CPT: Pharmacometrics & Systems Pharmacology

PERSPECTIVE OPEN ACCESS

Harnessing Open-Source Solutions: Insights From the First Open Systems Pharmacology (OSP) Community Conference

André Dallmann[1] | Denise Feick[2] | Pavel Balazki[3] | Salih Benamara[4,5] | Rolf Burghaus[6] | Marylore Chenel[7] | Siak-Leng Choi[8] | Henrik Cordes[2] | Mariana Guimarães[3] | Abdullah Hamadeh[9] | Ibrahim Ince[10] | Kathleen M. Job[11] | Tobias Kanacher[7] | Andreas Kovar[2] | Lars Kuepfer[12] | Jörg Lippert[6] | Julia Macente[13] | Nina Nauwelaerts[3,13] | Christoph Niederalt[6] | Sheila Peters[10] | Susana Proença[3] | Masanobu Sato[10] | Stephan Schaller[3] | Jan Frederik Schlender[14] | Annika Schneider[6] | Erik Sjögren[7,15] | Juri Solodenko[6] | Alexander Staab[10] | Paul Vrenken[16] | Thomas Wendl[6] | Wilhelmus E. A. de Witte[3] | Donato Teutonico[5]

[1]Bayer HealthCare SAS, Lille, France | [2]DMPK Modeling & Simulation, Sanofi R&D, Frankfurt am Main, Germany | [3]ESQlabs GmbH, Saterland, Germany | [4]Computational Pharmacology and Clinical Oncology, Inserm UMR1068, CNRS, Aix Marseille University, Marseille, France | [5]Translational Medicine & Early Development, Sanofi R&D, Vitry-sur-Seine, France | [6]Model-Informed Drug Development, Research & Development, Pharmaceuticals, Bayer AG, Leverkusen, Germany | [7]Pharmetheus AB, Uppsala, Sweden | [8]DMPK Modeling & Simulation, Sanofi-Aventis R&D, Vitry-sur-Seine, France | [9]School of Pharmacy, University of Waterloo, Kitchener, Ontario, Canada | [10]Clinical Pharmacology, Boehringer Ingelheim Pharma GmbH & co. KG, Ingelheim am Rhein, Germany | [11]Division of Clinical Pharmacology, Department of Pediatrics, School of Medicine, The University of Utah, Salt Lake City, Utah, USA | [12]Institute for Systems Medicine With Focus on Organ Interaction, University Hospital RWTH Aachen, Aachen, Germany | [13]Drug Delivery and Disposition, Department of Pharmaceutical and Pharmacological Sciences, KU Leuven, Leuven, Belgium | [14]Biomedical Research, Novartis, Basel, Switzerland | [15]Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden | [16]National and Kapodistrian University of Athens, Department of Pharmacy, Zografou, Greece

Correspondence: André Dallmann (andre.dallmann@bayer.com)

Received: 19 December 2024 | **Revised:** 14 February 2025 | **Accepted:** 3 March 2025

Funding: P.V. is part of the InPharma project that received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No. 955756. N.N. received a PhD scholarship from Research Foundation Flanders (1S50721N). N.N. and J.M. are involved in the IMI2 ConcePTION (Grant No. 821520) project. This article only reflects the personal views of N.N. and J.M. The research reported in this publication was supported in part by the Eunice Kennedy Shriver National Institute of Child Health and Human Development under Award Number K23HD112591. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

ABSTRACT

In 2017, the free and open-source software Open Systems Pharmacology (OSP) was launched. Since then, OSP has evolved from a small community into a diverse network of stakeholders committed to advancing open-source solutions for model-informed drug development (MIDD). In this context, the first OSP Community Conference was hosted by Novartis in Basel, Switzerland, on October 7–8, 2024, which gathered over 100 attendees from more than 40 institutions. This perspective synthesizes key insights from the conference.

