US, but so far there is no analysis of the European perspective.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ This study evaluated trends in PBPK modeling in regulatory submissions to the EMA and compared them to their reflection in public documents including drug product labels.

WHAT THIS STUDY ADDS TO OUR KNOWLEDGE

☑ This is the first work presenting the situation in the European Union and confirms what was detected by the FDA is a global trend.

HOW THIS MIGHT CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE

☑ This article, together with EU guidance currently under development, should serve to consolidate the role of PBPK in drug development and regulatory decision-making.

An entirely new, or an update to an existing, marketing authorization (MA) for a medicinal product in the European Union (EU) as a whole (i.e., a central authorization) will only be granted if the benefit–risk is considered positive for the target population in the specified clinical indication(s).[1] Such a decision by the European Commission will follow the recommendations made by the European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) based on its scientific evaluation of the clinical development program and, in particular, on the populations and conditions studied up to that point in time. Drug development is a fast-evolving field, and new approaches that involve computerized modeling and simulation are increasingly being seen in the context of regulatory submissions. These include the use of physiologically based pharmacokinetic (PBPK) models, which simulate the concentration of a drug over time in tissue(s) and plasma by taking into account the rate of its absorption into the body, distribution in tissues, metabolism, and excretion (ADME) on the basis of interplay among critical physiological, physicochemical, and biochemical determinants.

The information obtained through these models is aimed at providing detailed insight into different aspects of the pharmacokinetics (PK) of a drug, informing aspects of study design (e.g., dose selection, treatment duration, or sampling strategy) or evaluating the need to conduct studies (e.g., on *in vivo* drug–drug interactions (DDI)). It is anticipated that PBPK modeling will be increasingly useful to address specific scenarios such as DDI, or certain populations where clinical studies may be particularly challenging such as pharmacogenetic subgroups, organ-impaired patients, or pediatric subjects. The results of the models are presently reflected in some cases in the product label, termed the Summary of Product Characteristics (SmPC) in the

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Table 1 Summary of the centralized procedures included in the present analysis ($n = 97$)

	Model submitted ($n = 67$)	Model not submitted ($n = 30$)
Finalized procedures[a] ($n = 79$)	52	27
Ongoing procedures ($n = 18$)	15	3

[a]That is a public document is available.

EU. PBPK modeling, therefore, potentially informs prescribers and patients on the use of a drug while optimizing dedicated clinical studies. PBPK modeling is, consequently, receiving increasing attention from both pharmaceutical companies and regulators.

From a regulatory perspective, various analyses on the use of PBPK modeling in regulatory submissions have been published in recent years.[2,3] Also, in 2014 workshops on PBPK have taken place both in the US[4] and UK[5] to share the views of industry, regulators, and academia on the most important issues. At the EU level, several existing guidelines[6–8] refer to PBPK models and a guideline on the qualification and reporting of PBPK modeling and simulation[9] was released for public consultation by the EMA in July 2016 following the earlier publication of a concept paper.[10]

The present retrospective analysis was undertaken to give detailed insight into the use of these models in regulatory submissions to the EMA relating to centralized authorizations. Specifically, this work aims to evaluate trends in the frequency of submission of PBPK models in regulatory procedures to EMA up to the end of 2015, their use in supporting decision-making by the CHMP, and their reflection in SmPCs and in publicly available assessment reports.

RESULTS

A total of 117 procedures that included reference to a PBPK model were identified as described in the Methods section below. Four of these were in the context of periodic safety update reports and a further 16 related to nonclinical development or pediatric applications. These 20 procedures are considered outside the scope of the present review.

In 67 of the remaining 97 procedures, one or more PBPK models were submitted by a pharmaceutical company. In the other 30, the reference to a PBPK model was in the form of a request or a less binding suggestion from the regulators, but a model had either not been subsequently submitted as part of the procedure or was planned as a postauthorization measure (**Table 1**).

