Speaker Biographies and Abstracts

Day 1 – Monday, October 7, 2024

Jörg Lippert (Bayer) & Stephan Schaller (ESQlabs):
Keynote: The Roots and the Leaves of the OSP Suite

Jörg Lippert is VP and head of Model-Informed Drug Development (MIDD) at Bayer. He is a physicist and holds a PhD in Neuroscience. Jörg is one of the founding fathers of PK-Sim and MoBi and has driven the advancement and further development of PK-Sim and MoBi, as scientist and facilitator, throughout his career.

Stephan Schaller is the Founder and Managing Director of ESQlabs GmbH and holds a PhD in Computational Engineering. His passion lies in advancing knowledge- and mechanism-based modeling approaches such as PBK, and QSP/T to enable informed decision-making for MIDD, Healthcare and Next-Generation Risk Assessment (NGRA). Stephan is the current chair of www.Open-Systems-Pharmacology.com, and a coordinator and PI of German national and European multinational public grant research projects.

Mariana Guimaraes Sa Correia (ESQlabs):
Leveraging OSP for developing dissolution safe-space through IVIVC and VBE workflows: a qualification perspective

Mariana Guimarães, a pharmacist with a PhD in Biopharmaceutics from the University of Bath, has experience applying physiologically based biopharmaceutics modeling (PBBM) to inform formulation development and understand oral drug absorption risks. Before joining ESQlabs, Mariana worked at GSK on the biopharmaceutics team, applying tools for understanding absorption-related risks in adult and pediatric drug development programs, from early to late stage development.

Abstract
Physiologically based biopharmaceutics modeling (PBBM) has been increasingly explored to inform oral drug product development. One of the important applications of PBBM is the development of a dissolution safe-space, supported by *in vitro in vivo*

relationships/correlations (IVIVR/C), and virtual bioequivalence (VBE) analysis. Development of a PBBM-based dissolution safe-space is grounded on a high drug product understanding, establishing the link between the lab (i.e., dissolution testing) and clinical performance. This strategy facilitates patient-centric drug development and offers the possibility of broader regulatory flexibility. In this talk, the discussion will cover: i. the background information of safe-space, IVIVC and VBE; ii. list some of the OSP workflows available to establish dissolution safe-space during drug product development; and iii. the work developed to qualify these workflows, including current challenges and future plans.

Paul Vrenken (National and Kapodistrian University of Athens):
Extending the OSP oral absorption toolbox: An end-to-end Physiology Based Biopharmaceutics Modeling approach

Paul Vrenken obtained his master's degree in Drug Discovery and Safety from the Free University of Amsterdam. Currently he is completing his PhD at the National and Kapodistrian University of Athens as part of the InPharma Consortium, a European Industrial Doctoral program. His research focuses on reducing animal testing in oral drug development by advancing in vitro and in silico methods. Over the past three years, Paul has worked with Bayer and NKUA to expand the oral absorption modeling toolbox, supporting more efficient and ethical pharmaceutical drug development.

Abstract
This presentation introduces a fully open-source physiology-based biopharmaceutical modeling framework for oral drug products using the OSP (Open Systems Pharmacology) suite. The 3-pillar approach leverages the OSP solubility toolbox to determine API aqueous solubility and bile salt partitioning from in vitro data, incorporates an updated dissolution model to inform formulation release from in vitro experiments, and facilitates easy transfer to PK-Sim for whole-body PBPK modeling with refined gastrointestinal tract parameters. The framework has been successfully established and applied, enhancing OSP capabilities to reduce and replace animal testing and minimize human clinical studies in oral drug product development.

Fabian Winter (AbbVie):
Combination of in-vitro and in-silico tools for biopharmaceutical risk assessment in drug product development

Fabian Winter is a Senior Scientist at AbbVie in Ludwigshafen. He is a pharmacist by training and studied at the University of Greifswald and at the Pacific University in Portland Oregon. Before joining AbbVie in April of this year, he worked at AstraZeneca and in the working group of Werner Weitschies at the University of Greifswald. During this time, he specialized in integrating biorelevant dissolution data in PBBM models and biopharmaceutical risk assessment in formulation development. At AbbVie, he is part of the biopharmaceutics team in small molecules formulation development where he is involved in using custom PK-Sim/Mobi models for formulation screening and food effect assessment. Research initiatives currently include speciation of ASD formulations and establishing digital twins of biorelevant dissolutions methods.

Abstract

In its guidance on the use of Physiologically Based Pharmacokinetic Analysis for biopharmaceutical applications, the FDA specifically encourages the use of biorelevant dissolution for model validation and risk assessment. In this presentation, we will explore how we can use PK-Sim/MoBi to integrate biorelevant dissolution data into custom Physiologically Based Biopharmaceutics Models (PBBM). Two specific use cases are presented. First, we show that a digital replication of the tiny-Tim in MoBi can not only help interpret the results of this complex in vitro tool, but the information gathered can also be used to predict the effect of food on drug pharmacokinetics. In the presented example, we can show that this combination of in vitro and in silico tools can predict the in vivo dissolution and solubility much better than simply using the input biorelevant solubility. In the second case study, a model that incorporates the effect of the stomach road on drug pharmacokinetics is shown by incorporating the dissolutions results obtained in the GastroDuo. This highlights the capability of the PK-Sim/MoBi platform to quickly incorporate new observations or mechanistic processes.

