GMP

Groupe *de* Métabolisme *et* Pharmacocinétique

35th GMP SYMPOSIUM

18th - 20th October 2023

Paris -France

Espace centenaire

contact@gmp.asso.fr

www.gmp.asso.fr

GMP
Groupe de Métabolisme et Pharmacocinétique

35th GMP SYMPOSIUM

in Memory of Professors

Jean-Michel Scherrmann

&

Janine Brès

Jean-Michel Scherrmann

Janine Brès

18th – 20th October 2023

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GMP Groupe de Métabolisme et Pharmacocinétique

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Oral Communication (Abstract + Biography) **(with active links)**

Day 1 : 18th October 2023

Day 2 : 19th October 2023
What's new in the Biologics World?

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Oral Communication (Abstract + Biography) **(with active links)**

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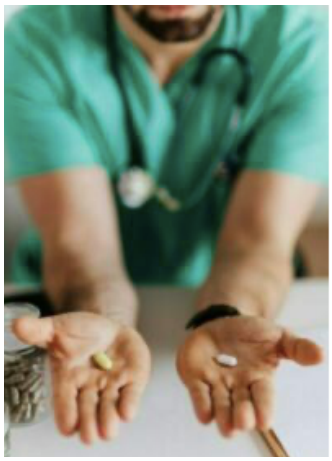
PROGRAM : detailed

Day 1 : 18th October 2023

09:30 – 12:30 **Workshops**

Pediatric PBPK workshop using GastroPlus™

In this 3-hour workshop, the general concepts of developing a PBPK model will be reviewed, followed by an in-depth focus on the use of PBPK modeling for pediatric simulation. The aim will be to understand the difference between adult and pediatric simulations, highlighting the points of attention to ensure quality predictions. Examples will be provided, and hands-on exercises performed.



Therapeutic Monitoring and Treatment Individualisation

Jointly organized by STP-PT (Suivi Thérapeutique Pharmacologique & Personnalisation des Traitements) unit of the SFPT (Société Française de Pharmacologie et de Thérapeutique), more information to come

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PROGRAM

Day 1 : 18th October 2023

12:30 – 13:30 **Arrival and Registration Welcome Coffee/Tea**

13:30 – 13:40 **Welcome to 2023 GMP Symposium**

13:40 – 15:10 **Session 1**

Translation of Drug-Drug-Interaction from *In-Vitro to In-Vivo*

Chairs: Olivier Nicolas (Sanofi)**, Jeremy Perrier** (PhinC)**,**
Yannick Parmentier (Servier)

Microphysiological systems aim to mimic the complex structure, microenvironment and physiological functions of human organs, so it has gradually become an ideal tool for in vitro ADMET, drug-drug-interaction and pharmacological studies. The aim of the session is to highlight the advantages of those models and how to translate the data generated to the human situation in particular for DDI predictions.

S1.1 Amélie Moreau (Servier)
MicroPhysiological Systems to address Pharmacokinetics or Drug interactions issues

S1.2 Christian Maass (EsqLABS)
Humanizing Drug Development. How Organ-on-Chips and their digital twins improve prediction of clinical outcomes

S1.3 Felicien Le Louedec (Institut Universitaire du Cancer, Toulouse) Bioavailability and the extent of drug-drug interactions with oral kinase inhibitors

15:10 – 15:13 **3 min Sponsor Talk** SOLVO® BIOTECHNOLOGY A CHARLES RIVER COMPANY

15:13 – 15:40 **Coffee Break and Poster Session**

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15:40 – 17:10 Session 2

Update on Drug Metabolism Strategy

Chairs: Madeleine Coimbra (Sanofi), **Olivier Nicolas** (Sanofi), **Yannick Parmentier** (Servier)

Over the last years, the field of metabolite investigations has evolved. New guidelines requirements and the emergence of new modalities and new technologies foster the choice of new strategies for the metabolite profiling studies. This session will provide an overview on the last trends for metabolite identification for biologics and small drugs, including the impact on DDI assessment.

S2.1 Jonathan Dhenin (Sanofi)
Monitoring biotransformations of biotherapeutics in mouse plasma using innovative top-down and middle-down mass spectrometry
S2.2 Esther Van Duijn (TNO)
The role of microtracers in drug development: Generating human mass balance data and metabolites profiles as early as possible
S2.3 Patricia Moliner & **Priscilla Brun** (Sanofi)
AMS to support human metabolism and DDI assessments of a highly metabolised compound

17:10 – 18:05 Student Poster Blitz sponsored by SOLVO BIOTECHNOLOGY A CHARLES RIVER COMPANY "Master 2" & SERB Pharmaceuticals "PhD"

Chairs: Sarah Lobet (Tours University), **Jessica Ou** (Aix-Marseille University), **Carla Troisi** (Bologne University), **Anna Zerdoug** (Rennes University)

18:05 – 19:30 Poster Session & Cocktail sponsored by Admescope A SYMERES COMPANY

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Day 2 : 19th October 2023

What's new in the Biologics World?

8:00 – 8:30 Welcome Coffee/Tea

8:30 – 9:30 Key Note Speaker: Daniel Kramer (Sanofi)

Immunogenicity: Challenges and Opportunities for the Development of Biotherapeutics

Chair: Madani Rachid (Sandoz)

Immunogenicity presents a major hurdle for the development of biotherapeutics as it can impair both efficacy and safety of the treatment. This lecture will introduce the audience to the concept of immunogenicity and will discuss the specific challenges it provides for the development of biologics. It will also review novel approaches to anticipate, predict and prevent the formation of anti-drug antibodies.

09:30 – 10:00 Coffee Break and Poster Session

10:00 – 12:00 Session 3

New Approaches in PK Modelling and QSP of Biologics

Chairs: Maxime Le Merdy (Simulations Plus), **Jeremy Perrier** (PhinC), **Carla Troisi** (Bologne university), **Sarah Lobet** (Tours University), **Isabelle Deprez** (Certara)

The world of Biologics is expanding with new entities and new targets, thus requiring new approaches to understand the PK and interactions with its biological environment.
This session will present how modeling is used to assess new targets and support the development of new biological drugs.

S3.1 Piet van der Graaf (Certara)
Quantitative Systems Pharmacology to guide complex biologics drug development and regulatory decision-making
S3.2 Wilbert de Witte (EsqLABS)
Integrated QSP-PBPK modeling for biologics in drug discovery and development

S3.3 Eric Gerard Fernandez (Boehringer)
An immuno-oncology QSP platform model for simulating treatment with oncolytic virus VSV-GP
S3.4 Jérémy Seurat (The Weitz group: Quantitative Viral Dynamics)
Modeling of in vivo bacteriophage dynamics

12:00 – 12:45 **GMP Assemblée Générale (ordinaire et extraordinaire)**

12:45 – 14:00 **Lunch & Posters**

14:00 – 15:30 **Session 4**

Spotlighting on Bioanalytical Data for Biologics PK Interpretation

Chairs: Christine Bain (Active Biomarkers)**, Madeleine Coimbra** (Sanofi), **Yannick Parmentier** (Servier)

Understanding the pharmacokinetics and pharmacodynamics of biologic therapeutics, and the bioanalytical methods they rely on, is key to build an optimal drug development plan. As the development of the drug progresses, so do the methods used for bioanalysis. The reliability of the bioanalytical results is a prerequisite for correct interpretation of PK profiles.
Therefore, for pivotal nonclinical and clinical studies, it is essential to employ well-characterized and fully validated bioanalytical methods to yield accurate and reliable results. This session will provide an overview of the methodologies and illustrate the topic with a few examples from in-vivo preclinical cases to clinical settings.

S4.1 Nicolas Fourrier (Inotrem)
Gearing up your bioanalysis for your drug development
S4.2 Erwan Werner (Servier)
PK assay design for biological entities – Why format and key reagents matter
S4.3 Maximilian Breitner (Sandoz)
Design, development and validation of a pharmacokinetics assay for the clinical development of a biosimilar

15:30 – 15:33 **3 min Sponsor Talk** Admescope A SYMERES COMPANY

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15:33 – 16:00 **Coffee Break and Poster Session**

16:00 – 17:00 **Session 5**

New Trends in PK and Immunogenicity Assessments in Ophthalmology

Chairs: Olivier Petricoul (Novartis)**, Olivier Nicolas** (Sanofi)

Over the last 10-15 years the treatment options in ophthalmology have considerably evolved. Injections of monoclonal antibodies and smaller proteins have emerged as a new standard of treatment, and recently gene therapy has also been introduced. In this session a few examples will be presented that highlight the new challenges of assessing PK and immunogenicity in ophthalmology and how to define the dose.

S5.1 Fraser McBlane (Novartis)
Dose selection for ocular gene therapies
S5.2 Katrijn Bogman (Roche)
The right regimen for every patient in ophthalmology, a drug development example

17:00 – 18:00 **One Step Aside**

Impact of Contaminants/Drugs on Public Health and Environment assessed by PBPK

Chairs: Fabrice Hurbin (Sanofi)**, Quyen Nguyen** (Novartis)

In a global context of environmental crisis, the chemical risk assessment is a matter of public health and environmental protection. This session will provide an overview on how PBPK modelling plays a key role for this risk assessment.
1. Thomas Gastellu (ANSES)
Lifetime exposure in the dietary risk assessment, usefulness of PBPK models
2. Katharina Brotzmann (Heidelberg University)
Fishing for answers: How zebrafish helps to assess the risk of pharmaceuticals in the aquatic environment

19:30 **Gala Dinner**

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Day 3 : 20th October 2023

8:30 – 9:00 **Welcome Coffee/Tea**

9:00 – 11:00 **Session 6**

Supporting Decision-Making in Drug Development

Chairs: Fanny Gallais (Pharmetheus),**Laurence Del Frari** (Pierre Fabre)**,**
Madani Rachid (Sandoz), **Quyen Nguyen** (Novartis)

Decision making occurs at all stages of drug development. Optimus Project from FDA as well as different tools such as clinical pharmacology and/or pharmacometrics are key to support decision making. In this session we will hear about examples of how to improve drug development decision-making.

S6.1 Matthias Hoch (Novartis):
Applying a totality of evidence approach including model-informed drug development (MIDD): asciminib development in the context of FDA's Project Optimus
S6.2 Andreas Lindauer (Calvagone)
From model to decisions: effective simulations to support drug development
S6.3 Niclas Jonsson (Pharmetheus)
Using Forest plots to support drug development decision making – difficulties and opportunities
S6.4 Roland Baumgartner (Sandoz)
Application of pharmacometrics analysis in clinical biosimilar development

11:00 – 11:30 **Coffee Break**

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11:30 – 12:30 **Session 7**

Digital Data Sciences in Drug Development

Chairs: Olivier Barberan (Elsevier)**, Etienne Chatelut** (Institut Universitaire du Cancer Toulouse), **Quyen Nguyen** (Novartis)

The use of digital tools and their impact on drug development will be discussed in this session. Illustration will be performed with case studies on Omics Sciences, Biomarkers and Digital Biomarkers along R&D value chain

S7.1 Sebastien Tourlet (Capgemini)
Data Science & Artificial Intelligence : enablers to support and accelerate drug development and translational science evidence

S7.2 Romain Clément (ArcaScience)
AI discovery of novel safety biomarkers in a preclinical environment applied to multiple sclerosis

12:30 – 12:45 **Master's Poster Awards sponsored by** SOLVO BIOTECHNOLOGY A CHARLES RIVER COMPANY

PhD's Poster Awards sponsored by SERB Pharmaceuticals

12:45 – 12:55 **Closing Remarks**

12:55 – 14:00 **Farewell Lunch**

GMP
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Oral Communication

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Session 1

Translation of Drug-Drug-Interaction from In-Vitro to In-Vivo

Session 1.1

MicroPhysiological Systems to address Pharmacokinetics or Drug interactions issues

Amélie Moreau, Associate Principal Scientist
Technologie Servier, Gif sur Yvette, France.

Pre-clinical Drug development requires the most relevant models to assess the issues occurring during drug candidate evaluation. Years of pharmaceutical research have explored many ways to answer these questions using engineered cell culture, dedicated animals and other models. During the last decade, cell model miniaturizing, 3-dimensional co-culture, dynamic fluid, biosensor, multicompartment systems have emerged, allowing us to go further and build new models that mimic better human physiology. At this stage, microphysiological systems term embrace a broad type of in vitro system which fit with different needs. In this talk, I will share with you the relevance of the use of specific model for ADME-T issues.