Reference to PBPK models in public documents relating to centralized procedures

Seventy-nine of the 97 procedures have been finalized (**Table 2**) and consequently a document detailing the scientific discussion and its outcome has been made publicly available at the EMA website. For 57 procedures relating to new MAs, a detailed European Public Assessment Report (EPAR) or a Withdrawal Assessment Report (WAR) has been published and 25 of these contain an explicit reference to a PBPK model. For 22 of the procedures that relate to a change in an existing MA, shorter summary reports have been published and only three of these have an explicit reference to a PBPK model. Therefore, for the majority of the finalized procedures (51), reference to a PBPK model does not appear explicitly in an assessment report in the public domain.

Table 2 Summary of the reference to PBPK in public assessment reports (EPARs, WARs, VARs) from finalized procedures included in the present analysis ($n = 79$)

	Explicit reference to PBPK ($n = 28$)	Absence of explicit reference to PBPK ($n = 51$)
MAA ($n = 57$)	25	32
Variation on an existing MA ($n = 22$)[a]	3	19

EPAR, European Public Assessment Report; MA, Marketing Authorization; MAA, Marketing Authorization Application; VAR, Variation Assessment Report; WAR, Withdrawal Assessment Report.
[a]VARs are usually short in length and therefore do not contain as much information as EPARs.

Three procedures have resulted in an explicit reference to PBPK in a published SmPC, namely eliglustat (Cerdelga), macitentan (Opsumit), and regorafenib (Stivarga). In at least another 11, the content of the SmPC statements is considered by the authors (taking into account the available information on the evaluation procedure) to be directly based on the results of a PBPK model.

Table 3 provides an overview of references to PBPK in public documents for the procedures included in this analysis, and **Table 4** details some examples of these references.

Table 3 Explicit reference to PBPK in product EPAR/WAR

Procedure start	INN (trade name)
2011	elvitegravir/Cobicistat/Emtricitabine/Tenofovir Disoproxil Fumarate (Stribild)[a], perampanel (Fycompa), ridaforolimus (Jenzyl)[b], ruxolitinib (Jakavi)
2012	canagliflozin hemihydrate (Invokana), cobicistat (Tybost)[a], dimethyl fumarate (Tecfidera), dolutegravir (Tivicay)[a], lomitapide (Lojuxta), lurasidone (Latuda), macitentan (Opsumit)[c], ponatinib (iclusig)[a], regorafenib (Stivarga)[c]
2013	darunavir/cobicistat (Rezolsta)[a], eliglustat (Cerdelga)[c], eribulin (Halaven)[d], faldaprevir (Faldaprevir Boehringer Ingelheim)[b], ibrutinib (Imbruvica), naloxegol (Moventig), ponatinib (Iclusig)[d], simeprevir (Olysio), vorapaxar (Zontivity)
2014	blinatumomab (Blincyto), cobimetinib hemifumarate (Cotellic), edoxaban (Lixiana), lenvatinib (Lenvima), lomitapide (Lojuxta)[d], panobinostat (Farydak)
2015	EPAR, European Public Assessment Report; INN, International Nonproprietary Name; PBPK, Physiologically Based Pharmacokinetic; WAR, Withdrawal Assessment Report

[a]PBPK model not submitted but planned as per the Risk Management Plan; [b]Withdrawal Assessment Report; [c]Reference to PBPK also on the Summary of Product Characteristics; [d]Postauthorization procedures.