Susana Proença (ESQlabs):
Towards an OSP IVIVE Toolbox

Susana Proença completed her Master's in Biopharmaceutical Sciences at the University of Lisbon in 2016, with a thesis focused on developing in vitro 3D models. This was followed by two internships at the Joint Research Center of the European Commission in Ispra, Italy, the first focused on making in silico simulations of in vitro kinetics and the second on curation of REACH dossiers' data for chemical safety. Susana then started her PhD at the Institute for Risk Assessment in Utrecht University. The PhD was focused on characterizing the in vitro kinetics of different chemicals in hepatic and neuronal in vitro models. In 2022, Susana moved to Wageningen University as a postdoc, working in the EU project ONTOX, a project focused in developing and integrating in vitro and in silico methods for performing chemical's risk assessment. In 2023 she moved to ESQlabs but continued working in the ONTOX project.

Abstract
In vitro ADME parameter derivation is of great value for developing PBPK models, as it reduces animal testing and increases testing throughput. However, in vitro-derived values necessitate extrapolation to in vivo conditions, accounting for differences in cell/enzyme numbers and fraction unbound. The extrapolation procedure can significantly impact accuracy, highlighting the need for standardization and evaluation, as exemplified in commercial tools like Certara's SIVA. To facilitate seamless integration with OSP tools, we are developing an R-based tool for ADME extrapolations. We will present our work on metabolic clearance, including the development of an in vitro kinetics compartmental model applicable to other ADME extrapolations. Finally, we will discuss potential future directions for this toolbox.

Choi Siak-Leng (Sanofi):
Organ-on-a-Chip (OoC) Digital Twins for Estimating Small Molecules' Human Hepatic Clearance and PK Profiles

Siak-Leng Choi (Choi) is currently the distinguished scientist in Sanofi's DMPK global M&S team. He has been working in the field of pharmacometrics in industry for 16 years. His background is biology and chemistry, specialized in toxicokinetics. After he earned his master's degree from National University of Singapore and Technical University of Munich, he started his career as

clinical pharmacometrician in Eli Lilly for 9 years, where he has performed mechanistic and discrete modeling to support dose selection and trial design from phase 1 to phase 3, and regulatory submissions for auto-immune diseases and diabetes. Subsequently, he has joined Grünenthal as a senior pharmacometrician to support early phase study design and pediatric dose selection regulatory submissions for analgesic drugs. Now, in Sanofi, he is focusing on human PK and PK/PD translation using preclinical data to support FIH dose projection and trial design, mainly for immuno-oncology, molecular oncology and neuroscience.

Abstract
In recent years, the FDA has promoted the 3Rs principles to reduce the use of animals in research and drug testing. One solution is using in-silico methods to analyze in-vitro data generated from cell cultures or human tissues. However, the performance of predicting human pharmacokinetics (PK) with in vitro-in vivo extrapolation (IVIVE) based on data from conventional in-vitro systems remains questionable. This is due to several reasons, particularly the limited longevity of cell phenotypes and experiments conducted under static conditions, which are physiologically irrelevant.
Hence, OoC has emerged as an alternative due to its microfluidic systems, which extend cell viability and enable the evaluation of multiple cell types and ADME properties in a single experiment. In this presentation, we will discuss the design of experiments to generate appropriate data using liver chips, as well as the structure of a Digital Twin model that mechanistically describes drug kinetics in OoC. The Digital Twin model establishes a connection between the chip's hardware architecture and a detailed mapping of the underlying biology. The intrinsic clearance of selected small molecule drugs was determined by analyzing the chip PK data using both the Digital Twin and conventional methods. These estimated intrinsic clearances were then integrated into the PK-SIM PBPK model to predict clinical PK profiles, with the Digital Twin model demonstrating superior accuracy. Additionally, the conditions of OoC experiments can be optimized by performing sensitivity analyses on the Digital Twin model.
Ultimately, this approach could be integrated as part of routine ADME evaluation in the drug discovery phase.

Denise Feick (Sanofi):

Prediction of human fraction absorbed from in vitro Caco-2 permeability – are we there yet?

Denise obtained her license as pharmacist in 2017. Afterwards, she wrote her doctoral thesis at Saarland University, focusing on the assessment of complex interactions involving transporter substrates. She continued her work at Saarland University as Postdoctoral Researcher before joining Sanofi in 2023. Her expertise includes PBPK modeling of complex drug-drug-gene interactions, model-informed drug development, in vitro-to-in vivo extrapolation and interspecies scaling.