Dr. Amélie Moreau has made her Ph.D. in molecular biology, dealing with Detoxication process and crosstalks occurring with other physiologic pathways within Pr. Patrick Maurel's Laboratory in Montpellier, France. She then joined Pr. Olivier Fardel's team in Rennes (France) where she explored deeper drug transporters functioning. Her experience in drug-drug interaction and in vitro pharmacokinetic in Servier DMPK's team help her to have a great overview on the different ways to explore drug fate in human body and strengthen her will to work with more relevant and inclusive models such as MPS to reach the goal of personalized medicine.

Session 1.2

Humanizing Drug Development.
How Organ-on-Chips and their digital twins improve prediction of clinical outcomes

Christian Maass, Principial Scientist, Lead Digital Organ-on-Chip Platform
esqLABS GmbH, Saterland, Germany

Organ-on-chips (OoCs) have emerged as a promising tool to revolutionize drug development, holding great potential to embody human physiology in vitro with greater precision than animal models. Yet, the comparative advantage of OoCs over other in vitro models and animal testing in predicting and translating to human outcomes remains to be established and thoroughly investigated.

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To overcome this hurdle, esqLABS is developing a cutting-edge workflow that marries OoC data with computational modeling – so called digital twins, offering a powerful tool to accelerate drug discovery. The synergy between these two technologies provides a deeper mechanistic understanding of the biological principles underpinning drug mechanisms of action. This knowledge can then be applied to optimize experimental designs, speeding up the drug discovery process and paving the way for more effective treatments, reliably, sustainable, and at reduced cost.

To demonstrate the impact of this new approach, esqLABS presents DigiLoCS, a digital liver-on-chip simulator for the simulation of hepatic metabolism. The developed software platform comprises an advanced mathematical description of the underlying biological processes in liver-on-chips. DigiLoCS outperformed state-of-the-art approaches by 70-100%, offering a more accurate prediction of human pharmacokinetics, without the need for animal testing or additional biological experiments.

To assess the impact of predicting human pharmacokinetics more accurately, esqLABS provides a head-to-head comparison with DigiLoCS and state-of-the-art approaches in a drug-drug interaction study.

Predicting the safety and efficacy of novel drugs before they are tested on humans is essential to de-risk drug development and accelerating the time to market in a more sustainable and reliable way.

Christian Maass is a physicist and computational biologist with over 15 years of academic and industrial international experience. He received his Master in Medical Physics from the University College London in 2012 and PhD from the University of Heidelberg in 2015 and worked as a postdoctoral researcher at the Massachusetts Institute of Technology (MIT), Cambridge, MA, USA until 2018. He specializes in developing and applying digital twins for micro-physiological systems and organs-on-chips (OoC). He is passionate about the integration of computational modeling and biological experiments for translational pharmacology applications. As a principal scientist in industry, Dr. Maass works on applications in various therapeutic areas, e.g. neurodegenerative, inflammatory, and metabolic diseases (Alzheimer, rheumatoid arthritis, NASH/NAFLD). Among others, he developed individualized PBK models for molecular radiotherapy (leukemia), automated workflows for big data (*omics), network-based analysis of inflammation diseases, and mechanistic modeling of OoC data. He is also leading the division to develop further strategies integrating OoC data and computational modeling for translational pharmacology applications.

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Session 1.3

Bioavailability and the extent of drug-drug interactions with oral kinase inhibitors

Félicien Le Louedec, PharmD, PhD
Institut Claudius Regaud, Institut Universitaire du Cancer de Toulouse Oncopole, Centre de Recherche en Cancérologie de Toulouse, INSERM U1037, Université Paul Sabatier, Toulouse France

Oral protein kinase inhibitors (PKIs) share many common physico-chemical and pharmacokinetic properties. However, their oral bioavailability varies greatly, from 3% for ibrutinib to nearly 100% for imatinib for instance. In addition, the extent of drug-drug interactions (DDIs) varies between them in spite of their common metabolism through the CYP3A4. We show that the lower the bioavailability, the higher is the interindividual variability of pharmacokinetics (PK) and the higher the extent of DDIs. We demonstrate that these differences are not only explained by variability in the resorption processes, but also in terms of metabolism, especially due to the first-pass effect in the gut more than in the liver. The benefit of the application of these concepts in clinical settings and in population modeling is also discussed. Overall, our objective is to apply fundamental PK concepts to the management of clinical issues encountered with these oral anticancer drugs.

Félicien Le Louedec graduated from Pharmacy at the University of Toulouse in 2019 after a 4-year residency in hospital pharmacy. He defended his PhD entitled “Model-informed precision dosing of anticancer drugs” in 2023. He is currently a clinical pharmacologist at the “Institut Universitaire du Cancer de Toulouse – Oncopole”, a teacher in Pharmacology at the University of Toulouse III and belongs to the Cancer Research Center of Toulouse. His research focus is the individualization of doses of anticancer drugs, especially the use of population pharmacokinetics models in the context of therapeutic drug monitoring. He has authored publications in the field of pharmacometrics and clinical pharmacology of anticancer drugs, whether about cytotoxics, monoclonal antibodies, or oral protein kinase inhibitors.

Session 2

Update on Drug Metabolism Strategy

Session 2.1

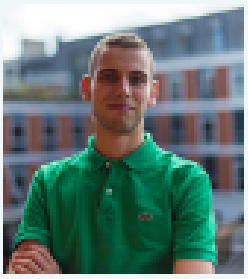
Monitoring biotransformations of biotherapeutics in mouse plasma using innovative top-down and middle-down mass spectrometry

Jonathan Dhenin[1], Valérie Lafont[1], Mathieu Dupré[1], Norbert Zombori[1], Olivier Pasquier[1], Alain Krick[1], Julia Chamot-Rooke[2], Christine Mauriac[1]

[1] DMPK, Sanofi R&D, Chilly-Mazarin, France

[2] Institut Pasteur, Université Paris Cité, CNRS UAR2024, Mass Spectrometry for Biology, Paris, France

Today, within the R&D portfolio of pharmaceutical companies, monoclonal antibodies are progressively supplanted by new generation biotherapeutics. Among these new drugs, hybrids or multi-specifics, in-house engineered constructs may present unexpected structural in vivo instabilities (also known as biotransformations) that will impact their activity. Therefore, it becomes important to characterize their metabolism to possibly re-design better candidates. All the methods developed for the analysis of small molecules have thus to be revised to face the challenges inherent to large hybrid molecules. Conventional mass spectrometry-based proteomics approaches at the peptide level are not sufficient for the characterization of the various forms of the biotherapeutic drug (proteoforms) potentially present in biological samples. For this reason, we developed complementary approaches at the scale of the intact protein or its subunits. These respectively so-called top-down and middle-down strategies hold great promise to precisely characterize the fate of biotherapeutics once administrated. This presentation will focus on the work undertaken to apply these yet innovative but still challenging strategies to in vivo samples from pharmacokinetics studies, especially regarding the efficient isolation of low abundance biotherapeutic metabolites from thousands of endogenous proteins by automated immunocapture. In combination with high resolution mass spectrometry, these innovative approaches can reveal, with an unprecedented sensitivity and resolution, multiple in vivo biotransformations undergone by engineered multi-specific hybrid biotherapeutics.



Jonathan Dhenin has an engineer degree in Analytical Chemistry from the ECPM Strasbourg (2018) and a PhD in Biological Mass Spectrometry from the Université Paris Cité (2023). Between 2018 and 2023 Jonathan gained expertise at the Institut Pasteur in various proteomics approaches to study protein-protein interactions as well as to characterize antibody-based biotherapeutics. In his thesis work Jonathan developed innovative proteomics strategies to characterize the in vivo metabolism of multi-specific hybrid biotherapeutics. Jonathan permanently joined Sanofi in 2023 as a Senior Scientist in the Metabolism team of the DMPK department where he pursues the implementation of innovative MS-based approaches to support metabolism studies of complex biotherapeutic modalities.

Session 2.2

The role of microtracers in drug development: Generating human mass balance data and metabolite profiles as early as possible

Esther van Duijn, TNO, Leiden, The Netherlands

It is possible to generate human ADME data early during drug development. Technological developments have led to the possibility to make adjustments to the clinical trial programs by the addition of a microtracer arm. Any Phase I study can become a human mass balance and metabolite profiling study, simply by including a microtracer in the cold dose. Due to the speed of the current AMS technology even discharge of subjects from the clinical site is supported in the mass balance part. Human metabolite profiling in combination with LC-AMS-hrMS will elucidate all human metabolites as early as Phase 1. Relevant metabolites can be selected for further toxicity testing in the appropriate animal species. Availability of the human metabolite profile early in development prevents late stage disappointment, saves animal lives and will direct (pre)clinical development. The technology has also been applied in a Phase 0/I single ascending dose study for a new biological entity. Early human PK data were generated showing dose-proportional pharmacokinetics across the doses administered.

Esther van Duijn is a senior research scientist within the biomedical AMS facility at the Netherlands Organization for Applied Scientific Research (TNO). She received her Ph.D. In the Biomolecular Mass Spectrometry group at Utrecht University focusing on native mass spectrometry. She continued to work in this field for several years. In 2012 Dr. van Duijn started her career within TNO and focused on the application of Accelerator Mass Spectrometry (AMS) and High Resolution Mass Spectrometry in drug development. She is the scientific expert within the AMS and Biomarker group and supports a fast-growing team of laboratory experts.

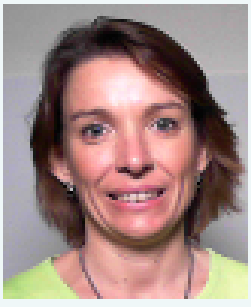
Session 2.3

AMS to support human metabolism and DDI assessments of a highly metabolized compound

Priscilla Brun, Patricia Moliner
Sanofi, Montpellier, France

Development of small molecule extensively metabolized may be an analytical challenge for metabolism and DDI evaluation. Through an example of a molecule under development, we will explain the strategy that has been put in place to evaluate highly metabolized compound. During in vivo metabolism profile comparison between human (using Ph1 MAD samples) and animals, the identification of metabolites highlighted two main circulating metabolites, above the 10% threshold of totality of quantify moieties in human plasma and exhibited higher human exposure than the parent drug.
Implementation of a fast-derisking strategy before Phase 3 start was decided. Despite a conventional approach for the human ADME study, due to the low level of circulating radioactivity, we were forced to use an ultra-sensitive and selective technique for counting single [14C] atoms: Accelerator Mass Spectrometry. The goal of this work was to support in vivo metabolism study in healthy male volunteers and refine the DDI plan.

Following graduate studies in cell biology and physiology, with a specialization in microbiology and virology at the University of Lyon I, Priscilla obtained her Master of Science degree in "evaluation of xenobiotics: use of in vitro models" at the University of Paris XII in 2005. Priscilla took charge of carrying out in vitro cardiovascular safety evaluation using manual and automated patch clamp in the DMPK-S department and then in DSAR-PS. In 2011, Priscilla took responsibility for the absorption, transport, and metabolic stability laboratory within the In Vitro Model entity, then enzymology and metabolism and took responsibility for the Enzymology and Metabolism group in 2020 in TMED/BCB.



Analytical chemist by training (BSc, ETSL Paris) Patricia Moliner worked more than 15 years in Bioanalysis as an expert in Mass Spectrometry to support PK analyses (2 French CROs and Sanofi). In 2012 Patricia developed her expertise in Mass Spectrometry in drug metabolism laboratory becoming an expert in Biotransformation and Metabolites Identification. She is now in charge of development projects for small molecule drugs from First In Human to Submission. She participates to 4 inter-companies working groups (IQ Consortium and EFPIA) to support new human ADME strategy.

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Key Note Speaker: Daniel Kramer

Sanofi, Frankfurt, Germany

Immunogenicity: Challenges and Opportunities for the Development of Biotherapeutics

Immunogenicity presents a major hurdle for the development of biotherapeutics as it can impair both efficacy and safety of the treatment. This lecture will introduce the audience to the concept of immunogenicity and will discuss the specific challenges it provides for the development of biologics. It will also review novel approaches to anticipate, predict and prevent the formation of anti-drug antibodies.