Table 4 Examples of references to PBPK made in EU SmPCs and/or EPARs

INN (trade name)	Year of application	Selection of statements related to PBPK in the EPAR (taken verbatim)
cobimetinib hemifumarate (Cotellic)	2014	Based on the results from population PK analysis, exposure-response analysis for efficacy and safety, and physiologically based PK simulations, cobimetinib may be administered with mild CYP3A inhibitors without any dose adjustment.
eliglustat (Cerdelga)	2013	The initial exclusion of PM and URM from the proposed indication was also questioned by the CHMP. During the procedure physiologically based pharmacokinetic (PBPK) simulations were conducted by the applicant, the outcome of these simulations lead to a recommendation for dosing in PM patients [. . .] Additional simulations using Physiologically Based Pharmacokinetic Modeling with SimCYP were carried out to cover additional interactions. [. . .] Based upon these data, Cerdelga is contraindicated in patients taking a strong or moderate CYP2D6 inhibitor concomitantly with a strong or moderate CYP3A inhibitor, which is agreed.
		SmPC wording: The recommended dosing regimens (see Discussion) are based on [. . .] physiologically based PK data for PMs
eribulin (Halaven)	2013	The MAH therefore made simulations using a physiologically based pharmacokinetic (PBPK) model, in order to predict the effect of eribulin on the sensitive CYP3A4 substrate midazolam. [. . .] The PBPK model prediction is considered sufficient to be used as a basis to update the SmPC recommendation, and a clinical interaction study with midazolam will not be considered necessary.
ibrutinib (Imbruvica)	2013	Due to degradation of ibrutinib *in vitro*, the submitted *in vitro* and PBPK model data cannot be considered sufficient to exclude a risk for clinically relevant CYP3A4 intestinal inhibition by ibrutinib. A PBPK model was built based on the available preclinical and clinical information and the aim of the model was to investigate the drug-drug interaction potential of CYP3A4 inhibitors/inducers on ibrutinib PK.
lomitapide (Lojuxta)	2012	Although the available data allow for understanding of the main pharmacokinetic characteristics, there are a number of issues that require further investigations. Therefore, the CHMP considered the following measures necessary to address the clinical pharmacology of lomitapide: [...] - Validation of the mechanistic (PBPK) model to predict lomitapide interactions with CYP3A4 inhibitors using the data from the above studies and the interaction with ketoconazole. - Depending on the results of the clinical studies and the reliability of the mechanistic (PBPK) model of lomitapide, further clinical drug-drug interaction studies for commonly coadministered drugs (potentially including coadministration of two weak CYP3A4 inhibitors) or further modeling work may be needed.
lurasidone (Latuda)	2012	The applicant was requested to use existing pharmacokinetic data to estimate product's bioavailability. In their response the applicant submitted an estimate based on mass-balance data and PBPK modeling. [. . .] Based on the provided results the committee considered that although the PBPK modeling could be improved *in vivo* data provided enough information for dosing recommendations.
macitentan (Opsumit)	2012	In post-hoc analyses, the predicted increase was approximately 3.0-fold in the presence of ketoconazole 200 mg twice daily, using physiologically based pharmacokinetic (PBPK) modeling. In conclusion, a potential increase in macitentan exposure when using strong CYP3A4 inhibitors could be of clinical relevance. In view of the non-clinical and clinical data, it is therefore acceptable to reflect this information in the SmPC in the Discussion.
		SmPC wording: In the presence of ketoconazole 400 mg once daily, a strong CYP3A4 inhibitor, exposure to macitentan increased approximately 2-fold. The predicted increase was approximately 3-fold in the presence of ketoconazole 200 mg twice daily using physiologically based pharmacokinetic (PBPK) modeling. The uncertainties of such modeling should be considered. Exposure to the active metabolite of macitentan was reduced by 26%. Caution should be exercised when macitentan is administered concomitantly with strong CYP3A4 inhibitors.