Abstract
In vitro to in vivo extrapolation of human intestinal permeability is challenging. The Caco-2 permeability assay is designed to support compound classification and ranking in drug research and is not optimized for application in translational modeling approaches. Applying permeability derived from the in vitro Caco-2 assay for intestinal permeability in PK Sim® shows poor predictability. We investigated how to improve applicability of Caco-2 derived permeability for translational modeling approaches to extrapolate human fraction absorbed.

Flora Musuamba (EMA, University of Namur):
Risk-based approach for model assessment

Flora Musuamba holds a Ph.D. in Pharmacy and biomedical sciences from Université Catholique de Louvain, in Belgium. She is a Pharmacometrics and Pharmacovigilance internal expert at the Belgian federal medicines agency (FAMHP). Flora Musuamba is the Chair of the European Medicines Agency Modelling and Simulation European Specialised Expert Community (ESEC) and the Modelling and Simulation Operational Expert Group (OEG) and a member of the the methodology (MWP) and scientific advice working parties (SAWP) at the European medicines agency (EMA). She is also Professor of Clinical Pharmacology and Pharmacotherapy at University of Namur and University of Lubumbashi.

Abstract
The value of modeling and simulation in drug development and evaluation has been demonstrated repeatedly and convincingly. While their benefits are now unanimously recognized, international standards for their evaluation, accepted by all stakeholders involved, are still to be established. In this presentation, a risk-informed evaluation framework will be presented for assessment of the models given their contexts of use and the Question they are intended to address. The central role of the risk assessment will be discussed from different stakeholders' perspectives. In particular, the impact on the regulatory requirements will be illustrated using use-cases.

Masanobu Sato (Boehringer Ingelheim):
Exploring PBPK Application Trends and Regulatory Conversations in New Drug Approvals in Japan

Dr. Masanobu Sato earned a PhD in Drug Transporter Research in 2010. Following his doctoral studies, he served as a reviewer at the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan from 2010 to 2017. From 2018 to 2021, Dr. Masanobu Sato was a Principal Scientist in the Clinical Pharmacology Department at Merck Sharp & Dohme in Japan. He then became the Group Manager of the Drug Transporter Lab at Boehringer Ingelheim in Kobe, Japan, before transitioning to his current role as Principal Scientist in Clinical Pharmacology at Boehringer Ingelheim in Biberach, Germany

Abstract
The use of Physiologically Based Pharmacokinetic (PBPK) models in new drug applications in Japan is increasing, as seen also in EU and US. Guidelines and technical guides issued by the Pharmaceuticals and Medical Devices Agency (PMDA), which define the content of PBPK reports and specifications for submitting PBPK model analysis data, provide a framework for successful use of PBPK models for new drug applications in Japan.
By examining the PMDA review reports, it is possible to identify the intended use of submitted PBPK models and how the results from the models are implemented in clinical use of the drug. As a result of the examination, PBPK model analysis is often used to support warnings about DDI involving CYP3A, and it has been found that it is also used in prediction of transporter mediated DDIs and DDIs in organ impairment.

In this presentation, the guidelines and technical guides issued by PMDA, and recent review cases of PMDA regarding PBPK modeling of complex drug interactions will be introduced.

Pieter J Colin (EMA, UMC Groningen):
EMA review of assessments of PBPK models from regulatory submissions

Pieter Colin (Pharm.D., Ph.D.) currently works as a seconded national expert in the Scientific Advice Office at EMA, providing specialized expertise in Modelling and Simulation across the Agency. In addition, he is an associate professor of anesthesiology at the University Medical Center Groningen (The Netherlands) where he leads a pharmacometrics group with a focus on treatment individualization in anesthesia, peri-operative and critical care medicine. Pieter has (co-)authored more than 60 publications covering different topics related to pharmacometrics and is frequently involved in teaching principles of pharmacokinetics, pharmacodynamics and clinical pharmacology to (post-)graduate students and healthcare professionals. Finally, Pieter is a member of the Modelling and Simulation Operation Expert Group at EMA and a consultant for the Belgian Medicines Agency (FAHMP).

Abstract
Physiologically Based Pharmacokinetic (PBPK) Models are routinely used in drug development and therefore appear frequently in marketing authorizations applications (MAAs) to the European Medicines Agency (EMA). For a model to be a key source of evidence for a regulatory decision, it must be considered qualified for the intended use. Advice on the data expected to allow qualification of a PBPK model or platform is provided in the EMA Guideline on the reporting of PBPK modeling and simulation. In my talk I will discuss an EMA review of the use of PBPK models in submitted MAAs in 2022 and 2023. There were 95 MAAs with a 'full' legal basis approved during these years and 25 of them contained PBPK modeling. There were 65 general areas of intended use for PBPK modeling identified across the applications, with the most common being prediction of drug-drug interactions with enzymes or transporters (69%). Our review showed that most of the models submitted in applications to EMA were not considered as qualified for the intended use(s). The reasons identified for this and potential implications for further EMA guidance on PBPK modeling will be discussed during the talk.