Dr. Daniel Kramer is currently "Global Scientific Advisor Immunogenicity" within the Translational Medicine & Early Development (TMED) function of Sanofi R&D. He holds a PhD in Biochemistry/Immunology from the University of Munich. In his current role at Sanofi he drives collaboration with project teams and helps resolving project issues, defines project strategies and facilitates regulatory aspects as related to immunogenicity. Prior to joining Sanofi as of December 2014, Daniel has held various positions with Merck Serono where he finally became responsible for all immunogenicity related issues and was the company´s point of contact to the health authorities. Daniel presented his work at numerous international immunogenicity conferences and is also chairman of the "European Immunogenicity Platform" EIP, bringing together participants from leading European biopharmaceutical companies and scientific institutions working in the area of immunogenicity

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Session 3

New approches in PK Modelling and QSP of Biologics

Session 3.1

Quantitative Systems Pharmacology to guide complex biologics drug development and regulatory decision makin

Piet H. van der Graaf, Certara, UK & Leiden University, The Netherlands

The significant potential impact of model-informed drug development (MIDD) on cost and efficiency of late-stage pharmaceutical R&D was already reported nearly 2 decades ago. However, despite adoption across industry and regulatory agencies, the attrition during earlier stages of drug development and discovery remains high, with Phase 2 success rate running well below 30% for most portfolios. More than a decade ago, this issue was recognized by the US National Institute of Health (NIH) who organized two workshops in response, which brought together leaders from academia, industry, and government in the field of systems biology and pharmacology/pharmacometrics. The white paper that arose from this initiative can be considered as one of the early milestones that defined quantitative systems pharmacology (QSP) as a sub-discipline within MIDD. Since this publication, QSP has been widely adopted across pharmaceutical industry and increasingly also by regulatory agencies.A main application of QSP is to guide discovery and development of complex biological drugs, since conventional pharmacokinetic/pharmacodynamic (PKPD) approaches often do apply to such novel therapeutic approaches. This will be illustrated with case studies from oncology, neuroscience, vaccines, and multi-specifics.

Piet van der Graaf is Senior Vice President and Head of Quantitative Systems Pharmacology at Certara and Professor of Systems Pharmacology at Leiden University. From 2013-2016 he was the Director of Research of the Leiden Academic Centre for Drug Research. From 1999-2013 he held various leadership positions at Pfizer in Discovery Biology, Pharmacokinetics and Drug Metabolism and Clinical Pharmacology. He was the founding Editor-in-Chief of CPT: Pharmacometrics & Systems Pharmacology from 2012-2018 before becoming Editor-in-Chief of Clinical Pharmacology & Therapeutics. Piet received his doctorate training in clinical medicine with Nobel laureate Sir James Black at King's College London and was the recipient of the 2021 Leadership Award from the International Society of Pharmacometrics (ISoP). He is an elected Fellow of the British Pharmacological Society.

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Session 3.2

Integrated QSP-PBPK modelling for biologics in drug discovery and development

Wilbert de Witte, esqLABS GmbH**,** Saterland, Germany

New modalities are rapidly increasing their share in the discovery and development of biologics. These new modalities introduce uncertainties with respect to their pharmacokinetics (PK), target interactions, and consequentially their pharmacodynamics (PD). The prediction of PD for new modalities in the absence of prior clinical or preclinical in vivo data is challenging, especially when the involved biological networks are not precisely known. However, the prediction of PK and target engagement can be based on PBPK models that contain the influence of the molecular properties in which the new modality differs from previously tested modalities. Such parameters are often available, especially in platform PBPK models that have been applied to small and large molecule drugs, large molecules of different sizes, in different species, for different targets, and for different diseases. The value of integrated PBPK and QSP models is illustrated by the example of FcRn inhibitors, where the new modality could be described by the existing PK-Sim large molecule model structure after updating the model implementation with preclinical model data. The value of target engagement models within whole-body PBPK models for biologics is illustrated by a recent investigation that demonstrated the impact of tissue volume, target turnover, target binding, and molecular size on tissue concentrations and target occupancy. A range of literature values for these parameters can be used for novel modalities where the system-specific parameters are unknown. We conclude that the integration of PBPK and QSP models offers valuable information and insight into the most relevant molecular and system-specific properties of (novel) biologic modalities in drug discovery and development.

Wilbert de Witte is a principal scientist at esqLABS, where he is responsible for the development and application of integrated PBPK-QSP models for large molecules.
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 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.

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Session 3.3

An immuno-oncology QSP platform model for simulating treatment with oncolytic virus VSV-GP

Eric Fernandez, Dr; Gabriela Gremel, Dr; Philippe Slos, Dr; Eva Germovsek, Dr; Fabio Savarese, Dr
Boehringer Ingelheim Pharma, Germany

Immunotherapy is one of the most promising therapeutic options of the last two decades in the cancer treatment area. However, there are also many challenges, such as, understanding the mechanism of action of targeted therapies, understanding the underlying immunosuppressive biology, its interaction with the immune system, the possible synergy with combination treatments such as other immunotherapy agents or standard of care options, and identifying additional biomarkers. A QSP platform model has been established to support immunotherapy programs at Boehringer Ingelheim, for example, the oncolytic virus VSV-GP. VSV-GP productively replicates in cancer cells, leading to a direct cancer cell lysis. In addition, it can activate the host innate and acquired immune responses via the release of cancer and viral antigens. The interplay of all these processes is complex and believed to be time dependent, therefore a comprehensive understanding of the numerous biological mechanisms involved is fundamental. Here we demonstrate the utility of a whole-body QSP model, initially calibrated using preclinical data, incorporating key processes such as immune system cell maturation, regulation, and trafficking as well as virus and cancer cell population dynamics. This model may prove an option to optimize VSV-GP treatment, either as a single agent or combined with other therapies such as immune checkpoint blockers.

Eric Fernandez is a geneticist who developed his career into systems biology in the early 2000s at the European Bioinformatics Institute, UK. He worked 10 years at a CRO where he collaborated with pharma companies on cancer systems pharmacology modelling. He then joined GSK Systems Modelling group in stevenage, UK, before joining Boehringer Ingelheim in 2018 in Biberach, Germany. At BI he works mainly on Quantitative Systems Pharmacology modelling in immuno-oncology.

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Session 3.4

Modeling of in vivo bacteriophage dynamics

Jérémy Seurat, The Weitz group: quantitative viral dynamics, Georgia Tech & University of Maryland, USA

The clinical development of bacteriophage therapy to treat antibiotic resistant infections faces the challenge of understanding the dynamics of phage-bacteria-host interactions. The proper kinetics of the phage in the lung has been studied in non-infected mice. Then, from data in pulmonary infected mice, a model recapitulating the key interactions has been built and allows to estimate parameters for phage therapeutic efficacy. In particular, it quantifies the impact of dose and route of phage administration as well as the synergism of phage and the innate immune response on bacterial clearance.

I joined the Weitz group (Georgia Tech & Univ. of Maryland) for a postdoc almost 2 years ago, after a 1-year postdoc and a PhD in Biostatistics & Biomathematics in the group of France Mentré (Université Paris Cité). I also completed my PharmD in 2016 at the Université Paris Descartes. I am interested in modeling bacteriophage-bacteria interactions and bacterial infectious diseases

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Session 4

Spotlighting on Bioanalytical Data for Biologics PK Interpretation

Session 4.1

Gearing up your bioanalysis for your drug development

Nicolas Fourrier
Inotrem, France

Bioanalysis, particularly the quantification of biotherapeutic concentrations in biological matrices and the evaluation of anti-therapeutic antibodies, plays a pivotal role in the development of biotherapeutics. These measures not only serve to document drug exposure but also supports drug safety. Consequently, the design and validation of these assays are paramount, ensuring their suitability for the intended purpose.

As drug development progresses, adherence to regulatory guidelines becomes indispensable. These assays must align with specific standards established by regulatory authorities, often involving rigorous validation criteria to ensure their reliability and reproducibility.

Setting up the methodologies for these assessments is often intricate. Such processes necessitate specific instruments and specialized reagents whose production can be very long and complex. Factors like specificity, sensitivity, and the dynamic range of these assays further complicate their development.

This presentation aims to delve into these complexities, offering insights into best practices, challenges, and potential solutions. We'll explore strategies to streamline assay development, ensure compliance with regulatory standards, and anticipate potential pitfalls in the bioanalysis of biotherapeutics

Nicolas Fourrier was awarded a doctorate in biochemistry from Royal Holloway, University of London in 2005. He then joined the Binding Site Group Ltd. in 2006 as protein purification scientist and promoted to team leader in 2007 for the development and validation of immunoassays for the diagnoses of B-cell malignancies onto clinical analyzers. In 2012, he began leading the development and validation team at SGS France, and by 2016, he was the Director of the Biomarker and Biopharmaceutical Testing Group and was responsible for all bioanalytical activities supporting biotherapeutic drug development program. In 2021, he joined Inotrem as Clinical Biomarkers, Translational Research and Biologistics Director. Alongside these roles, Dr. Fourrier has also been active as an independent consultant and trainer in bioanalysis

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Session 4.2

PK assay design for biological entities – Why format and key reagents matter

Erwan WERNER, Scientific Director DMPK / Translational Medicine
Servier, Institut de Recherche et développement Servier Paris-Saclay, France

Each development of a PK assay has different constrains and challenges. Ligand-binding assays (LBAs), in contrast to other analytical technologies, need specific biomolecular interactions between the analyte and reagents. Knowledge about the analyte before starting development is of major importance. Assay format plays a crucial role in the ability to select a specific form of the analyte (free, bound, total), and how results can be interpretated as regard PD. So-called "critical" reagents are also essential components of LBAs. Their unique characteristics are key to assay performance.Using several examples, the presentation will illustrate how these two factors are key drivers of the adequacy of the assay with its intended use and expected performance.

Erwan Werner is Scientific Director, DMPK-Translational Medicine at Servier. He holds a Doctor of Pharmacy degree and a Ph. D. in Chemistry from the University Paris-Saclay.
After his Ph.D at the French Alternative Energies and Atomic Energy Commission (CEA), where he worked on technical development in metabolomics and their applications in the pharmaceutical field, he started his career at Servier in 2008 as project leader in Metabolism. He then implemented and led the small molecule biomarker platform (metabolomics), while representing DMPK activities in project teams. In 2016, he was appointed Head of Bioanalysis and non-clinical pharmacokinetics, leading internal bioanalytical labs (LC-MS and LBA) and overseeing all nonclinical PK & bioanalytical activities for all modalities.
His current domains of interest include immunogenicity, decentralized trials, Bioanalysis and DMPK.

Session 4.3

Design, development and validation of a PK assay for the clinical development of a biosimilar

Maximilian Breitner, PhD
Sandoz, Holzkirchen, Germany

Clinical development of biosimilars serves to investigate the effect of remaining uncertainty regarding the similarity between a reference compound and a proposed biosimilar. It includes bioequivalence studies to compare pharmacological fates between the products. Sensitive and precise bioanalytical methods are required for the bioanalytical quantification of analytes in the clinical study sample in order to generate meaningful output for a pharmacokinetic interpretation. In this presentation, the challenges, risks and opportunities of PK bioanalysis in support of clinical biosimilar development are shared, all in terms of method development & validation and study sample measurement.

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Maximilian Breitner works at Sandoz as a Laboratory Head in Bioanalytics. In this function he oversees the development and use of bioanalytical methods in support of clinical studies in biosimilar development. Previously he was responsible for assay development services at BioSIMS SAS, a bioanalytical instrument manufacturer and, with a focus on biomarkers at Firalis SAS. Maximilian has a PhD from the University of Turin in Italy and is a trained biochemist.

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Session 5
New Trends in PK and Immunogenicity Assessments in Ophthalmology

Session 5.1
Dose selection for ocular gene therapies

Fraser McBlane
Novartis, Basel, Switzerland

Dose selection considerations for viral gene therapies differ from low molecular weight compounds and biologics in several ways. In gene therapies, the active drug product is not dosed directly, but rather is only produced after the injected virus reaches and enters its target cell, the viral transgene is expressed, and the transgene product is secreted from the cell or reaches the required intracellular or transmembrane location. Pharmacokinetics of the gene therapy product is therefore not easily correlated with the dose of infectious viral particles. The immune response to AAV includes innate, humoral and cellular responses to the viral capsid and to the transgene product. These can influence both safety and efficacy and are important factors to consider during development of a gene therapy. Bioanalytical strategies and dose predictions for AAV gene therapies will be discussed.