Table 4 Continued on next page

Table 4 Continued

INN (trade name)	Year of application	Selection of statements related to PBPK in the EPAR (taken verbatim)
perampanel (Fycompa)	2011	The CYP3A4 inhibitor ketoconazole increased the AUC(0-inf) of perampanel by 20% (Study 005). From PBPK simulations it was shown that a higher extent of interaction could result from co-administration of inhibitors with longer half-lives (e.g., itraconazole) or for longer than 10 days, because of the long half-life of perampanel. Appropriate SmPC (Discussion) wording highlights these conclusions.
		SmPC wording: Larger effects cannot be excluded when perampanel is combined with a CYP3A inhibitor with longer half-life than ketoconazole or when the inhibitor is given for a longer treatment duration.
ponatinib (Iclusig)	2012	The Applicant has therefore included "Treatment of patients receiving concomitantly CYP3A4 inhibitors" as important missing information in the RMP, pending results of PBPK modeling of the interaction of ponatinib with twice-daily ketoconazole dosing. Results of this modeling experiment are expected to be available by the end of 2013.
ponatinib (Iclusig)	2013	Update of Discussion section of the SmPC and the Package Leaflet with regard to interaction with CYP3A4 inhibitors further to the results physiologically based pharmacokinetic modeling to determine the impact of different ketoconazole dosing regimens, conducted as a postauthorization measure of the RMP.
regorafenib (Stivarga)	2012	Available clinical data and physiology based pharmacokinetic modeling indicate similar steady state exposure of regorafenib and its metabolites M 2 and M 5 in patients with mild and moderate renal impairment compared to patients with normal renal function. The pharmacokinetics of regorafenib has not been studied in patients with severe renal impairment or end stage renal disease. However, physiology based pharmacokinetic modeling does not predict any relevant change in exposure in these patients.
		SmPC wording: Renal impairment: Available clinical data and physiology-based pharmacokinetic modeling indicate similar steady-state exposure of regorafenib and its metabolites M-2 and M-5 in patients with mild and moderate renal impairment compared to patients with normal renal function. The pharmacokinetics of regorafenib has not been studied in patients with severe renal impairment or end-stage renal disease. However, physiology-based pharmacokinetic modeling does not predict any relevant change in exposure in these patients.
ruxolitinib (Jakavi)	2011	Potent CYP3A4 inhibitors such as ketoconazole give rise to an approximate doubling of ruxolitinib exposure. CYP2C9 inhibitors are also likely to give rise to increased exposure. A PBPK simulation on the exposure after treatment with fluconazole, which is a mild to moderate dual CYP3A4 and 2C9 inhibitor, predicted a 3-fold increase in ruxolitinib. Thus, a dose reduction of approximately 50% is appropriate.
vorapaxar (Zontivity)	2013	The ketoconazole dose however is not considered to represent the worst case as vorapaxar has a long half-life, therefore PBPK modeling is suggested to model the effect of ketoconazole 200 mg bid.

Note: In cases where the year of application is 2015, the procedure was still ongoing by the data lock point (31 December 2015), and therefore EPARs on these procedures were not yet available.
CHMP, Committee for Medicinal Products for Human Use; EPAR, European Public Assessment Report; INN, International Nonproprietary Name; MAH, Marketing Authorization Holder; PM, Poor Metabolizers; PBPK, Physiologically Based Pharmacokinetic, SmPC Summary of Product Characteristics; URM, Ultra Rapid Metabolizers.

PBPK models submitted: numbers, triggers, and purposes

PBPK model(s) were submitted in a total of 67 procedures involving 55 products. More than one model might have been submitted as part of a certain procedure. All of these were developed using commercially available specialized PBPK platforms. **Figure 1** shows that the frequency of submission of PBPK models has increased markedly in recent years.

In 36 procedures the PBPK model(s) were included in the first instance as part of the initial documentation submitted by a pharmaceutical company (**Figure 2**). For a further 25, the model was submitted during a procedure in order to address an issue (e.g., a need for further information on DDI) identified by the regulators. For five of these, the PBPK model was submitted following a request or suggestion by the regulator, while in 20 cases it was on the initiative of the pharmaceutical company. For the remaining six a model was submitted as a postauthorization measure in the context of risk management.

Table 5 details the intended purpose of the PBPK models submitted. A specific model might have been submitted with more than one purpose. In 60 cases, the model related to DDI at an