1 | Conference Sessions and Covered Topics

An overview of the conference sessions, key points, and speakers is provided in Table 1. Application areas of the OSP suite are visually summarized in Figure 1, highlighting topics discussed at the conference. Table S1 in the Supporting Information lists novel software enhancements presented at the conference, along with links to their resources. Further

information, including the agenda and presentations, can be found on the conference website (https://www.open-systems-pharmacology.org/conference_2024.html).

2 | In Vitro-In Vivo Translation for Absorption, Distribution, and Clearance

A major theme of the conference was the translation of in vitro measures into clinical pharmacokinetics. Various physiologically-based biopharmaceutics modeling (PBBM) applications were presented in Session I, including a workflow for virtual bioequivalence, which is currently being developed, and a digital replication of the tiny-Tim model in MoBi, which successfully simulated the effect of food on drug exposure. Additionally, an enhanced PBBM framework was introduced, featuring (1) a toolbox for characterizing drug solubilization, (2) a versatile dissolution model for bridging in vitro test conditions in MoBi, and (3) an experimental PK-Sim version that integrates whole-body PBPK with updated in vitro dissolution functions. These advancements link in vitro dissolution testing to the clinical performance of oral drug products.

Session II focused on challenges and advancements in in vitro-in vivo extrapolation (IVIVE), particularly in predicting human intestinal absorption and hepatic clearance. An IVIVE method for predicting intestinal absorption by utilizing Caco-2 permeability and categorization of metabolism and transport was presented and the impact of assay conditions on translatability was discussed. For hepatic clearance, various case examples were presented that demonstrated improved predictive performance of PBPK models when simulating data from organ-on-a-chip (OoC) systems in MoBi for subsequent integration into PK-Sim. Noteworthy, the fraction unbound in the in vitro system significantly influenced prediction quality.

To enhance user-friendliness for IVIVE, a new R-based toolbox was introduced to derive parameter values from in vitro data for incorporation in PK-Sim. Importantly, this toolbox uses algorithms to calculate the fraction unbound in the in vitro assay that are consistent with those used in PK-Sim to calculate tissue/plasma partitioning. Furthermore, it accounts for experimental artifacts by incorporating adjustments for plastic partitioning and volatility. The necessity for standardization in IVIVE applications was also discussed, along with recent efforts to achieve this goal [1].

3 | Special Populations

PBPK modeling for special populations, particularly in obstetric populations, was another significant focus of the conference (Session VIII). Pregnancy PBPK models are valuable tools for predicting PK alterations and drug exposure in utero, helping to identify risks for both mother and fetus while providing an ethical alternative to studies involving pregnant people. Despite growing use, documented applications of pregnancy and lactation PBPK models in drug labeling remain scarce. However, with an increasing number of required post-marketing studies for pregnancy and lactation issued by the US Food and Drug Administration (FDA) [2], PBPK modeling has untapped potential for these populations.

Discussions on lactation PBPK modeling emphasized the need for robust methodologies to assess drug transfer into human milk and subsequent infant exposure. Various PBPK frameworks were presented to predict drug concentrations in human milk. While the models demonstrated reasonable predictive performance for several drugs, some instances of overprediction were noted. These overpredictions indicate that further model refinement along with additional physiological data during lactation is necessary.

Challenges associated with drug use in patients with hepatic impairment were also addressed. To enhance PBPK modeling in cirrhotic patients, a comprehensive pathophysiology repository was introduced, which is based on continuous disease progression rather than relying on discrete categories like Child-Pugh scores and incorporates population variability. This repository aims to provide a more nuanced understanding of the pathophysiological changes associated with liver cirrhosis, which may improve the predictive accuracy of PBPK simulations and allows informed predictions of pharmacokinetic variability in this population.

4 | Beyond Small Molecules: Modeling Biologics

Key discussions on large molecule modeling in Session VII included the integration of PBPK models that account for binding to the neonatal Fc receptor (FcRn) in plasma (pH 7.4) and the endosomal space (pH 6). The model implemented in PK-Sim was extended to make it applicable to molecules that show FcRn binding in plasma, which is especially important for adequate prediction of drug clearance, half-life, and the effect of novel modalities, such as FcRn inhibitors or FcRn-mediated sweeping antibodies [3]. The updated model was extensively analyzed using repeated sensitivity analysis and compared with the original model, demonstrating greatly enhanced sensitivity to FcRn binding at pH 7.4.