Fraser McBlane is the PK Sciences (PKS) lead for ocular gene therapies at the Novartis Institutes for BioMedical Research (NIBR) in Basel, Switzerland. He is PKS Global Program lead for several AAV gene therapy programs from preclinical discovery to post-marketing project phases, providing the bioanalytical strategies for viral biodistribution, shedding and immunogenicity, which support the clinical rAAV dose selection. He is also the PKS Science Lead for gene therapies. Fraser graduated in Genetics from the University of Edinburgh and obtained his PhD in Molecular Biology from Kings College London. After a postdoc in immunology at the National Institutes of Health in Maryland, USA, he became a group leader at the Basel Institute for Immunology and Director of Molecular Immunology at the European Institute of Oncology in Milan, Italy. Within PKS at NIBR, Fraser led the development of the clinical bioanalytics strategy for the first approved CAR-T cell therapy, Kymriah (Tisagenlecleucel), before switching to AAV gene therapies.

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Session 5.2

The right regimen for every patient in ophthalmology, a drug development example

Katrijn Bogman, PhD
Roche Innovation Center Basel, Roche Pharma Research and Early Development, F. Hoffmann-La Roche Ltd
Basel, Switzerland

Treatment of retinal diseases requires frequent injections in the eye, which represent an important treatment burden for the patients and may lead to compliance issues and loss of efficacy. Minimizing treatment frequency is therefore important and the optimal dosing regimen might be identified during clinical development of new treatments. From dose selection for first in man trials through dose ranging in Phase 2 trials and exploration of individualized treatment regimens in Phase 3 trials, pharmacokinetic and pharmacodynamic models were used to guide decisions. Here, we summarize the main steps throughout the development cycle that contribute to dose selection of an intravitreally administered drug.

Katrijn Bogman is a senior Clinical Pharmacologist at F. Hoffmann-La Roche based in Basel, with 20-year experience in drug development. In her role as clinical pharmacologist, she has worked on compounds for various indications including diabetes, cardiovascular diseases, oncology and last but not least ophthalmology. She embraces innovative trial designs and data-driven decision making.
Her driver is determining the right dose for every patient through characterization and integration of clinical pharmacology aspects of new compounds through the different stages of drug development.
Katrijn received her Pharmacy degree from the University of Ghent , Belgium. She holds a PhD in Clinical Pharmacology with a focus on clinical implications of drug transporters from the University of Basel , Switzerland.

One Step Aside
Impact of Contaminants/Drugs on Public Health and Environment assessed by PBPK

Lifetime exposure in the dietary risk assessment, usefulness of PBPK models

Thomas Gastellu[1 2], Bruno Le Bizec, Prof, PhD, HDR[1] , Gilles Rivière, PhD, HDR[2]

[1]Oniris, INRAE, LABERCA, Nantes, France
[2]Anses, Risk Assessment department, Maisons-Alfort, France

Food is a source to a wide range of chemical substances, both anthropogenic (pesticides, POPs) and non anthropogenic (trace elements, mycotoxins). Chronic exposure to mixtures of chemical substances can trigger health adverse effects on the population throughout lifetime due to accumulation and changes of exposure. However, current risk assessments generally only take into account a single substance for a single route of exposure and do not always consider the kinetics of the substances. In addition, several chemicals can cause the same harmful effect, be absorbed by several routes of exposure and accumulate in body's organs. The use of PBK models has become more and more used in the field risk assessment to estimate the body burden of chemicals or to extrapolate physiological mechanisms between species and reduce uncertainties. A methodology has been developed integrating dietary lifetime exposure into risk assessment in order to integrate the changes occurring throughout life. This methodology, coupled to a PBK model aims to simulate the changes in body burden throughout life. The results of the methylmercury case study will be presented to demonstrate the usefulness of the lifetime exposure coupled with PBK models. New methodologies are needed in order to integrate the entire chemical exposome considering different sources and routes of exposure throughout life and to better characterise the risk for different adverse health effects.

Thomas Gastellu, after obtaining a Master's degree in ecological and environmental sciences at Paris-Saclay University, started a doctorate co- supervised by Oniris (Ecole Nationale Vétérinaire de Nantes) and Anses (French National Agency for Food, Occupational and Environmental Safety). His project focuses on developing new methodology in risk assessment to integrate exposure to mixture of chemicals during lifetime, particularly in the case of heavy metals. He is also involved in the European Partnership for Assessment of Risks from Chemicals (PARC) to develop and refine PBK models.

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One Step Aside

Impact of Contaminants/Drugs on Public Health and Environment assessed by PBPK

Fishing for answers: How zebrafish helps to assess the risk of pharmaceuticals in the aquatic environment

Katharina Brotzmann

Aquatic Ecology and Toxicology, Centre for Organismal Studies (COS), University of Heidelberg, Im Neuenheimer Feld 504, Heidelberg, Germany

The continuous development and improvement of therapeutic drugs presents both benefits and challenges to modern society. Increased consumption, improper disposal and wastewater releases have resulted in pharmaceuticals entering natural ecosystems and impacting non-target organisms even at low concentrations. To protect the environment and human health, hazard and risk assessments are now a mandatory part of regulatory procedures and ecotoxicological studies. However, the extensive use of traditional mammalian models for toxicity testing has raised ethical concerns. Consequently, there is a pressing need for the development and application of alternative methods for toxicity and ecotoxicity screening.

To address these challenges, aquatic organisms such as mollusks, crustaceans, and algae were used to detect, track, and assess the impact of pharmaceuticals in limnic and marine ecosystems. Additionally, for vertebrate studies, zebrafish (Danio rerio) embryos have become a valuable resource for rapidly evaluating e.g., the potential neurotoxicity, hepatotoxicity, and the potential for endocrine disruption caused by these substances, both during drug development and in ecotoxicological studies. For instance, in the assessment of teratogenic effects, the antiepileptic drug valproic acid was tested using the Fish Embryo Acute Toxicity (FET) assay (OECD TG 236). To improve the predictions and explanations of developmental toxicity, toxicokinetic data and a physiologically-based pharmacokinetic model were included. This approach may provide a finer-grained analysis of teratogenic effects in zebrafish embryos compared to the OECD's method alone, aiding in understanding the impact of pharmaceuticals on aquatic ecosystems and extrapolate potential developmental toxicity effects of pharmaceuticals to other organisms.

Considering the diversity of therapeutic drugs, the zebrafish embryo can be used as a rapid and simple screening model for toxicity and ecotoxicity testing, and the data obtained could be further used for e.g., PBRK and multistate models.

Katharina Brotzmann is a biologist, expert in (eco)toxicology, and postdoctoral researcher at the Ruprecht-Karls-University in Heidelberg, Germany.
After finishing her state examination in biology and German studies in Heidelberg in 2016, she investigated the suitability of the zebrafish embryo as an alternative model organism in comparison to the mouse for teratogenicity testing of various chemicals. In 2021, she graduated with a doctoral degree from the University of Heidelberg and by pure chance got a postdoc position at the same institute (I swear it was not intentional). Currently, she is working in the Aquatic Ecology and Toxicology-group within the Centre for Organismal Studies, teaches about zoology, and assesses the presence, behaviour, and risk of pharmaceuticals in the marine environment. She is interested in everything related to toxicology, pharmacology, ecology and zoology, and how to refine, reduce and replace animal tests for future toxicity studies.

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Session 6
Supporting Decision making in Drug Development
Session 6.1

Applying a totality of evidence approach including model-informed drug development (MIDD): asciminib development in the context of FDA's Project Optimus

Matthias Hoch,
Novartis, Basel, Switzerland

Asciminib is a novel tyrosine kinase inhibitor (TKI) which has recently been approved for the treatment of chronic myeloid leukemia in chronic phase (CML-CP). Asciminib has a distinct mode of action from other TKIs used in CML treatment, inhibiting BCR::ABL1 by specifically targeting the ABL myristoyl pocket (STAMP). In January 2023, the FDA launched Project Optimus, an initiative to reform the dose optimization and dose selection paradigm in oncology drug development. Even though the FDA guidance was not available at the time, the development of asciminib closely followed the approach and goals of Project Optimus: the establishment of appropriate phase 2/3 dose(s) relied on leveraging all clinical and non-clinical data, including intense mechanism-based exposure-efficacy and exposure-safety analyses, as well as physiologically-based pharmacokinetics (PBPK) simulations. This enabled the FDA approval of asciminib at not only the dose tested in phase 3 (40 mg twice-daily) but also at a more patient-centric 80 mg once-daily dose, as well as a 5-fold higher dose of 200 mg twice-daily for patients harboring the T315I mutation, which drives resistance to most TKIs and constitutes a particularly high unmet need. This approach successfully overcame the challenges posed by the limited availability of clinical data.

Dr. Matthias Hoch is a Clinical Pharmacology expert at Novartis. He has more than 15 years of experience in clinical development in several different global pharmaceutical companies, including Novartis, AstraZeneca and Actelion. He is the global Clinical Pharmacology leader for numerous new drug candidates in early to late-stage clinical development, and has worked across different therapeutic areas, including oncology, neuroscience and auto-immune diseases. He studied molecular biology at the University of Basel and received his PhD from the University Hospital of Basel, Switzerland. In his leisure time, he likes to spend time with his family, doing sports and flying with his model airplanes.

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Session 6.2

From model to decisions: effective simulations to support drug development

Andreas Lindauer, PhD, Senior Consultant
Calvagone, Liergues, France

In this talk, several examples will be discussed that illustrate how simulations helped convey important modeling insights. Some examples will be drawn from the development of the immune-oncologic drug pembrolizumab, where the speaker was involved. It will be shown how simulations with a complex semi-physiological mouse-to-man translational model supported the justification of the dose range in clinical trials. The visualization of the uncertainty of assumptions by way of a sensitivity analysis helped to build trust in the simulation and clarified its limitations. A step further in the development of pembrolizumab, simulations with an empirical PK/PD model helped designing an innovative Phase 1 trial with intra-patient dose escalation, which was crucial in defining the concentration-response relationship of the drug.

A second case example will show how first-in-human dose predictions with a very simple model were used at an early stage in the development of a small molecule against Alzheimer's disease to compare two candidate compounds. Despite uncertain parameters and assumptions, simulations helped manage expectations about the potential dose range in humans. The team could visually judge which features of the molecules (i.e., PK parameters) were most influential in achieving a target dose and hence deserved greater focus in further development.

The final case will illustrate how PK/PD simulations were the basis of an in silico feasibility assessment of a novel mucosal delivery formulation of paracetamol. Several literature models for adults and pediatric patients with different routes of administration were combined and compared. Different scenarios regarding the speed of absorption and the dose were simulated for the novel formulation, providing the company with a realistic picture of their project's feasibility.

In conclusion, these examples highlight the importance of simulations in pharmacometrics and their usefulness as a tool to effectively communicate modelling results to clinical teams and decision makers. By placing more emphasis on the execution and presentation of simulations, we can improve communication and facilitate better decision-making in drug development.

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Andreas studied pharmacy at the University of Bonn where he obtained his license in 2006. Thereafter he started his PhD research at the Department of Clinical Pharmacy at the same university, focusing on PK/PD modelling in oncology and CNS. He completed his research Biomarker Response to Venlafaxine and Sunitinib Administration ». In 2009, he moved to Barcelona where he joined Ferrer Internacional, as a pharmacometrician. At Ferrer he was mainly working on the development of anti-infective agents and drugs for the treatment of sleep disorders. In 2011, Andreas joined Merck, Sharp & Dohme in the Netherlands where he worked in several multi-disciplinary clinical development teams in CNS, infectious diseases, cardiovascular diseases, hematology and oncology, and had the opportunity to contribute to the Keytruda (pembrolizumab) development. From 2014 until 2019 he worked as a senior consultant at SGS Exprimo, on a variety of M&S projects in diverse areas including epilepsy, pain, oncology and endocrinology for large and small companies. Andreas joined Calvagone in 2019.