Hao Zhu:
Use of mechanistic modeling to support new drug development and decision-making

Hao Zhu has more than 20 years of working experience in pharmaceutical sciences. He is enthusiastic in applying quantitative tools to support new drug development and improve patient care. Serving as a thought leader in the community, he promotes the use of innovative modeling approaches to improve trial efficiency, to allow early patient access for an effective therapy, and to individualize treatment based on features of each patient.

Abstract
Model Informed Drug Development (MIDD) refers to the development and application of exposure-based, biological, and pharmacological models derived from preclinical and clinical data sources to address drug development or regulatory issues. Multiple

quantitative tools, including mechanistic models, are broadly used to streamline new drug development and improve patient care. As reported in the literature, there has been an increased number of submissions to the US FDA where mechanistic modeling is used to support various drug development programs. In this presentation, 2 cases based on physiologically based pharmacokinetics (PBPK) modeling and 2 cases based on quantitative system pharmacology (QSP) modeling will be discussed. Through these cases, it is shown that mechanistic modeling has been applied to understand drug-drug interactions, the potential for drug repurposing, pediatric extrapolation, and assessment of treatment duration. Overall, mechanistic modeling has played increasingly important roles to facilitate new drug development

Pavel Balazki (ESQlabs):

PBPK-QSP: Model Modularization and Qualification with OSP Suite v12 – aka "OSMOSES"

Pavel Balazki works as Senior Scientist and Lead Software ToolChain at ESQlabs. Pavel is a bioinformatician by training with more than 9 years of industry experience in PBPK and QSP modeling using the OSP software. He focuses on the development of complex PB-QSP disease platforms and leads the software development team at ESQlabs.

Abstract

The integration of complex mechanism-based quantitative systems pharmacology (QSP) models into physiologically based pharmacokinetic (PBPK) modeling frameworks leads to an ever-increasing model complexity. Maintenance and extension of such platforms become challenging and error-prone. The complexity of the integration of such models limits their life cycle and distribution in the scientific community.

Version 12 of the Open Systems Pharmacology Suite software introduces a new modularization concept to address the above-discussed challenges. The QSP modeling tool MoBi organizes a modeling project in modules. A module can be a full PBPK model, an extension of the default PBPK backbone (a new organ or administration site), an effect, or a disease module. By combining modules, the user can create simulations with different individuals, medications, disease states, and levels of detail required for a particular use case. The modules can be distributed separately and reused in different projects.

The modularization concept allows the implementation of the automated re-qualification framework, which is scheduled for the following releases. The framework will support report generation for separate modules and whole platforms for specified application scenarios.

CONCLUSION: The integrated qualification framework allows continuous quality control, qualification, and deployment of complex PB-QSP models and will support the use of PB effects modeling for regulatory submissions. The modular concept simplifies the process of model exchange and integration into existing projects, facilitating the reusability of modeling activities and promoting exchange within an open science community.

Day 2 – Tuesday, October 8, 2024

Thomas Wendl (Bayer AG):
PBPK DDI Network Qualification and Regulatory Application

Thomas Wendl is a Scientist in Systems Pharmacology and a Senior Science Fellow in the department of Model-Informed Drug Development (MIDD) at Bayer. Since he started at Bayer in 2007, he is working in the field of Physiologically-based Pharmacokinetic (PBPK) modeling with a focus on drug-drug-interactions and pediatric populations. Thomas studied biology and mathematics at the University of Tübingen, Germany, and University of Granada, Spain, and holds a PhD in developmental biology from the University of Cologne.

Abstract
Regulatory guidelines promote the use of PBPK modeling in lieu of conducting clinical drug-drug-interaction (DDI) studies and require a robust evaluation of the models, processes and platforms for this purpose. choose an appropriate study design or to deal with complex DDIs. In this presentation, the steps from platform qualification for the intended use of CYP3A4 DDI modeling, using the Open-Systems-Pharmacology (OSP) platform and the example of finerenone (Kerendia®), an investigational drug product at BayerOSP platform to facilitate the prediction of DDIs, but also scientific challenges that remain are presented.

Sheila Peters (Boehringer Ingelheim):
Optimal Use of Static and Dynamic Models for DDI Assessment along the Value Chain

Dr. Sheila Annie Peters is an Early Asset Lead at Boehringer-Ingelheim, Germany. She completed her PhD in Chemistry from Indian Institute of Technology, Chennai. She started her career in Pharma R&D in 1999, working at Cyprotex, UK. Later, she joined AstraZeneca, Mölndal, where she developed and applied a generic whole-body PBPK model to support drug discovery and early development projects across different R&D sites. Here, she won the AstraZeneca Innovative Medicines Science Award for the "Design and Development of LungSim Simulation tool for Inhalation PK Modelling". Sheila served as Head of Translational Quantitative Pharmacology group at Merck KGaA, Darmstadt for 6 years before joining Boehringer Ingelheim. Sheila served as the EFPIA Topic leader for the ICH M12 group focused on harmonizing drug-drug interaction (DDI) guidelines. She has published several papers on PK, PBPK, human dose predictions, gut metabolism and DDI in high impact journals and authored a book on PBPK.