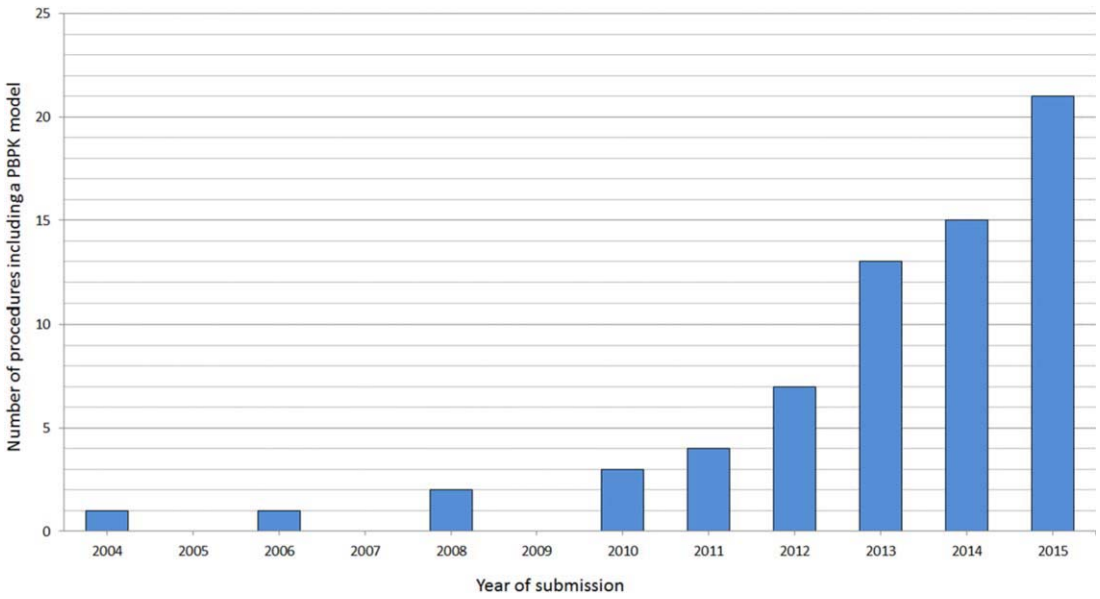

Figure 1 Submissions of procedures including PBPK models to the European Medicines Agency over time. [Color figure can be viewed at wileyonlinelibrary.com]

enzyme (mainly CYP3A) level, where the drug is being analyzed as a victim or as a perpetrator (either as inhibitor or as inducer). In 11 cases the information obtained from the models were used to investigate DDI involving a variety of transporters, including P-glycoprotein (Pgp), breast cancer resistance protein (BCRP), and transporters of the organic anion-transporting polypeptide (OATP) and organic cation transporter (OCT) families. In another five cases PBPK modeling analyzed other interactions (e.g., with food, with drugs that alter gastric pH, or with cigarette smoke as an inducer of CYP1A1). Another important use of PBPK models was to describe general PK parameters of a drug, e.g., absorption, bioavailability, or clearance (eight cases) or possible differences in specific population subgroups (20 cases) such as organ-impaired subjects. Finally, there are examples of models that compare different strengths and formulations. It should be noted that not all the models listed in **Table 5** have had the same impact on the regulatory decision-making.

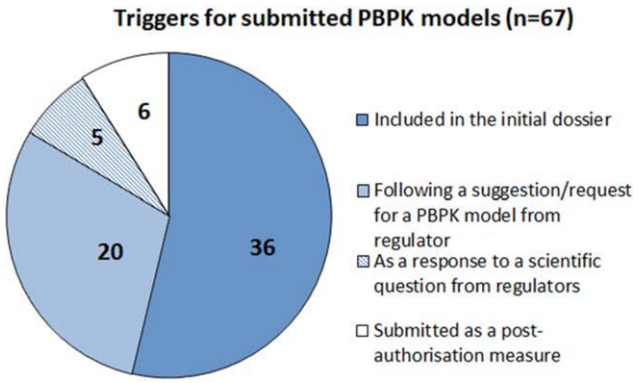

Figure 2 Triggers for submitted PBPK models. [Color figure can be viewed at wileyonlinelibrary.com]

DISCUSSION

Increasing use of PBPK models but limited reflection in public assessment documents

PBPK modeling is an approach with broad potential. A variety of different scenarios can be simulated, and models can be refined during the drug development cycle as new clinical data are available. The EPARs for eliglustat or regorafenib exemplify how PBPK modeling can add information or support nonclinical or clinical data in order to explore possible PK differences across carriers of a range of genetic polymorphisms or concomitant medical conditions. The results of the present analysis support that PBPK modeling is receiving increasing attention from pharmaceutical companies and EU regulators during the development and centralized assessment of medicinal products. This is in line with the findings of previous analyses focused on submissions to the US Food and Drug Administration (FDA)[3,11] and with the experience of the coauthors, who have also seen a number of PBPK models in their assessment of noncentralized procedures submitted to National Competent Authorities in EU Member States. In addition, our findings support that interest in the development of PBPK models comes not only from companies but that regulators also request these models *de novo* during the evaluation of procedures.