Session 6.3

Using Forest plots to support drug development decision making- difficulties and opportunities

Niclas Jonsson, PhD and Joakim Nyberg, PhD
Pharmetheus AB, Uppsala, Sweden

An informed evaluation of covariate effects in pharmacometric models is important for correct drug development decisions, optimization of treatment strategies, and supporting personalized therapies based on patient characteristics.
The evaluation of covariates effects using Forest plots requires careful consideration of the choices made during the creation of the plots. These choices have a significant impact on the interpretation of covariate effects. This presentation highlights the importance of viewers being aware of these choices to ensure accurate interpretation of the results.
Transparency in the construction of Forest plots is the responsibility of the creator of the plots. Choices such as the analysis method, uncertainty estimation, selection of covariate values for visualization, and definition of clinical relevance criteria influence the visual representation and subsequent conclusions. By providing this information, creators enable viewers to understand the context and limitations of the presented results.
Equally crucial is the responsibility of viewers to actively integrate the information provided by the creator of the Forest plots in their interpretation of the results. Awareness of how these choices shape the Forest plots allows viewers to make informed judgments about the magnitude and significance of covariate effects.

The presentation will outline the important choices to make, how they influence the interpretation and how they should be communicated to the viewer.
In conclusion, the interpretation of covariate effects using Forest plots is influenced by choices made by the creator of the Forest plots. Viewers must be aware of these choices and actively consider them to ensure accurate interpretation. Transparent reporting by creators and informed judgment by viewers creates a collaborative approach that enhances the reliability of conclusions drawn from Forest plots.

Niclas Jonsson has an M.Sc. in Pharmacy and a Ph.D. in Biopharmaceutical Sciences from Uppsala University, Sweden. He initiated and co-developed the software programs Xpose4 and PsN. After a postdoctoral position at the University of California San Francisco, USA, he returned to Uppsala University as a Senior Lecturer and Associate Professor of Applied Pharmacometrics. Jonsson has held roles in industry, including Global Head of Modeling and Simulation at Hoffman-La Roche, Switzerland, and Senior Consultant at Exprimo NV, Belgium. In 2012, he co-founded Pharmetheus, where he participates in client projects and leads pharmacometrics research efforts in his role as Pharmacometrics Platform Science Lead.

Session 6.4

Application of pharmacometrics analysis in clinical biosimilar development

Roland Baumgartner, PhD**,** Barbara Vogg**,** PhD
Hexal AG/Sandoz Biopharmaceuticals, Holzkirchen, Germany

Biosimilar products significantly reduce health care costs and increase patient access to life-saving biologic drugs. Demonstration of similarity between a proposed biosimilar (test) and an originator (reference) product follows a sequential approach. In a first step, similarity of critical drug attributes is established at the molecular/analytical.
Residual uncertainty regarding similarity is subsequently addressed with dedicated clinical studies. Typically, a pharmacokinetic (PK) or combined PK/pharmacodynamic (PD) study is performed to demonstrate similar drug absorption, disposition and PD between test and reference products in a sensitive clinical setting.

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Model based simulations play a central role to inform the design of clinical similarity studies and its use is encouraged by regulatory agencies. Several case studies will be presented to demonstrate how PK/PD information can be leveraged in the design of pharmacology components of clinical biosimilar programs. Model-based simulations are utilized to assess the impact of covariates and to define the study population. Model derived interindividual variability informs sample size estimation. Further, simulations demonstrate the sensitivity of PK/PD endpoints to ensure that differences between test and reference product can be detected. Model-optimized PK sampling designs represent another important application. Overall, model-based simulations proved highly valuable for study optimization and represent an efficient tool to communicate clinical pharmacology considerations to regulatory agencies.

Roland Baumgartner obtained a PhD in structural biology from the Ludwig-Maximilian University, Munich. Since then, he held several positions in the field of translational and clinical pharmacology. He can look back on more than 24 years of work experience in the biotech and pharmaceutical industry. He acquired in depth understanding of the drug discovery and clinical development process for small molecule therapeutics as well as monoclonal antibodies, in the field of inflammatory diseases and immuno-oncology. His prime interest focuses on model informed drug development and applying quantitative pharmacology concepts, PK/PD modeling and pharmacometrics approaches to all stages of clinical development, including the development of biosimilars. Currently, he is holding a position as senior global clinical pharmacology manager at Sandoz Biopharmaceuticals

Session 7

Digital Data Sciences in Drug Development

Session 7.1

Data Science & Artificial Intelligence : enablers to support and accelerate drug development and translational science evidence

Sebastien Tourlet
Capgemini,France

Data Science & Biomarkers

- Definition of Data Science vs Data Engineering vs (Biofinformatics, Chemoinformatics, Biostat.)
- Biomarker vs Digital Biomarker along R&D value chain

Use Cases

- Use Case OMICS & identification of biomarkers
- Use Case AI analysis of Voice (Digital Biomarkers)
- Use Case GenAI

Sebastien is Doctor of Science with more than 20 years of experience in both pharmaceutical and drug medical device industry. He developed a transversal and double expertise in data and precision medicine along the drug development cycle. Sébastien is an expert in NLP and Graph Science applied to healthcare. He held several consulting positions and was head of data analytics in large pharmaceutical groups, biotechs, and groups of hospitals. In parallel, he is largely implicated in rare diseases and disabilities, for instance, he founded a nonprofit tech for good company developing an AI generative technology to support patients, researchers, and physicians. Today, Sébastien is Director in Data Science and Engineering in Data and Analytics for Intelligent Industry team dedicated to Life Sciences sector.

Session 7.2

Artificial Intelligence discovery of novel safety biomarkers in a preclinical environment applied to multiple sclerosis

Romain Clément, ArcaScience SAS
Paris I Pantheon Sorbonne, Paris

The identification and analysis of novel safety biomarkers in a preclinical environment are critical steps in advancing the field of multiple sclerosis research. This conference explores the role of artificial intelligence (AI) in facilitating the extraction and analysis of relevant data from diverse textual sources, which are categorized as non-structured, semi-structured, and structured.

In the context of non-structured data, the conference highlights the inherent challenges in distinguishing specific information pertinent to safety biomarkers, given the encapsulation of data in documents or databases where text searches may yield non-specific matches. The discussion extends to semi-structured data, emphasizing the limitations posed by heterogeneous representation schemas and the potential for conceptual incoherence in existing biomedical ontologies.

Furthermore, the conference delineates the development of AI models adept at identifying sentences that pertain to adverse events, a critical component in the discovery of safety biomarkers. These models are designed to detect explicit or implicit mentions of biomarkers, including verified occurrences and potential non-occurrences, thereby aiding in the aggregation of data relevant to safety biomarker research.

By focusing on the methodological advancements in AI, the conference presents a comprehensive view of the current capabilities and gaps in utilizing AI for the extraction of safety biomarker data. It underscores the potential of AI in enhancing the precision and efficiency of data extraction processes, thereby contributing to the ongoing efforts in multiple sclerosis research.

Romain Clement is a french entrepreneur and lecturer specialized in biomedical data management and natural language processing. He is the founder of ArcaScience, a french leading AI company aiming at giving pharmaceutical companies, CROs and academics, the ability to de-risk their drugs by giving them access to a unique AI data browser. He holds a position at Paris Panthéon Sorbonne University as a lecturer and researcher specialized in philosophy and the impact of AI on healthcare, for which he held several lectures at Stanford University in 2019 and 2022.

GMP
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Posters

35th GMP SYMPOSIUM

18th – 20th October 2023

Paris -France

Espace centenaire

Master 2/ Pharmacy Posters

Poster 1: Predicting pulmonary xenobiotic absorption in humans using combined in vitro tools and in silico kinetic models

R. BOUFALAAS[1], M. FLOREANI[1], S. E. ESCHER[2] , G. LACROIX[1 3] , P.-A. BILLAT[1]

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[3]Peritox, Amiens, France.

Background and objectives: An alternative to traditional experimental toxicology, the development of New Approach Methodologies (NAMs) for the evaluation of chemicals is gaining increasing interest. Indeed, these approaches offer many benefits over traditional in vivo assays, including ethical considerations, cost- and time efficiencies, mechanistic insights, and lower variability. Among these approaches, in vitro experiments are the most widespread tools, with the use of nominal concentrations for the establishment of concentration-response relationships. However, this dose doesn't appear to be an accurate proxy for exposure, as chemicals can be differentially partitioned into different compartments within the in vitro assay, including serum components, plate plastic, and the headspace. This frequently results in "underdosing" the cells, reducing the free concentrations of chemicals that the cells are exposed to (1). In the context of the evaluation of pulmonary permeability to xenobiotics, we have further adapted an existing model, the Virtual in vitro Distribution (VIVD) model (2), to the pulmonary case study.

Material and methods: Experimental assays were performed to determine the fraction of the compound bound to the plastic of the experimental device, the free fraction in biological matrices (such as culture media, lysed lung cells, and rat lung), and the concentration leading to cytotoxicity. These assays were carried out to improve our understanding of the exposure test system. Five xenobiotics, namely: propranolol, sumatriptan, hippuric acid, phthalic acid mono 2-ethylhexyl ester, and thymol were selected based on their physicochemical properties, low toxicity, limited metabolism, large logP range, and large permeability range observed in Caco-2 cells. These xenobiotics were tested at two different concentrations (1 and 10 µM) on two different types of lung cells: Calu-3 and h-AELVI cells.

Results: The results will be valuable for the development and validation of in vitro permeability assays and for subsequent refinement of the model. The updated mass balance model estimates the free dissolved concentrations in both apical and basolateral media, and the cell/tissue concentrations corresponding to the initial nominal concentration, under different experimental conditions, based on the physicochemical properties of the xenobiotics and the characteristics of the cell line used (size, lipid content, intracellular protein binding, cell growth).

Conclusion: Considering the project's perspective, the prediction of the current model will undergo a rigorous comparison with experimental in vitro and in vivo pulmonary permeability data, a crucial step in validating and refining the model. This process ultimately enables the performance of robust in vitro in vivo extrapolations (QIVIVE) for accurate estimation of pulmonary absorption.

Keywords: NAMs, in vitro assays, biokinetics, pulmonary absorption, QIVIVE.

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Poster 2: Evaluation of the Boruta Machine Learning Algorithm for Covariate Selection

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Background & Objectives: In the last few years, several machine learning algorithms have been applied for covariate selection. The objective of this work was to evaluate the performance of the Boruta algorithm (BOAL) [1] implemented in R independently and in combination with Lasso [2] as a new framework for covariate selection for population PK models.

Methods: Using a target mediated drug disposition model [3], several scenarios were simulated in NONMEM [6] where different covariate combinations were added to the model parameters. For each scenario 100 simulation datasets were created including 180 subjects with rich PK sampling following single dose administration (from 35 up to 1500 mg) and for each dataset twenty covariates were sampled from the NHANES database[4].

The scenarios explored were: (1) no covariate; (2) one covariate effect on CL; (3) (4) (5) one or (6) two covariate effectson V1; (7) two covariate effects on V1 and one covariate effect on CL; (8) two covariate effectson V1 and on CL.

For each dataset, the individual parameters were estimated using the model without covariate. The type I error (only for scenario 1) plus two different power calculations (for the rest of the scenarios) were performed for BOAL alone or in combination with Lasso to reduce the impact of correlation between covariates. Type 1 error was defined as the false positive rate in scenario (1), Power (P1) was defined as the ability to identify the correct covariates together with additional ones on EBEs, and Power (P2) was defined as the ability to identify exclusively the correct covariates. A k-fold cross-validation (KCV) step (k=5 fold, 80/20 split)was implemented in the Lassofollowed by BOAL search to repeat the entire processon different splits.

Results: All parameters were well estimates (RSEs<15%) in all scenarios, confirming that the simulation design was appropriate. The parameters showed a low shrinkage (<5%) in all scenarios except for the CL parameter(~20%).

When applying KCV on BOAL and Lasso step on EBEs, the scenario 1 without covariates showed 6% and 0% of Type 1 error for CL and V1.

For scenario 2 and 3, KCV on BOAL and Lasso step resulted in a P1 of 57% and 95% and P2 of 55% and 86%, respectively. The use of BOAL alone, without Lasso and KCV, shows a significant decrease in P1 and P2. For scenario 7, KCV on BOAL and Lasso step for V1 resulted in a P1 of 95% and P2 of 72%. And for CL, P1 and P2 are comparable to scenario 2.

Conclusion: BOAL proved to have a high power to select the right covariate even in combination with additional covariates. BOAL preceded by Lasso and the addition of the KCV step improved the power to identify the right covariates. These results show that the covariate selection process can become more efficient using ML algorithms as it reduce the number of covariates to be assessed for their relevance.

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Poster 3: PBPK to explore blood/milk barrier in dairy cows and estimate milk withdrawal period.