A comprehensive, quantitative systems pharmacology (QSP) model for predicting subcutaneous absorption, bioavailability, and immunogenicity was also presented. This model was evaluated using in vivo pharmacokinetic data from 31 biologics, primarily monoclonal antibodies (mAbs). Model evaluation demonstrated good predictive performance, capturing the area under the concentration-time curve and maximum plasma concentration within a 0.80–1.25-fold error range for 60% of mAbs. The need for ongoing collaboration between researchers and regulatory bodies to ensure the effective application of PBPK modeling for large molecules was emphasized.

5 | Expanding OSP: Novel Tools, Extensions, and Software Updates

The conference showcased novel tools and extensions for OSP that are, or will be, freely shared with the community. Table S1 provides an overview of these enhancements, which aim to improve usability and efficiency of OSP in MIDD.

TABLE 1 | Sessions, speakers, and key points at the OSP Community Conference 2024.

Session name & chairs (affiliation)	Key points	Speakers (affiliation)
Session I: Physiologically Based Biopharmaceutics Modeling (PBBM) Chairs: André Dallmann (Bayer), Erik Sjögren (Pharmetheus)	Discussing the importance of PBBM in creating a dissolution safe-space. Introducing a new open-source framework for linking in vitro dissolution and in vivo pharmacokinetics using R and OSP. Showcasing case studies in PK-Sim/MoBi for biopharmaceutical risk assessment.	Mariana Guimaraes (ESQlabs), Paul Vrenken (National and Kapodistrian University of Athens), Fabian Winter (AbbVie)
Session II: In Vitro-In Vivo Extrapolation Chairs: Tobias Kanacher (Pharmetheus), Donato Teutonico (Sanofi)	Presenting an R-based toolbox for deriving parameter values from in vitro data that can be directly incorporated in PK-Sim. Demonstrating improved human hepatic clearance predictions when using organ-on-a-chip systems. IVIVE method utilizing Caco-2 data to predict human intestinal absorption in OSP.	Susana Proença (ESQlabs), Siak-Leng Choi (Sanofi), Denise Feick (Sanofi)
Session III: Perspectives on the use of PBPK in regulatory submission Chairs: Ibrahim Ince (Boehringer Ingelheim), Stephan Schaller (ESQlabs)	Emphasizing the importance of a risk-informed credibility assessment of PBPK models based on their context and intended use in regulatory interaction. Reviewing trends in PBPK model applications in new drug approvals in Japan, highlighting CYP3A4-mediated DDIs as major application scenario. Analyzing PBPK model applications in regulatory submissions to the EMA, highlighting common issues and areas for improvement. Highlighting the increasing use of mechanistic modeling in drug development, with case studies submitted to the US FDA demonstrating its utility.	Flora Musuamba (EMA, University of Namur), Masanobu Sato (Boehringer Ingelheim), Pieter Colin (EMA, UMC Groningen), Hao Zhu
Session IV: Integrated PBPK-PD/QSP modeling Chairs: Henrik Cordes (Sanofi), Stephan Schaller (ESQlabs)	Introducing a modular approach in the OSP Suite to simplify model integration and enhance reusability.	Pavel Balazki (ESQlabs)
Session V: Drug–Drug Interaction Modeling Chairs: Marylore Chenel (Pharmetheus), Alexander Staab (Boehringer Ingelheim)	Qualifying the OSP platform for predicting CYP3A4-mediated DDIs and applying it for regulatory purposes. Using the example of finerenone, it was shown how clinical trials could be replaced and the drug label informed by PBPK modeling. Evaluating the optimal use of static and dynamic PBPK models for DDI assessment, advocating for a pragmatic approach based on specific applications.	Thomas Wendl (Bayer), Sheila Peters (Boehringer Ingelheim)
Session VI: PBPK Best Practice & Introduction to the ICH MIDD Guidance Chairs: Rolf Burghaus (Bayer), Jan Schlender (Novartis)	Presenting best practices and guidance documents for developing PBPK models with OSP. Providing an overview of the ICH M15 guideline for model-informed drug development, emphasizing risk-based assessments and multidisciplinary collaboration. Discussing the development of a Model Master File framework to standardize modeling practices, illustrated using a mechanistic dermal absorption model in OSP.	Jan Frederik Schlender (Novartis), Nicolas Frey (Roche), Abdullah Hamadeh (University of Waterloo)
Session VII: Large Molecules Modeling Chairs: Christoph Niederalt (Bayer), Wilbert de Witte (ESQlabs)	Describing capabilities in OSP for modeling large molecules and the significance of FcRn binding in pharmacokinetics. Presenting a framework for modeling subcutaneous absorption and immunogenicity of therapeutic proteins, demonstrating good predictive performance.	Wilbert de Witte (ESQlabs), Erik Sjögren (Pharmetheus), Salih Benamara (Sanofi)