Abstract
Mechanistic static and dynamic physiologically based pharmacokinetic (PBPK) models are used in clinical drug development to assess the risk of drug–drug interactions (DDIs). Currently, the use of mechanistic static models (MSM) is restricted to screening DDI risk for an investigational drug, while dynamic PBPK models are used for quantitative predictions of DDIs to support regulatory filing. However, PBPK model development by sponsors as well as a review of models by regulators require considerable resources. There is growing evidence to suggest that quantitative predictions that are comparable with those from PBPK are possible with MSM by using appropriate driver precipitant concentrations. A pragmatic approach would be to leverage the strengths of MSM or PBPK for an intended purpose, limiting the use of PBPK models to those applications that can benefit from its unique strengths, such as what-if scenario testing to understand the

effect of dose staggering, and extrapolating DDI effects from studied to unstudied populations.

Nicolas Frey (Roche):
ICH M15 Model Informed Drug Development – Steps Toward Harmonized Guidance

Nicolas Frey is a senior leader in Predictive Modeling and Data Analytics at Hoffmann-La Roche, with over 25 years of experience in applying pharmacometric approaches to clinical drug development within the pharmaceutical industry. He has contributed to more than 20 global filings across various therapeutic areas. He currently serves as the EFPIA Topic Leader in the ICH M15 Expert Working Group.

Abstract
M15 is a multidisciplinary guideline endorsed for development by ICH in November 2022. Once completed, it will provide overarching principles and good-practices guidance for model-informed drug development (MIDD), applicable to all current modeling and simulation approaches (doi:10.1002/cpt.3006). The guideline introduces the concept of risk-based assessment and advocates for upfront cross-functional strategic planning, along with enhanced multidisciplinary communication within and between regulatory agencies and industry scientists. This approach aims to improve the efficiency of drug development and regulatory decision-making. The guideline is scheduled for public consultation in Q4 2024. This presentation will introduce the concept of risk-based assessment, highlight the value of multidisciplinary team alignment on MIDD strategy, and emphasize the importance of early alignment with regulators.

Jan Schlender (Novartis):
Best Practices in PBPK for the OSP Suite Community

Jan is a Director and Site Head for Modeling & Simulation at Novartis in Basel. He has more than a decade of experience in pharmacometrics and mechanistic modeling and simulation in the pharmaceutical industry. Jan studied pharmacy at the University of Bonn, the National Taiwan University and University of Florida. He did his PhD in PBPK modeling of elderly individuals at Bayer in affiliation with the University of Bonn. After graduation, he worked at Bayer in different roles in model-informed drug development.

Abdullah Hamadeh (University of Waterloo):
The FDA Model Master File: Standardization of M&S practices to support the development and approval of dermatological products

Abdullah Hamadeh received his PhD in control systems engineering from the University of Cambridge and conducted postdoctoral work in systems and synthetic biology at MIT. He is currently a Research Associate with the School of Pharmacy at the University of Waterloo. His broad research interests encompass pharmacokinetic modeling, quantitative systems pharmacology, and epidemiology. Presently, his work centers on developing open-source computational tools for in vitro-in vivo extrapolation, virtual bioequivalence assessment, and

global sensitivity analysis, with a particular focus on mechanistic dermal absorption modeling. He is also a contributor to the Open Systems Pharmacology Suite.

Abstract
Approaches to the development of a pharmacokinetic Model Master File (MMF) framework have, in recent months, been the subject of active discussions between drug regulatory agencies, academia, and industry. An MMF may be viewed as a validated repository of the ADME mechanisms governing drug pharmacokinetics in a range of specified contexts. Its value lies in its capacity to robustly predict drug disposition and its acceptance as a reference model structure, with associated parameter values, all supported by experimental data and documentation.
Within the Open Systems Pharmacology (OSP) Suite, the well-established Qualification Framework ensures the validity of the platform's PBPK models with each new release, addressing many of the intended goals of an MMF.
This presentation will explore recent developments and challenges in advancing the OSP Skin Permeation Model toward an MMF. It will also discuss how these approaches can be generalized to other mechanistic models simulating localized drug disposition. Key topics will include defining the scope of an MMF, managing uncertainty and variability, and modeling formulation effects.