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Background and objective: PBPK can be an important tool to assess antimicrobial resistance by health agencies, because it allows without risks the prediction of human and animal exposition to medicines and xenobiotics as marbofloxacin (fluoroquinolone antimicrobial).

Indeed, with PBPK we can quantify residuals of medicines in specific tissues and estimate milk withdrawal period which is the time between administration of the drug and the time when milk contains concentrations lower than the maximal residual limits MRL authorized by health agencies.

The objective is to assess Marbofloxacin pharmacokinetics in cows and estimate milk withdrawal period after marbofloxacin administration.

Materiel and methods:

PBPK model:

A PBPK with ten compartments: deposit compartment, veinous and arterial compartments that link the mean organs (lung, muscles, adipose, liver and kidneys) the udder (compartment of interest) and the rest compartment was built to describe the passage of oxytetracycline into the milk of lactating species and to predict its distribution.

Our goal is to adapt this model to marbofloxacin, to assess it pharmacokinetic in cows, and to estimate the withdrawal period of milk for food safety.

The physico-chemical properties of Marbofloxacin were integrated into the model, but physiological parameters are the same as for oxytetracycline model.

In vivo data (observations):

We have used six cows to obtain experimental data, marbofloxacin concentration in plasma and milk was determined by HPLC. Those observations were used to calibrate and evaluate the predictive performance of our model.

Software: Monolix to build the model and estimate Kim and Simulx to run Monte Carlo simulation and perform PBPK pop; R for model evaluation.

Results: The ratio prediction/observation should be between 0.5 and 2. 100% of plasmatic predictions and 67% of milk predictions fell within a factor of 2 of the experimental data. Milk withdrawal period after marbofloxacin administration is 29.5 hours, which is approximated to 36h because milking occurs each 12hours.

Conclusion: Our PBPK model predictions of marbofloxacin concentrations in plasma and milk are accurate, as well as the estimation of the withdrawal period which is as mentioned in the summary of product characteristics) 36h.

Key words: PBPK, Marbofloxacin, withdrawal period, cow, milk.

Poster 4: Evaluation of semi-automatic covariates model building methods in population pharmacokinetics: a case study for an antibody-drug conjugate

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Background and objectives: In population pharmacokinetics (popPK) estimation runtimes have greatly lengthened with the increasingly models complexity often characterized by many parameters to be estimated for which relationship to covariates should be explored. Therefore, covariates model building using standard Stepwise Covariate Modeling (SCM) can be time consuming and challenging for those complex models. To overcome these limits, more sophisticated tools have emerged in the area of pharmacometrics, such as Machine Learning (ML) or automatic procedure (e.g., Conditional Sampling used for Stepwise Approach based on Correlation tests (COSSAC) [1], Stochastic Approximation for Model Building Algorithm (SAMBA) [2]). This work consisted of evaluating several tools to speed up the covariates popPK model building of tusamitamab ravtansine, an Antibody-Drug conjugate targeting carcinoembryonic antigen-related cell adhesion molecule 5 with a potent cytotoxic maytansinoid derivative, DM4. A complex semi-mechanistic popPK model had been developed based on First in Human study data. [3,4] Semi-automatic covariates model building approaches (ML with Random Forest (RF), COSSAC and SAMBA) were compared to standard SCM.

Material and methods: COSSAC and SAMBA are two algorithms implemented in Monolix©. RF is implemented using R software along with ranger package. Before the use of COSSAC and SAMBA, a pre-screening step was performed based on graphical and statistical analysis to identify relationships between individual PK parameters sampled from conditional distribution and covariates (Pearson/ANOVA p.value <0.1 required for statistical significance).

Selected covariates were implemented into COSSAC and SAMBA. A deletion step was performed on the full covariates model obtained after automatic algorithm processing. RF was used as an alternative pre-screening method before COSSAC and SAMBA processing. To compare all these approaches, impact of the final retained covariates was evaluated on structural PK parameters and on exposure PK parameter (AUCTAU at steady-state) as well. Computation was performed on a 32GB RAM and 24 cores CPU computer.

Results: All identified covariates in the reference model were also selected by the evaluated procedures with similar magnitude of effect (<20% difference). The automated algorithms were more conservative for covariates selection than the standard SCM approach. The number of retained covariates by each method was higher (about 8 extra covariates) than that of SCM approach. However, all additional retained covariates by the automated processes have a limited impact on drug exposure but one covariate shows a percentage change in AUCTAU for the typical patient larger than 40%. The runtime was around 2 weeks for the standard SCM approach while runtime for COSSAC and SAMBA processing were 4 days and 6 hours, respectively. The runtime for the RF was below 5 minutes. Screened covariates from RF were implemented into COSSAC leading to a 2-time faster runtime, reducing the COSSAC's duration from 4 to 2 days.

Conclusions

The different strategies to build covariates models with COSSAC, SAMBA and ML algorithms, enabled to save a lot of time as these procedures are straightforward, continuous and without downtime. They avoid many intermediate estimation steps and even more when combining with ML tool (e.g., RF selection followed by COSSAC procedure). Similar results to the reference model were obtained although automatic procedures tend to be more conservative in terms of selected covariates into the final model. Such approaches seem robust and can be used for rapid analyses with tight time constraints and/or for exploratory covariate analyses of complex models.

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Poster 5: Linking exposure and toxicity in real-life Olaparib-treated patients

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Background and objectives: Olaparib is an inhibitor of the human PARP (poly-(ADP-ribose) polymerase) enzyme. It acts by interfering with the DNA repair processes, thereby inducing cancer cell death.It is indicated in ovarian, breast, prostate and pancreatic cancers[1]. Olaparib frequently causes anaemia requiring dose reductions or interruptions [1]. In addition, increase in serum creatinine has been observedin patients treated with olaparib, which is, partially related to the inhibition of its renal tubular secretion via organiccation transporter 2 (OCT2). The aim of our work was to describe the pharmacokinetic/pharmacodynamic (PK/PD) relationships between olaparib plasma concentrations, anaemia and hypercreatininemia in a real-life population, in order to propose a target concentration for therapeutic drug monitoring (TDM).

Patients and methods: A multicenter retrospective study was conducted in Dijon's clinical cancer center and in several Parisian hospitals. All patients initiating treatment with olaparib between March 2015 and December2021 and followed up in the study centers were included.

As TDM of olaparib was routinely performed in the centers, olaparib plasma concentrations were available.
The patient data and observations (haemoglobin, serum creatinine) required to develop the PK/PD models were collected from the medical records.
To develop the PK/PD models, a non-linear mixed-effects modelling approach was applied using Monolix® version 2023R1 (Lixoft SAS, Antony, France). Individual pharmacokinetic parameters were estimatedusing a previously developed population pharmacokinetic model for olapariband were used as individual constants (regressors in Monolix®) in the PK/PD models as an input to obtain olaparib plasma concentrations. Several PK/PD models were tested in order to find the one that best described the data.
Covariate selection was carried out in several stages: graphically, using Pearson correlation tests and by a Forward/Backward approach. Final model selection was based on a comparison of the objective function value (OFV) between nested models, the relative standard error (RSE %) of the estimated parameters and several graphic evaluation methods.
Results: A total of 233 haemoglobin and 191 serum creatinine concentrations were available for 37 and 36 patients, respectively.
The PK/PD model that best describes the relationship between olaparib plasma concentrations and haemoglobin evolution over 3 months is a model inspired by Friberg's model [2] with five compartments (1 compartment representing stem cells, 3 transit compartments, and 1 compartment representing circulating haemoglobin), a feedback mechanism(reflecting the effect of the erythropoietin on the red blood cell production) and a linear effect of the drug, leading to a decrease in stem cell proliferation. Type of primary cancer (ovarian cancer vs. other cancer types) had a significant impact on BASE, reducing the OFV by 20.61 points. The parameters were well estimated (RSE inferior to 47, 3 %) and the proportional residual error was 9, 7 %
The model that best described the relationship between olaparib plasma concentrations and serum creatinine kinetics over 6 months was inspiredby the basic structural models belonging to the indirect resThponse model family described by Sharma and Jusko [3], with a single compartment representing circulating serum creatinine, a zero order input rate and a first order elimination rate constant on which the drug acts with a linear effect, leading to a delayed elimination. All the parameters were estimated with RSE inferior to 56 % and the proportional residual error was 10 %.
Conclusions: Two PK/PD models describing the evolution of haemoglobinemia and creatininemia as a function of time, based on real-life data, were developed. These models will help to define target olaparib concentrations to prevent risk of anaemia and to guide individual dose adaptation. The increase in serum creatinine by olaparib will be further correlated to the dynamics of cystatine C which is a specific marker of renal function.

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Poster 6: Log P and Log D are good descriptors for assessing the choice between standard, gel or mechanical separator tubes for therapeutic drug monitoring/toxicology screening procedures.

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Background and objectives: Recovery data of drugs in gel-based or mechanical separation blood collection tubes are lacking for therapeutic drug monitoring or clinical toxicology. Different experiments alreadystudied the impactof gel separator tubes on common therapeutic drugs and found a correlation between physico-chemical properties and recovery. The study exploredthe impact of BD Vacutainer® PST™ II and Barricor™ separators on the recovery of a panel of 167 common drugs. Our objectives were to set and comparea logP and logD threshold value associated to a decreaseddrug recovery for these tubes.

Material and methods: Of the 167 compounds, 13 were analgesics, 26 antidepressants, 12 anti-infectious agents,25 anxiolytics, 29 cardiovascular drugs, 26 drugs of abuse, 13 neuroleptics and 23 other drugs. A 20 ng/mL mix for each drug was prepared in whole blood from one healthy volunteer without any medication. Spiked blood were poured in the following sets: LH, PST™ II or Barricor™. Analyses was performed by UPLC-MS/MS system, operated in positive mode in multiple reaction monitoring mode. Six samples for each condition allowed robust evaluation of dispersion and LH tube were used as control. LogP and logD values were calculated using MarvinSchetch 22.19 software. Statistical analyses and receiver operating characteristic (ROC) curve were performed using R software (v4.2.3). A 95% confidence interval (CI95%) on the area under the ROC curve (AUC) was derived from a bootstrap method.

Results: As expected, the impact of PST™ II gel on drugs recovery was variable accordingto the drugs families. Obtained results suggest a possible role of the drug chemical properties and led us to study the correlation between analyte recovery and the hydrophilic-lipophilic balance (log P). While log P is a useful parameter, it fails to account variation in the lipophilicity of a drug with respect to the ionic states presentat key physiological pH values.Log D is calculated similarly but also considers the ionized form of the drug in the water. We observed a significant correlation between recoveries and log P (R^2=0.29) or log D values (R^2=0.22) with p-value < 0.0001. To find a cut-off values for log P and log D parameters the logistic regression model was applied,which included a singular variability due to the drug log P or log D values and did not include interindividual variability, as blood was provided by one person. A logP > 2.5 was estimated as a cut-off value at a 0.51 Youden Index to predict a potent lack of drug recovery (< 85%) with an 89.3% sensitivity and a 62.1% specificity (ROC curve AUC (CI95%) = 0.801 (0.734 to 0.868)). Similarly, a Log D > 1.59 was estimated as a cut-off value with a 85.7% sensitivity and a 68.5 % specificity AUC (CI95%) = 0.711 (0.780 to 0.849) at a 0.54 YoudenIndex. For the BarricorTM tubes,results will be reviewed and discussed as well.

Conclusions: Separator blood collection tubes are associated with a decrease in many drug concentrations, due to their composition as well as the considered drug classes and their physico-chemical characteristics. We propose a simple mean to assess the behavior of a given compound towards the gel by using either its logP or log D. A value below 2.5 or 1.59 for Log P and log D respectively, may generally allow the quantitation of a compound in blood drawn on PST™ II tubes, with Log D providing improvement for the majority of weak based ionized drugs at the relevant physiological pH.