(Continues)

TABLE 1 | (Continued)

Session name & chairs (affiliation)	Key points	Speakers (affiliation)
Session VIII: Special Populations in the OSP Suite Chairs: André Dallmann (Bayer), Ibrahim Ince (Boehringer Ingelheim)	Highlighting good predictive performance of available pregnancy PBPK models using OSP and equivalent model performances for passive renal processes between different software tools (Simcyp, GastroPlus, and OSP). Discussing challenges and methodologies for modeling drug exposure during lactation, emphasizing advantages of opportunistic pharmacokinetic studies and the need for flexible modeling tools. Demonstrating a PBPK workflow for pharmacokinetic predictions in human milk, relying on empirical approaches or integrating in vitro data from human mammary epithelial cells (IVIVE). Introducing a new pathophysiology repository for liver cirrhosis that is based on continuous disease progression and incorporates population variability.	André Dallmann (Bayer), Kathleen M. Job (University of Utah), Julia Macente (KU Leuven), Nina Nauwelaerts (KU Leuven), Annika Schneider (Bayer)
Session IX: Community Engagement – OSP Suite Qualification & Release Chairs: Rolf Burghaus (Bayer), Donato Teutonico (Sanofi)	Outlining strategic processes behind OSP Suite management, release planning, platform qualification, and quality assurance protocols. Highlighting criteria for new software contributions to the OSP platform, encouraging active participation from the community and reinforcing the commitment to quality standards.	Stephan Schaller (ESQlabs), Juri Solodenko (Bayer)
Session X: OSP community building, funding, and management Chairs: Alexander Staab (Boehringer Ingelheim), Andreas Kovar (Sanofi)	Discussing OSP community building and funding, emphasizing sustained and sustainable community growth through institutionalization within a foundation and fundraising.	Stephan Schaller (ESQlabs)

Abbreviations: CYP, Cytochrome P450; DDI, drug–drug interaction; EMA, European Medicines Agency; FcRn, Neonatal Fc receptor; FDA, Food and Drug Administration; ICH, International Council for Harmonization of Technical Requirements; IVIVE, In vitro-in vivo extrapolation; MIDD, Model-informed drug development; OSP, Open Systems Pharmacology; PBBM, physiologically based biopharmaceutics modeling; PBPK, physiologically based pharmacokinetics; PD, pharmacodynamics; PK, pharmacokinetics; QSP, quantitative systems pharmacology.