Wilbert de Witte (ESQlabs):
PBPK-QSP of FcRn Inhibitors and the use of the PK-Sim FcRn Model

Wilbert de Witte is a principal scientist at ESQlabs where he leads the large molecule platform. Before joining esqLABS, he worked at Ablynx NV, later Sanofi Ghent, on the preclinical and clinical development of NANOBODY® therapeutics. He developed several PBPK and PBPK-QSP models as well as traditional TMDD and PKPD models for mechanistic analysis of in vitro, in vivo, and clinical data. He accumulated in-depth knowledge on the behavior of large molecules in different modalities and with various target binding characteristics. Wilbert de Witte obtained his Master's degree in Bio-Pharmaceutical Sciences from Leiden University (the Netherlands). For his PhD thesis, he studied the impact of drug-target binding kinetics on in vivo drug action at the department of Pharmacology at Leiden University.

Abstract
The OSP suite is equipped with a valuable large molecule model to describe the biodistribution and catabolism of (protein-based) large molecules. An important parameter in this model that determines the pharmacokinetic half-life of large molecules is the affinity to FcRn. Monoclonal antibodies, endogenous IgG, and serum albumin bind to FcRn in the endosome for salvaging and recycling after pinocytotic uptake, which prolongs their half-life. This mechanism has been broadly recognized and is incorporated in currently available PBPK models.
Newer types of large molecules have been designed and developed, which also bind to FcRn in the plasma space for various mechanistic reasons. To incorporate FcRn binding affinity in PBPK models, binding in the plasma space and subsequent internalization into the endosome needs to be explicitly represented. Here we describe the large molecules model in PK-Sim® and its applicability to molecules with FcRn binding affinity in plasma. We also describe an extension of this model to ensure a more mechanistic description of the internalization of FcRn and the FcRn-drug complexes. Finally, we explore both the newly developed model and the original FcRn model to obtain a better understanding of

the driving parameters for the model behavior and how the model can be adapted if necessary.

Erik Sjögren (Pharmetheus) & Salih Benamara (Sanofi):
Modeling Subcutaneous Absorption & Immunogenicity of Large Molecules

Erik Sjögren, Ph.D., is a principal consultant and the PBPK-QSP platform scientific lead at Pharmetheus, focused on model informed drug development and strategies for application of physiologically based pharmacokinetics (PBPK), quantitative system pharmacology (QSP) and biopharmaceutics modeling. As Associate Professor at the Department of Pharmaceutical Biosciences, Uppsala University, his research involves PBPK and QSP as well as drug absorption, pharmaceutical formulations, and drug delivery. He has published over 50 articles in peer-reviewed journals. In addition, he tutors courses, supervises students, and contributes to scientific networks and meetings. He acts as Pharmetheus' and Uppsala University's representative in the Management Team of the Open System Pharmacology (OSP).

Salih Benamara is a pharmacist with a Master's degree in Pharmacokinetics, specializing in PBPK modeling for large molecules. He previously completed a project focused on evaluating the biologic module of GastroPlus© and developed a beta version that incorporated the expression of soluble antigen targets in the blood compartment during an internship with SimulationPlus and Phinc Development. He is currently pursuing a PhD in PBPK modeling for biologics in collaboration with Sanofi, Pharmetheus, and the University of Aix-Marseille in France. The project aims to expand the large molecules model in PK-Sim©, which was originally designed for intravenous administration of monoclonal antibodies, to include the modeling and prediction of drug absorption and bioavailability following subcutaneous administration.

Abstract
Subcutaneous (SC) injection is a common route of drug administration for both small molecules and biologics. For therapeutic proteins (TPs), there is an unmet need for means to adequately characterize absorption, bioavailability, and immunogenicity after SC administration, due to the limited predictive reliability of animal studies. This presentation will include following aspects, 1) the outlines of a physiologically based SC absorption model and a quantitative systems pharmacology (QSP) model for local and systemic immunogenicity implemented in MoBi, 2) an evaluation of the model's capability to predict TP absorption and bioavailability.
1) The open-source platform Open Systems Pharmacology Suite (OSPS) was used for model development with PK-Sim and MoBi. Briefly, the SC absorption model adopts spatial-temporal SC tissue distribution harmonized to the general compartmental organ structure in PK-Sim. A model for local immunogenetic processes was implanted and linked to a systemic QSP model of immunogenicity previously reported, both including key biological processes for immunogenicity as well as protein and host-specific characteristics.
2) The evaluation of SC absorption and bioavailability was performed using a database containing in vitro drug properties and in vivo PK data of 31 biologics (mainly mAbs) following IV and SC administration. Briefly, IV plasma concentrations data for each drug were used to estimate the binding to FcRn receptor (FcRn Kd). The established IV model was then used to inform the SC model. Model performance was evaluated by visual comparison of the simulated concentration-time profiles to the observed in vivo PK data and predictive errors for AUC, Cmax and bioavailability. The SC PBPK model, informed by the estimated FcRn Kd, was able to successfully capture, within a 0.80-1.25-fold difference, observed AUC and Cmax for 60% of the database (18 mAbs), across studies

and doses. Furthermore, the model achieved prediction accuracy within 0.50–2.00-fold range for most of the examined cases, 100% for Cmax and 94% for AUC.
As the SC route of drug administration gains popularity, there is an increased need for means to support SC specific decisions at different stages of the drug development process. The favorable predictive performance achieved by the implemented SC module confirms the potential of the physiologically based components in the OSPS platform, highlighting its usefulness as a valuable tool for enhancing PBPK modeling of mAbs administered SC.