Poster 7: Evaluation of the semi-automatic model development tools in pharmr

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Background and objectives: Recently, an automatic model development (AMD) tool using Python language, called Pharmpy package, has been developed by the University of Uppsala. Its interface in R (Pharmr) makes it accessible to R users. The aim of this tool is to completely automatize the population pharmacokinetic (PopPK) modeling enabling model development from a dataset as an input [1]. Moreover, several sub-tools are available: Model search for the structural model, IIV search for the interindividual variability model, RUV search for the residual unexplained variability model, IOV search for the interoccasion variability model, Allometry for the allometric scaling and COV search for the covariate model. These sub-tools can be used separately in a semiautomatic approach giving the user greater control over the search space and the models can be checked after each step to serve as a start model for the next step
The objective of this research is to explore the tools of semi-automatic model development using Pharmr and to evaluate it by comparing the semi-automatic models with the manually made ones.
Material and methods: Pharmr 0.91.0 was used in the version 4.2.0 of R with the version 7.5.1 of NONMEM. Each sub-tool ran successively. At each step the model with the lowest BIC and meeting all the acceptance criteria (successful minimization, covariance step completed, acceptable correlation and relative standard errors of parameter estimations) has been selected.
The interpretability and the pharmacological relevance of the proposed models were also verified.
All runs were launch with the FOCE Interaction method and the matrix R was chosen for the covariance step. The start model for the Model search is a one compartment with first order elimination (and first order absorption for extravascular administration). IIV search was applied first with the brute force no of ETAs algorithm and the add diagonal strategy followed by the brute force block structure algorithm. IOV was tested on all the parameters with IIV excluding the volumes of distribution. For COV search, all covariates and equations were included in the search space as well as all the parameters with estimated interindividual variability.
The semi-automatic development tool was evaluated to develop the PopPK models of the following molecules for which a pharmacometrician had manually developed a model: X drug administered per os in 222 adult patients (2434 PK observations) and Y drug administered per IV in 67 patients (2806 PK observations).

Results: It took approximately 400 models run to find the best final model for each drug. For X and Y drugs, the same structural model that the pharmacometrician chose was found by Model search. For both drugs, IIV search found one less IIV parameter than those included in the models of pharmacometricians. RUV search found a different residual error model for X drug, and none of the proposed RUV models worked for Y drug. One parameter was included in the IOV model of X drug by IOV search compared to the two parameters in the manual model. The COV search found the same covariates and similar covariate-effects that pharmacometricians for both molecules. The final models developed by the semi-automatic approach have slightly higher BIC than the manually developed models.

Conclusions: The final models found with the semi-automatic model tools were similar to the manually developed models. This tool allows to save time and to reduce the number of code errors. The semi-automatic usage of AMD has a large potential to facilitate the PopPK modeling in the pharmaceutic development.

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Poster 8 : MaInteraction model between clindamycin and rifampicin after oral and iv administration

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Background and objectifs: Clindamycin is an antibiotic frequently used in the treatment of bone and joint infections (BJIs) and is often co-administered with rifampin to ensure efficacy and avoid the emergence of resistance in Staphylococcus spp infections. However, an important clindamycin-rifampicin pharmacokinetic (PK) interaction has been reported, particularly when these molecules are used orally (1,2). Intravenous (IV) administration by continuous infusion (ci) of clindamycin can, nevertheless, lead to a satisfactory concentration (in term of pharmacodynamics (PD)), even when rifampicin is coadministered (3).

Population PK models exist, but only describe the pharmacokinetics of clindamycin per os (PO) alone (4) or with rifampicin (1), with no data on IV administration.

Objectives: To develop a complete population PK model of clindamycin following IV and PO administration with and without rifampicin. Calculate the probability of achieving PK-PD targets (PTA) in particular for continuous and intermittent infusion (ii).

Materials & Methods: Pharmacological data were extracted from two trials: CLIRIFA and CLINDA-RIFAM. CLIRIFA included 39 patients receiving clindamycin PO then by ci: 20 patients received only clindamycin and 19 patients received the combination of rifampicin and clindamycin. CLINDA-RIFAM included 85 patients receiving IV clindamycin by ci: clindamycin alone, followed by the combination. All were treated for BJIs for ≥10 days.

Population PK analysis was performed using the Monolix v2023R1 Stochastic Approximation Expectation Minimization (SAEM) algorithm. Clindamycin plasma concentrations after PO or IV administration by ci or bolus, without and with rifampicin, were simulated with different dosing regimens from 600 mg q8h to 1200mg q6h. The PK-PD targets tested were minimal plasma concentrations 8 times higher than the MIC in plasma.

Results: A linear one-compartment model with first-order absorption and elimination was developed using 518 plasma concentrations from the 124 patients. The absorption rate constant was set at 4.06 L/h, using only PO data without rifampicin. Mean clindamycin bioavailability, clearance and volume of distribution were equal to 0.51, 10.74 L/h and 56.34 L, respectively. Concomitant administration of rifampicin increased clindamycin clearance by an average factor of 3. The impact on clindamycin bioavailability was also significant and dose-dependent: with 600 mg q12h and 900 mg q12h of rifampicin, F decreases to 0.111 and 0.038, respectively. Global PTAs were highly variable according to the mode of administration. The following results are presented considering susceptible Staphylococcus aureus strains. On one hand, for PO administration of clindamycin without co-administration of rifampicin, more than 72.8% of individuals would reach the PK-PD targets, whatever the dose regimen, even with a low clindamycin dose (600mg q8h). For the same strain, when rifampicin was coadministered, global PTAs dropped to 6.5%, even with the highest dose regimen of clindamycin (1200mg q6h).

On the other hand, when clindamycin is administered by ci at a dose of 1800 mg per day, more than 99.9% of individuals would reach the PK-PD targets without co-administration of rifampicin and more than 96.8% with co-administration of rifampicin.

Lastly, for ii, more than 90.0% of individuals would reach the PK-PD targets without coadministration of rifampicin with the smallest dose regimen (600mg q8h) but no more than 57% with co-administration of rifampicin, even when using the highest dose regimen of clindamycin tested (1200mg q6h).

Conclusion: To conclude, this model is more accurate than previous models and demonstrates the effect of rifampicin on clindamycin bioavailability and clearance. As previously described, the therapeutic range cannot be achieved when this combination is administered orally. However, IV administration of clindamycin by ii, or even better by ci can limit this impact.

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PhD Posters

Poster 9: Gene transfer in differentiated HepaRG™ cells: Application to the modulation of specific hepatic functions.

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Background and objectives: Primary cultures of Human Hepatocytes (PHH) are considered as the gold standard of in vitro hepatocytic cell models to conduct metabolism and toxicity studies of xenobiotics. The shortage in liver biopsies and high variability between donors considerably reduce their use. In contrast, human hepatoma cell lines such as HepG2 and Huh7 can be expanded but these cells express low levels of liver specific functions limiting their relevance to assess metabolism and toxicity of xenobiotics. The HepaRG human hepatoma cells show the remarkable ability to differentiate into hepatocyte-like cells exhibiting a metabolic profile close to PHH (1, 2). Development of efficient gene transfer technologies for HepaRG cells has become a pertinent task in order to modulate gene expressions and specific metabolic pathways with a strategy of a gain or loss of liver specific functions. Herein, we present our recent optimizations in gene transfer of HepaRG cells using various technologies with examples of gain of functions.

Material and methods: Progenitor HepaRG cells were expanded and differentiated as previously reported (3). For lipofection, lipoplexes were formulated using cationic lipophosphoramidate-based liposome (SYN1) and pMaxGFP DNA plasmid. For electroporation of GFP encoding plasmid or mRNA, HepaRG cells were subjected to electric pulses of 1500V for 20ms (Neon™ device). Lentiviral transductions of progenitor HepaRG cells were performed to achieve enforced expression of the cytochrome P450 2E1 (CYP2E1) in cells differentiated into hepatocytes. GFP expression was analyzed by flow cytometry (Becton Dickinson LSR-Fortessa™ X-20 FACS and FACSDiva software). Gene expressions were studied by western-blot, RT-qPCR, and enzymatic activities.

Results: We demonstrated that SYN1 liposomes allowed high GFP expression in progenitor HepaRG cells while lipofection of differentiated cells was poorly efficient most likely because hepatocyte-like cells are quiescent. We developed the mitogenic stimulation of differentiated HepaRG cells and showed that proliferation strongly enhanced lipofection efficiencies using Syn1-based liposomes, which were used to express the cytochrome P450 2D6 in HepaRG cells (4). Independently, we also derived transgenic HepaRG cell lines expressing higher levels of CYP2E1 to overcome its low levels in the parental line (5). Progenitor HepaRG cells transduced with lentiviruses encoding the human CYP2E1 cDNA stably express this phase I enzymes at levels similar to primary hepatocytes. This cell model was used to further decipher the metabolism of the chlorzoxazone (5). More recently, we compared the gene transfer in both progenitor and differentiated HepaRG cells using electroporation of plasmids and mRNA encoding GFP. This technology allows remarkably efficient transfections especially with mRNA and gives the opportunity to express genes of interest at levels that can be adjusted by modulating the amounts of nucleic acid templates.

Conclusions: These optimizations have enabled us to develop new approaches for transient and stable transfection of differentiated HepaRG cells, as well as new applications for this cell line, notably by modulating the expression level of xenobiotic metabolism enzymes to better understand the metabolization of existing or new drugs.

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Poster 10: Rituximab in Anti-Neutrophil Cytoplasmic Antibodies (ANCA)-associated vasculitis: population PK/PD modeling and simulations of alternative dosing schedules

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Background and objectives: Rituximab is a monoclonal antibody directed against transmembrane antigen CD20 expressed by B cells. It is approved for the treatment of patients with Anti-Neutrophil Cytoplasmic Antibodies (ANCA)associated vasculitis. The treatment consists in an induction phase (375 mg/m2 once a week for 4 weeks or 1000 mg at day 0 and day 14) followed by a maintenance phase (from 500 mg every 6 months to 1000 mg every 4 months) for 18 to 36 months. There is no standardization of the induction and maintenance dosing schedules and data regarding the comparison of different dosing schedules are lacking. The objective of this study was to develop a population pharmacokinetic-pharmacodynamic (popPK/PD) model for rituximab, serum gamma globulins and ANCA (MPO and PR3) based on real world data from patients with ANCA-associated vasculitis. The model was used to simulate induction and maintenance dosing schedules in order to guide the selection of the best schedule associated with target biomarker response (ANCA < 20 UI/mL).

Methods: This retrospective analysis included patients with ANCA-associated vasculitis treated with rituximab in the Cochin University Hospital (Paris, France). Plasma concentrations of rituximab were measured using a validated liquid chromatography method coupled with tandem mass spectrometry detection (LC-MS/MS) using mAbXmise kit (Promise, France) [2]. ANCA (MPO and PR3) and gamma globulin levels were collected from each patient starting two weeks prior to the first administration of rituximab until the last PK sampling. Concentration-time data were analyzed using Monolix 2022R1.

A two-compartment structural model with linear clearance (CL) from the central compartment was tested. The following covariates were tested on CL and central volume of distribution (V1): age, sex, body weight (BW), C-reactive protein (CRP), serum albumin, and estimated glomerular filtration rate (eGFR). Covariate analysis was performed using a full model estimation followed by a backward selection method with a Wald test (p-value < 5%). Different models were tested to describe ANCA dynamics: indirect, Friberg and variation of Friberg models [3,4]. Model evaluation and validation were based on goodness of fit plots, pcVPC and likelihood-ratio test using BICc. The final model was used to simulate alternative induction and maintenance dosing schedules.

Results: A total of 296 rituximab plasma concentrations (99 and 197 in the induction and maintenance phases, respectively) were collected from 120 patients. A linear two-compartment model was developed, and the mean (RSE) estimates were: CL = 0.18 L/day (5%), V1 = 2.9 L (4%), V2 = 9.5 L (13%), Q = 0.091 L/day (8%). Interindividual variability (IIV) on CL and V1 was 39% (9%) and 15% (18%), respectively. The proportional residual error was estimated at 20% (7%). Serum gamma globulin dynamics was described with a turnover model and an Emax inhibition of their synthesis by rituximab. ANCA were described with a Friberg model without transit compartments and an Emax inhibition of ANCA proliferation by rituximab. The pcVPC of the final model showed that the observed and simulated data were in good accordance. Simulations showed that two alternative induction schedules are equivalent in terms of achievement of target ANCA concentrations. Concerning the maintenance phase, more frequent dosing (every 4 months instead of every 6 months) allowed to maintain ANCA levels below 20 UI/mL, regardless of the dose level.

Conclusion: For the best of our knowledge, this is the first popPKPD model of rituximab in a real-world ANCA-associated vasculitis population. Our simulations show that more frequent dosing in the maintenance phase could be more efficient in preventing major relapse in this population.