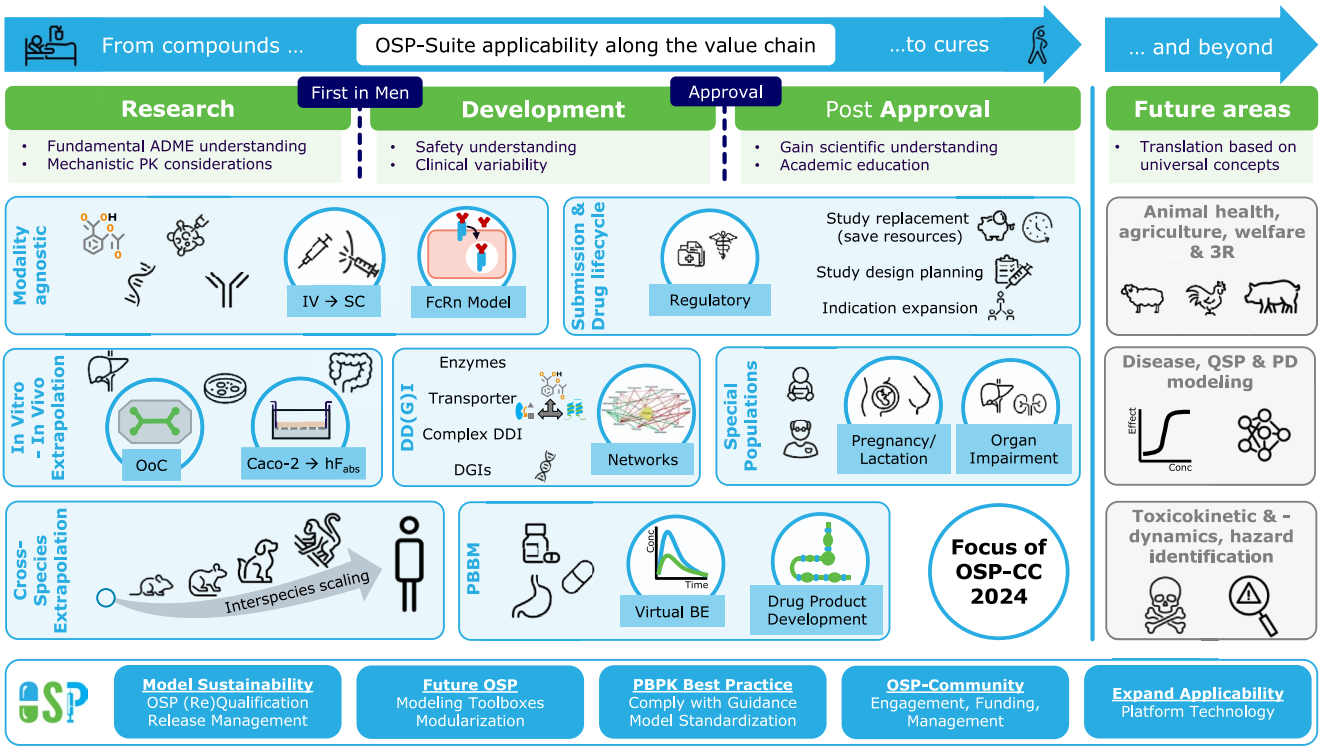

FIGURE 1 | Applicability of the OSP-Suite along the value chain and beyond. Application areas are represented by boxes, the pictograms present the capabilities of the OSP-Suite. Circles emphasize the targeted topics at the OSP Community Conference in 2024. 3R, Replace, Reduce, Refine; ADME, Absorption, distribution, metabolism, excretion; BE, Bioequivalence; DD(G)I, Drug–drug(–gene) interaction; FcRn, Neonatal Fc receptor; hFabs, Human fraction absorbed; IV, Intravenous; OoC, Organ on a chip; OSP, Open Systems Pharmacology; PBBM, Physiologically Based Biopharmaceutics Modeling; PD, Pharmacodynamics; PK, Pharmacokinetics; QSP, Quantitative systems pharmacology; SC, Subcutaneous.

Of note, Session IV introduced a new modularization concept for the upcoming OSP version 12. This concept organizes complex models (such as coupled PBPK, QSP, pharmacodynamic, and disease models) into distinct, manageable modules. These modules can be easily combined, which simplifies model maintenance, extension, and integration. This modularization may also enhance model reusability across various projects, promoting collaboration within the OSP community.

6 | OSP (Re-)qualification and Application in Regulatory Submissions

The importance of the current (re-)qualification framework for OSP [4] was addressed throughout the conference. Rigorous quality assurance protocols were presented in Session IX, including comprehensive platform validation and qualification for specific intended uses. These measures are critical for maintaining high-quality standards and ensuring that the platform aligns with regulatory requirements.