André Dallmann (Bayer HealthCare SAS):
Modeling Motherhood I: Pregnancy PBPK in the Era of Personalized Medicine

André Dallmann is a Scientist for Systems Pharmacology and Science Fellow in the department of Model-Informed Drug Development at Bayer. He completed his PhD at the University of Münster, Germany, in 2017 with a focus on PBPK modeling in pregnant populations. After being a postdoctoral researcher at the University Children's Hospital in Basel, he joined Bayer in 2018. Earlier this year, he was elected as editorial board member of The Journal of Clinical Pharmacology. His research interests include obstetric pharmacology and PBPK modeling for pregnant people. He has co-authored more than 50 peer-reviewed articles and book chapters together with multiple scientists across academia, industry, and regulatory agencies.

Abstract
Drug use among pregnant individuals is common and increasing. Anatomical and physiological changes during pregnancy, such as increases in total body water, fat mass, and cardiac output, along with the induction or suppression of drug-metabolizing enzymes and transporters, can significantly alter drug pharmacokinetics. However, the underrepresentation of pregnant individuals in clinical trials results in a lack of safety and efficacy data, posing a public health challenge. Physiologically-based pharmacokinetic (PBPK) modeling shows promise in enhancing a mechanistic understanding of pharmacokinetic changes during pregnancy. Reflecting this potential, publication rates of pregnancy PBPK models have recently surged, with over 250 articles since 1980. Today, pregnancy is the 3rd most frequently covered research topic in OSP-based articles and pregnancy PBPK models developed in OSP have been presented for more than 30 compounds. For 22 of these compounds, pharmacokinetic parameters were available in vivo and were used for model evaluation, showing a good predictive performance, with 71% and 98% of predicted maternal AUC values falling within a 1.25-fold and 2-fold error range, respectively. Despite this progress, fetal exposure modeling remains challenging, requiring additional clinical data and refined models. With the FDA increasingly issuing post-marketing required (PMR) studies, there is an opportunity to leverage PBPK models to improve therapeutic outcomes for pregnant patients while reducing the reliance on PMR studies.

Kathleen Job (The University of Utah):
Modeling Motherhood II: An approach to modeling drug exposure during lactation

Dr. Kathleen Job is currently a Research Assistant Professor with the Department of Pediatrics, University of Utah School of Medicine, and a delegate of the American Board of Clinical Pharmacology. She earned her PhD in Bioengineering, and subsequently completed the Utah

Clinical Pharmacology Fellowship Program. Dr. Job has over 7 years of experience in the design of both drug and device clinical studies in diverse populations. Dr. Job's clinical research expertise focuses on understanding drug disposition and action from conception through adulthood, with a focus in pregnancy and lactation. Dr. Job's interests are in integrating physiology and pharmacology into approaches for designing, conducting, and interpreting clinical trials.

Abstract
Many mothers and their medical providers struggle with the decision to take necessary medications. Over 89% of pregnant mothers and up to 80% of lactating mothers will use at least one prescription or over-the-counter medication. Most of the prescribed medications are used off-label as most medications have insufficient published data to determine efficacy for mother and safety for baby. Determining efficacy and safety through traditional clinical trials is challenging due to ethical, legal, and practical reasons. In special populations such as pregnant and lactating mothers, the use of opportunistic sampling studies combined with physiologically-based modeling techniques is a growing method to 1) address the challenges of conducting intensive pharmacokinetic studies in these populations, and 2) better understand pharmacokinetic changes in the absence of sufficiently informative clinical data. The utility of this method is demonstrated by a recently built pharmacokinetic model for oxycodone transfer into breast milk.

Julia Macente (KU Leuven) & Nina Nauwelaerts (KU Leuven): Modeling Motherhood III: Lactation PBPK modeling

Nina Nauwelaerts obtained her Master's in Drug Development at KU Leuven, and Julia Macente is a pharmacist with a Master's degree in Pharmaceutical Sciences from the State University of Maringá. They are currently pursuing their PhDs at KU Leuven in Belgium under the supervision of Dr. Pieter Annaert at the Drug Delivery and Disposition lab. Their research focuses on developing PBPK models to evaluate drug exposure in human milk and the subsequent systemic exposure in infants. This work is part of the IMI project Conception, which aims to generate information about the use of medicines during pregnancy and breastfeeding.