Reference to PBPK in public documents varies between procedures. In many examples there are objective statements regarding the use or results of a model, but in some cases the detailed positions of regulators regarding a specific model are also reflected (e.g., ibrutinib (Imbruvica)) or encouragement to submit a model for vorapaxar (Zontivity) (**Table 4**). Sometimes the use of PBPK modeling to obtain certain data is also explicitly mentioned in the SmPC (e.g., macitentan or eliglustat). The level of detail of these references is also variable, from a mention that a PBPK model has been submitted or will be submitted (e.g., ponatinib

Table 5 Purpose of PBPK models submitted to EMA in finalized and ongoing procedures up to 31 December 2015[a]

Main categories	Specific purpose		Number
Intrinsic factors	General description of PK parameters		8
	Organ impairment (hepatic and/or renal)		8
	Effect of polymorphisms		7
	Effect of ethnicity		4
	Differences across disease states (hepatitis C virus infected patients)		2
	Differences across age groups		1
Extrinsic factors (interactions)	DDI involving enzymes	drug as victim	37
		drug as perpetrator	23
	DDI involving transporters	drug as victim	3
		drug as perpetrator	8
	DDI based on gastric pH changes		2
	Food-drug interactions		2
	Interaction with cigarette smoke		1
Drug parameters	Comparison between strengths/formulations		8

DDI, drug-drug interactions; EMA, European Medicines Agency; PBPK, Physiologically Based Pharmacokinetic; PK, pharmacokinetics.
[a]Note: A given model may have been submitted with more than one intended purpose and/or more than one model may have been submitted within the same procedure.

(Iclusig)), to a wider description of the model (e.g., eribulin (Halaven)). On the other extreme, the use of PBPK models is often not explicit in the public domain, particularly in the case of postauthorization procedures. However, the use of PBPK models to inform the SmPCs is not as infrequent as may be deduced just from direct reading of the SmPC. Sometimes only combined reading of the SmPC and the EPAR allows an understanding that certain information in the SmPC might be based on a PBPK model (e.g., perampanel (Fycompa)). Also, in a number of cases statements in the SmPCs are based on PBPK models, but these are not reflected in either the EPAR or in the SmPC. The authors consider the major reason for this is the traditionally limited space available for information on PK in these documents rather than a lack of consideration of PBPK models by regulators.

Use of models in regulatory decision-making

At present, the acceptance and impact of submitted models is variable. The difference in acceptance generally reflects the current level of confidence in PBPK models. This confidence depends both on the availability of supporting data (qualification) for the use of the PBPK platform in the intended way and on the predictive performance of the specific model for the pharmacokinetics of the drug(s). At present, commercially available PBPK platforms may have a number of possible simulation modes but qualification data supporting their use in a given regulatory submission may be limited, or lacking, and therefore they do not allow full elucidation of the performance of a given model for the intended purpose. The importance of the qualification and evaluation of the performance of the models for regulators is even captured in the public domain (as in lomitapide (Lojuxta) EPAR). The regulatory impact of the modeling is also variable and it ranges from relatively low (e.g., used as a preliminary analysis to determine the need for further studies) to high impact (e.g., determining dose recommendations in the SmPC or waiving of studies).[12] The required qualification and validation of a model depends on the importance that it has in the context of a high-impact decision. As an example of this, dose recommendations are generally based on mixed approaches combining *in vitro*, *in silico*, and/or *in vivo* data (e.g., for cobimetinib (Cotellic), macitentan, or ruxolitinib (Jakavi)), and in some cases a PBPK model may have had particular relevance in supporting a decision (e.g., eliglustat, eribulin, or lusaridone (Latuda)).