Several examples were discussed that demonstrate how OSP has been successfully used in regulatory interactions. For example, Session V presented a PBPK model for finerenone that was coupled with the independently validated network of CYP3A4 modulators in PK-Sim. The simulation results contributed to the overall drug–drug interaction (DDI) assessment, replaced clinical DDI studies with in silico analyses, and successfully informed the prescription label of finerenone [5]. The discussed examples, along with the fact that PK-Sim and MoBi files are accepted formats for regulatory submissions, highlight the acceptance of OSP as a free and open-source tool in regulatory interactions.

In Session VI, complex dermal absorption modeling was presented as a prototype example for the Model Master File framework since the FDA has begun accepting mechanistic dermal absorption models as substitutes for in vivo bioequivalence trials [6]. However, the lack of consensus around the pharmacokinetics of a given drug could lead to regulatory decisions based on inconsistent science. To address this, the FDA proposed the Model Master File framework, encouraging the use of standardized models that incorporate key accepted absorption, distribution, metabolism, and excretion (ADME) mechanisms relevant to specific drug products. While the development of these standardized models faces challenges due to limited incentives, academic-industrial partnerships leveraging OSP as an open-source tool offer a promising solution.

7 | Navigating Regulatory Landscapes

As PBPK modeling gains traction, understanding regulatory implications is crucial; thus, Session III addressed regulatory requirements and interactions. Speakers from the European Medicines Agency elaborated on the risk-informed credibility assessment framework, emphasizing the need for international standards that consider the context of model use, specific questions they

aim to address, and potential risks in case model predictions are inaccurate. This framework aligns with the ICH draft guideline on MIDD (https://database.ich.org/sites/default/files/ICH_M15_EWG_Step2_DraftGuideline_2024_1031.pdf) and is intended to foster collaboration among stakeholders, thereby ensuring that PBPK models meet regulatory expectations, while supporting decision-making during drug development.

A comprehensive review of all European Public Assessment Reports (EPARs) from approved marketing authorization applications in 2022–2023 showed that 25 of the 95 applications (26%) included PBPK models (independently of the software used) [7]. The assessment revealed an overall qualification rate of 28%, with a 37% acceptance rate for models used to support claims in the Summary of Product Characteristics (SmPC). Key concerns for non-qualification included structural omissions in the PBPK model, insufficient justification of assumptions, and poor predictive performance. These concerns are areas for improvement in future submissions.

Insights into the regulatory landscape in Japan indicated increased acceptance of PBPK models in new drug applications and labeling by the Pharmaceuticals and Medical Devices Agency. Since 2015, 33 drug product labels have incorporated PBPK modeling results, primarily in oncology. The predominant application has been the assessment of CYP3A4-mediated DDIs, specifically when the drug was co-administered with moderate or weak CYP3A4 modulators.

A similar trend for PBPK-related submissions was observed for the FDA along with a notable increase in the number of submissions containing QSP [8]. Four case examples from interactions with the FDA were presented, demonstrating the application of PBPK or QSP modeling to understand DDIs, explore drug repurposing, conduct pediatric extrapolation, and assess treatment duration. These examples demonstrate the growing recognition of PBPK and QSP modeling as valuable tools in regulatory decision-making.

8 | Conclusion

The recent advancements in PBPK and QSP modeling discussed at the OSP Community Conference have significant potential for MIDD. Since its launch as free and open-source software in 2017 [9], OSP has fostered a diverse and rapidly expanding community [10], reflected in the wide range of topics and innovative tools showcased at the conference. Ongoing collaboration among stakeholders will be vital for enhancing the software's functionality and usability. The successful utilization of OSP in regulatory submissions further emphasizes its value as a transparent and open-source solution. This approach has the potential to streamline innovation, optimize resource allocation, and increase public trust in drug development.