Abstract
Breastfeeding is associated with beneficial effects for both mother and infant. More than 50% of postpartum women require medication; however, there is a lack of information to support risk assessment during lactation and ensure the safety of breastfed infants. This work aimed to develop a framework for physiologically-based pharmacokinetic (PBPK) predictions of the transfer of medicines into human milk and the subsequent infant exposure to maternal medicines via breastfeeding. PBPK models were developed for non-lactating adults in PK-Sim/MoBi v9.1 (Open Systems Pharmacology). The PBPK models were then extended for postpartum women, and the concentration of medicines in human milk was parameterized based on the semi-mechanistic model developed by Koshimichi et al. (2011). Simulations were performed for the postpartum population, estimating the total medicine exposure in human milk relative to maternal plasma (M/P ratio) and infant exposure. The lactation PBPK models provided reasonable predictions for eight medicines, while two medicines showed overprediction of human milk concentration. Ongoing efforts focus on integrating in vitro permeability coefficients across the blood-milk barrier into the PBPK models. PBPK models hold promise for reliable and early predictions of medicine exposure during lactation, informing product labeling in the absence of clinical data.

Annika Schneider (Bayer AG):
PBPK Modeling for Hepatically Impaired Patients

Annika Schneider holds a Bachelor's degree in Molecular Biomedicine from the University of Bonn and a Master's degree in Systems Biology from the University of Heidelberg. She completed her PhD at RWTH Aachen in collaboration with Bayer AG, focusing on "Model-informed Treatment Optimization of Liver Cirrhosis Patients." Since 2021, Annika has been working at Bayer AG in model-informed drug development, specializing in Physiologically Based Pharmacokinetic (PBPK) modeling. Recently, she has taken on the role of PBPK Lead.

Abstract
Liver cirrhosis is a progressive disease that is accompanied by various pathophysiological changes. Due to multiple ADME-related pathophysiological alterations, the estimation of the net PK change in cirrhotic patients is complex. Its mechanistic nature makes PBPK modeling a valuable tool to link knowledge on physiological changes in diseases and to predict their influence on drug PK. For the integration of pathophysiological changes into a PBPK model, such changes need to be quantified appropriately. To date, published liver cirrhosis pathophysiology repositories contain only average changes for three distinct disease stages based on the Child-Pugh classes, which limits the clinical applicability. Therefore, the aim of this study was the development of a pathophysiology repository that (1) describes continuous system changes throughout the disease progression, (2) quantifies mean changes as well as population variability, and (3) contains information on parameters that have not been included in the published repositories. For this purpose, data was gathered in an extensive literature research and processed using an elaborate MCMC-based approach that allowed the proper handling of heterogeneous literature data and information on population variability. The resulting repository is based on 216,609 data points from 68 literature studies and 208,851 patients from real-world data and contains information on 30 physiological parameters. The ensuing simulations of the pharmacokinetics of several drugs in cirrhosis patients revealed good predictive performance of the approach. In summary, the approach provides an advancement in the field of PK modeling in liver cirrhosis patients, possibly facilitating the planning and analysis of clinical studies in these patients and bringing the field closer to the replacement of clinical studies in liver cirrhosis patients with virtual studies.

Stephan Schaller (ESQlabs):
OSP Community Engagement & Dissemination

Juri Solodenko (Bayer AG):
OSP Software Release Management and (Re-)Qualification Framework

Juri Solodenko studied mathematics and computer science at the University of Hannover, Germany, and received his diploma in 2001. He then joined the process engineering software development team at Bayer AG. Since 2017 he has been working for Bayer Pharmaceuticals R&D. His main focus is the development of software solutions in the area of physiologically based pharmacokinetic / pharmacodynamic modeling. Since 2002 he is one of the main software developers of the Open Systems Pharmacology Suite.

Abstract
This presentation will explore the strategic processes behind the release planning and management of the Open Systems Pharmacology (OSP) Suite, highlighting our commitment to maintaining high quality standards for new developments. Central to our discussion will be the rigorous quality assurance protocols we employ, with a particular focus on

- **Platform validation**: refers to the process of confirming that the PBPK software platform accurately represents the mathematical models and algorithms it is supposed to implement. This involves verifying that the software correctly performs the calculations and simulations based on the underlying physiological and pharmacokinetic principles.
- **Platform qualification for intended use**: involves demonstrating that the PBPK software platform is suitable for the specific research or regulatory purpose it is intended to be used for. This goes beyond general validation and includes assessments of the platform's features, functionalities, and performance metrics in the context of specific use cases. For instance, if a platform is intended for predicting drug-drug interactions, qualification would involve showing that it can accurately model and predict these interactions for a range of compounds.

In addition, we will provide an in-depth look at the OSP (Re-)Qualification Framework, highlighting its automation and the role it plays in the software lifecycle. This framework is central to ensuring that the OSP Suite remains reliable, meets quality standards and is suitable for the various scientific or regulatory purposes it serves.
The presentation will conclude with a discussion of the criteria for new software contributions to the OSP platform in the context of our established quality assurance strategy.

Stephan Schaller (ESQlabs):
Building and Funding a Sustainable Community for the OSP Suite