Taking into account that it is considered likely that the positive trend of the increasing number of submissions including PBPK is maintained in the future, the requirement for more specific guidance has been recognized.[10] The EMA is, therefore, finalizing guidance on the qualification and reporting of PBPK modeling, which will undergo a public consultation in 2016. In addition, a workshop at EMA is also planned for November 2016 to finalize some of the concepts in the guidance with input from companies and PBPK platform developers. The "PBPK guideline" will provide regulatory guidance regarding aspects such as the qualification of PBPK platforms and evaluation of the predictive performance of the drug model(s). As such, it is expected to improve the acceptability of the submitted models by EU regulators in the future. This and other efforts in the development and refinement of PBPK models by all stakeholders are expected to lead to a continued increase in their reliability and application for a wider range of regulatory purposes.

Limitations of the performed analysis

The results of the present study are likely to underestimate the number of procedures containing data based on PBPK models in

the EU. Only selected centralized procedures have been evaluated and this excludes PBPK models submitted to National Competent Authorities for noncentralized procedures. It is also acknowledged that PBPK modeling is abundant in scientific advice and pediatric procedures,[13] but these have also not been included in the analysis. With reference to the dataset, the fragmentation of data, the use of a variety of terms, or the lack of an explicit reference to PBPK in the assessment reports complicate the identification of references to PBPK models. Furthermore, exploratory PBPK models used during the development of a drug may not necessarily be submitted to regulators at the stage of MA application (MAA) or postapproval changes. An example of this could be early dose selection models that are useful to support decisions in the context of a clinical development program but are not relevant to establish the benefit–risk. Alternatively, the use of a model might not be mentioned in the assessment, and therefore it is not possible to be exact in terms of quantifying absolutely the use of PBPK models. In addition, some procedures were ongoing and not finalized at the time of the data lock point, so it may be that more of the included procedures lead to an explicit reference in the EPAR and/or SmPC.

Conclusion

In summary, this work has shown that there is an increasing trend in the use of PBPK models in drug submissions to the European regulators, with a variety of purposes, among which the simulation of DDI predominates. The increasing use of PBPK modeling is not always evident when looking only at public documents, as this work has demonstrated that the presence of these models within a procedure is often not included in these documents. Although underrepresented in public documents, PBPK models are valuable tools for drug developers and they are taken into consideration by regulators to support decision-making and recommendations in the SmPCs. It is therefore essential to use well-qualified platforms with a good predictive performance, and this fact emphasizes the need for the EU regulatory guidance that is under development in order to further drive and develop the regulatory use of PBPK.

METHODS

The EMA electronic records management system was searched using the term "PBPK" for relevant documentation, including the different Assessment Reports (ARs) generated during the evaluation of procedures, to identify those that included reference to PBPK modeling. The data lock point was 31 December 2015. This search was supplemented with input from members of the PKWP based on their personal experience. In cases where the reference to PBPK lacked detail or was unclear, all related documents were reviewed and a consensus decision between the authors was reached on inclusion in the analysis. Procedures other than those relating to either a new MAA or a significant change to an existing MA and those related to pediatric or nonclinical development were excluded from further analysis. A final list of procedures that included reference to PBPK modeling was compiled. These were further categorized based on whether a PBPK model had, or had not, been submitted.

The assessment of each procedure on the list was subject to in-depth manual review to identify the type and time of application, the intended purpose of the PBPK model(s), the status of the procedure (i.e., ongoing or finalized), and whether submitted models were developed spontaneously by a company or following a request from a regulator. Similarly, the EMA public website was also searched for relevant documentation, in particular EPARs and SmPCs to identify where reference to PBPK modeling was in the public domain, using the terms "PBPK," "physiologically," and "associated software" as keywords ("explicit references").

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DISCLAIMER

The views expressed in this article are the personal views of the authors and may not be understood or quoted as being made on behalf of or reflecting the position of the regulatory agencies or other organizations the authors work for.

CONFLICT OF INTEREST/DISCLOSURE

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AUTHOR CONTRIBUTIONS

K.V.B., E.L., S.C., A.N., C.V., and E.G.B. wrote the article; K.V.B. and E.L. designed the research; E.L., S.C., A.N., C.V., and E.G.B. performed the research; K.V.B. and E.L. analyzed the data.

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