Conflicts of Interest

A.D., H.C., I.I., L.K., S.S., J.F.S., W.E.A.d.W., and D.T. are members of the organizing committee for the OSP Community Conference 2024. R.B., I.I., A.K., L.K., J.L., S.S., J.F.S., E.S., A.S., and D.T. are members of the OSP Management Team. S.B., H.C., D.F., A.K., S.-L.C., and D.T. are Sanofi employees and may hold shares and/or stock options in the company. P.V. is part of the InPharma project that received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No 955756. N.N. received a PhD scholarship from Research Foundation-Flanders (1S50721N). N.N. and J.M. are involved in the IMI2 ConcePTION (Grant No. 821520) project. This article only reflects the personal views of N.N. and J.M. The research reported in this publication was supported in part by the Eunice Kennedy Shriver National Institute of Child Health and Human Development under Award Number K23HD112591. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

References

1. J. Louisse, M. Alewijn, A. A. C. M. Peijnenburg, et al., "Towards Harmonization of Test Methods for In Vitro Hepatic Clearance Studies," *Toxicology In Vitro* 63 (2020): 104722.

2. J. Krastein, L. Sahin, and L. Yao, "A Review of Pregnancy and Lactation Postmarketing Studies Required by the FDA," *Pharmacoepidemiology and Drug Safety* 32 (2023): 287–297.

3. W. E. de Witte, L. B. Avery, B. C. Mackness, T. Van Bogaert, A. Park, and M. L. Sargentini-Maier, "Mechanistic Incorporation of FcRn Binding in Plasma and Endosomes in a Whole Body PBPK Model for Large Molecules," *Journal of Pharmacokinetics and Pharmacodynamics* 50, no. 3 (2023): 229–241, https://doi.org/10.1007/s10928-023-09849-9.

4. S. Frechen, J. Solodenko, T. Wendl, 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 & Systems Pharmacology* 10, no. 6 (2021): 633–644, https://doi.org/10.1002/psp4.12636.

5. T. Wendl, S. Frechen, M. Gerisch, R. Heinig, and T. Eissing, "Physiologically-Based Pharmacokinetic Modeling to Predict CYP3A4-Mediated Drug-Drug Interactions of Finerenone," *CPT: Pharmacometrics & Systems Pharmacology* 11 (2022): 199–211, https://doi.org/10.1002/psp4.12746.

6. E. Tsakalozou, A. Babiskin, and L. Zhao, "Physiologically-Based Pharmacokinetic Modeling to Support Bioequivalence and Approval of Generic Products: A Case for Diclofenac Sodium Topical Gel, 1%," *CPT: Pharmacometrics & Systems Pharmacology* 10, no. 5 (2021): 399–411, https://doi.org/10.1002/psp4.12600.

7. P. Paul, P. J. Colin, F. Musuamba Tshinanu, C. Versantvoort, E. Manolis, and K. Blake, "Current Use of Physiologically Based Pharmacokinetic Modelling in New Medicinal Product Approvals at EMA," *Clinical Pharmacology & Therapeutics* 117 (2024): 808–817.

8. J. P. Bai, J. P. F. Bai, J. C. Earp, et al., "Quantitative Systems Pharmacology: Landscape Analysis of Regulatory Submissions to the US Food and Drug Administration," *CPT: Pharmacometrics & Systems Pharmacology* 10, no. 12 (2021): 1479–1484, https://doi.org/10.1002/psp4.12709.

9. J. Lippert, R. Burghaus, A. Edginton, et al., "Open Systems Pharmacology Community—An Open Access, Open Source, Open Science Approach to Modeling and Simulation in Pharmaceutical Sciences," *CPT: Pharmacometrics & Systems Pharmacology* 8, no. 12 (2019): 878–882, https://doi.org/10.1002/psp4.12473.

10. A. Dallmann, D. Teutonico, S. Schaller, R. Burghaus, and S. Frechen, "In-Depth Analysis of the Selection of PBPK Modeling Tools: Bibliometric and Social Network Analysis of the Open Systems Pharmacology Community," *Journal of Clinical Pharmacology* 64 (2024): 1055–1067.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.