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Poster 11: Characterization of metabolic enzymes in human hepatocyte isolated from chimeric TK-NOG mice (HepaSH)

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Background and objectives: The metabolism of xenobiotic compounds, including pharmaceutical drugs, is principally carried out in the liver. The study of this drug metabolism is required by drug agencies before marketing authorization for new small molecules. For this purpose, primary human hepatocytes (PHH), used as suspensions or cultures, are recognized as the gold standard in vitro. However, this model does not proliferate in standard culture, its availability is rather rare and scarce and its cost is rather expensive. To overcome these issues, alternative models such as mice with humanized liver have been developed in the past decade. In particular, mice with humanized liver, such as TK-NOG mice1, can be an expanding source of human hepatocytes2. In this work, we evaluate whether such hepatocytes from the humanized mouse TK-NOG (called HepaSH cells) may be useful as surrogates of PHH for cytochromes and drug transporter studies.

Material and methods: Fresh HepaSH cells (from different mice engrafted with hepatocytes from various donors) were obtained after 72h of transportation (from the Japanese site of production) and used as monolayer culture. The mRNA expression of main hepatic SLC drug transporters was assessed by RT-qPCR. NTCP, OATPs and OCT1 activities were investigated in hepatocytes in culture, using specific radiolabelled substrates. Activities of cytochromes P-450 (CYP1A2, CYP3A4/5, CYP2B6 and CYP2D6) were assessed by measuring substrate disappearance by HPLC-MS-MS.

Results: In monolayer culture, fresh HepaSH cells present hepatocyte morphology for 14 days in culture. Relative high activities of CYP1A2 and CYP3A4 activities are easily detected at day 1, day 7 and day 14 of culture, suggesting that these cytochromes remain functional during time. Even though CYP2B6 and CYP2D6 activities are decreased on day 14, they remain detectable in cultured HepaSH cells. In this model, an induction of the expression and the activity of CYP1A2, CYP2B6 and CYP3A4 in response to reference inducers has been detected. Regarding the SLC transporters, HepaSH cells express in a stable manner NTCP, BSEP, OATP1B1 and OCT1 during time of culture. Moreover, NTCP, OATPs and OCT1 activity has been measured at day 1 and these transporters remain functional at day 7 and day 14. Finally, a biliary efflux index (BEI) has been detected from day 1 and the biliary ducts remain active until day 14 of culture.

Conclusions: HepaSH cells express transporters and cytochromes P-450 for 14 days in culture. Moreover, the expression of cytochromes is inducible. Taken together, these data suggest that the HepaSH cell model may be useful for pharmaceutical companies for drug interaction studies.

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Poster 12: Multivariate Exact Discrepancy: a new tool for pharmacokinetic/pharmacodynamic model evaluation

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Background and objectives: The criteria used to validate pharmacokinetic model can be grouped into two families. The first family comprises metrics based on the prediction of individual pharmacokinetic parameters. These metrics may not always be appropriate, especially when the predictions suffer from shrinkage [1]. The second family includes methods that compare distributions provided by the data and distributions imposed by the model. The most well-known methods are Visual Predictive Check (VPC) and Normalized Prediction Distribution Error (NPDE). Despite their usefulness, these methods have some limitations. Indeed, VPC does not consider the dependence between concentrations measured in the same patient, while NPDE uses decorrelated concentrations but this does not imply that they are independent [2]. The aim of our work is to propose an evaluation method that accounts for the dependency between concentrations.

Material and methods: The first step of the method consists in simulating the concentrations of "clones" for each individual (same sampling times, same covariate values and same dosage regimen) using the tested model. Then, for each individual, the probability density function (PDF) of the simulated joint concentration vectors is computed. The second step is to determine 1) the smallest level set of the PDF containing the observed concentration vector and 2) to determine the probability that a new vector of concentrations belongs to this level set. The resulting probability can be interpreted as the probability of observing the individual's vector of concentrations. If the model describes the data well, the distribution of the probability of each individual should be drawn from a uniform distribution on [0, 1]. The third step involves verifying the uniformity of the probability distribution. We conducted two types of simulations to evaluate the performances of our method in detecting a misspecification of the structural model. In the first type, we evaluated the type I error, as the ability to not reject a good model. We generated data sets of 2 observed concentrations for 200 individuals using a mono compartmental kinetic, IV administration. The residual error was assumed to be proportional with 20% variability, and the two parameters had lognormal distributions with variances of 10% for maximal concentration and elimination rate constant. The model tested was the model used to simulate the observed concentrations. We used our method and NPDE to evaluate the percentage of rejected models. In the second type, we generated data sets of 2 observed concentrations for 200 individuals using a bicompartmental kinetic IV route.

We assumed a residual error proportional to 20% variability and lognormal distribution with variances of 10% for the four parameters. We then constructed a one compartment model with IV administration that best fit the data. The residual error was assumed to be proportional with 48% variability, and the two parameters had lognormal distributions with variances of 14% and 8.8% for maximal concentration and elimination rate constant, respectively. We performed power tests to determine the percentage of rejected models using our method and NPDE.

Results: In the first simulation, when the nominal error was set at 5%, the power test was equal to 4.8% for our method and 2.5% for NPDE. In the second simulation, with the same type I error, our method achieved a detection power of 100% for identifying model misspecification, whereas NPDE has a detection power of only 51.5%. These results show that our method controls the type I error and outperforms NPDE in detecting structural model misspecification.

Conclusion: We propose a straightforward method for evaluating models during their development. In our preliminary results, this method demonstrated greater power than NPDE in detecting model misspecification. However, given that these results are preliminary, further evaluation on a larger scale is now necessary.

Keywords: Model evaluation, NPDE, VPC

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Poster 13: C-reactive proteinas a biomarker of responseto meropenem therapyin oncohematologic patients with febrile neutropenia: a population PK/PD approach.

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Background: Oncohematologic patients with febrile neutropenia (FN) are at high risk of developing severeinfections due to multidrug-resistant Gram-negative pathogens. Meropenem is a beta-lactam commonly used as a second-line antimicrobial for patients not responding to piperacillin/tazobactam. Although the use of 24h-continuous infusion (CI) administration coupled with TDM may optimize meropenem exposure, patient response to therapy is still difficult to predict, and the identification of clinical biomarkers of response may be highly beneficial. The aim of this study is to assess the pharmacokinetic/pharmacodynamic (PK/PD) relationship between 24h-CI meropenem and C-reactive protein (C-RP) in a cohort of onco- hematological patients with FN.

Methods:

This retrospective study was conductedamong onco-hematological patientsadmitted to the Clinic of Hematology of the IRCCS Azienda Osepdaliero-Universitaria of Bologna, Italy between Jan 2021 and Mar 2022. All patients received 24h-CI meropenem for the treatment of FN. TDM-based clinical pharmacological advice was applied for guiding meropenem dosages, with the intent of targeting meropenem steady-state concentration (Css) over MIC ratio (Css/MIC) between 4 and 8. Meropenem Css and C-RP concentrations were collectedduring therapy, along with demographics and clinical data. A joint population PK/PDmodel was adoptedto fit meropenem Css and C-RP values by means of Monolix software. As all patients were treated with 24h-CI, only a one-compartment model was considered for pharmacokinetic analysis.

Estimated glomerular filtration rate (eGFR) was included as a covariateaccording to previousfindings. PK/PD analysiswas conducted by evaluating differentindirect PK/PD models linking C-RP and meropenemconcentrations, namely inhibition of production, dissipation of response, stimulation of production or dissipation of response models.
Monte Carlo simulations were generated to obtain C-RP concentrations-vs-time profiles ac- cording to different meropenem dosages optimized for renal function, namely 1000 mg q8h by CI, 1000 mg q6h by CI, and 1250 mg q6h by CI in patients with eGFR classes of 50-89, 90- 129 and >130 mL/min/1.73 m2, respectively. The probability of target attainment (PTA) was defined as the proportion of patients having a 50% reduction of C-RP levels from baseline in each simulated scenarioat days 3 and 7from starting therapy.
Results: A total of 58 patients (68.9% males, 40/58) were included. Acute myeloid leukemia was the most frequent hematological malignancy in the population (65.5%, 38/58). Patients with a decrease, unaltered or increased C-RP trend from baseline were 65.5% (38/58), 15.6% (9/58) and 18.9% (11/58), respectively. The median (min-max range) number of meropenem concentration and C-RP measurements per patient were 2 (1-7) and 13 (2-28), respectively.
A total of 112 meropenem plasma Css and 696 plasma C-RP measurements were included in the PK/PD modelling. The population PK estimateof CL was 13.87 L/h with an inter-individual variability of 53.3%. An inhibition of production indirect response model was selected for pharmacodynamic analysis. The IC50 was 26.88 mg/L, which is consistent to therapeutic concentrations observed in patients. The other pharmacodynamic parameters were estimated with good precision, as RSE% was less than 30% for all of them. The prediction-corrected visual predictive check (pcVPC) of the PK/PD model confirmed the adequacy of model predictions. PTAs of C-RP reduction by 50% at days 3 and 7 associated with the three tested dosages ranged between16.2-18.4% and 50.8-55.8%, respectively.
Conclusion: The decrease of C-RP in onco-hematological patients treated with meropenem for FN is slow duringthe first two weeks of therapy. C-RP does not represent a reliable biomarkerof quick response to meropenem therapy.Possible factors affecting C-RP may includethe type and state of the underlying hematological disease. Furtherstudies are neededto assess the role of C-RP in relation to the type of hematological malignancy for guidingantimicrobial therapy.

Poster 14: Analysis of therapeutic molecules adsorption on PDMS, a Teflon-based polymer, glass and polystyrene

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Background and objectives:
The use of Organ-on-Chip for pharmaceutical studies is quickly growing, especially to develop new analytical models to better mimic human physiology. However, the use of PDMS as standard material for those chips has shownstrong limitations, mostlybecause of unspecific binding of molecules (small molecules, proteins,etc.). This concernis especially reinforced with lipophilic molecules [1]. The BMBI lab has already validated the use of a Teflon-based polymer (TbP) to develop and characterize a “PDMS-free” liver-on-Chip (LoC), using hepaticcell lines and testing the adsorption of several compounds [2].

The final goal of our project is to demonstrate the interest of this polymer using a model of co-culture with primary human hepatocytes and to test it on a wider set of compounds. We aim to prove that this material is more suitablethan PDMS to make biochipsfor pharmaceutical studiesthanks to its different properties: O2 permeability, transparency, and a low non-specific binding. The final goal is to adapt the BMBI patented PDMS-based toolbox allowing the perfusion of 12 OoCs in parallel, a user-friendly platformin an industrial environment, in response to the standardization issue.

Material and methods:

Biochips were made with the TbP, and their hydraulic resistance were compared with those obtained with PDMS chips as control, using a pressure controller from 0 mbar to 300 mbar.

We studied the adsorption of 11 small molecules (Midazolam, Hydroxymidazolam, Glu-Midazolam, Phenacetin, APAP, Tolbutamide, Hydroxytolbutamide, Dextrometorphan, Dextrorphan, Dronedarone, Propanoïc Acid Dronedarone) and 2 biologics (Adalimumab, Bevacizumab). These molecules were incubated at 1µM during24 hours in 4 different conditions: glass Petri dishes, glass Petri dishes covered withPDMS, glass Petri dishes coveredwith the TbP and in 6-wells polystyrene culture plates. Samplingwas made at 0h, 1h, 6h and 24h. This study has been realized with one well per sampling time, with each conditionin triplicate. The samples were analyzed in Liquid Chromatography - Mass Spectrometry (LC-MS) to determinethe kinetic profiles.

As a first approachwe cultivated HepG2/C3a cell lines during 3 days in staticin those chips to recreatea biological environment. At the end of the 3 days their morphology was observed with an electronic microscope. Immunostaining and live/dead assays will be completed soon to further characterize cell growth in those chips.

Results:

The comparison of the hydraulic resistance between PDMS chips and TbP chips showed similar responses, allowing the TbP chips to be used in the dynamic platform. HepG2/C3a were successfully cultivated during the 3 daysin both PDMS and TbP chips, with a confluent cellularlayer.

The experiment for adsorbance measurement has justbegun so we don't have the results yet.However, we expecta significant lower adsorption of those moleculeson glass and on the TbP than on PDMS.

Conclusions:

This experiment showed that the TbP seems to be an interesting substitute to PDMS in biochips. TbP chips showed interesting similarities concerning hydraulic resistance and cell adhesionand morphology. The results obtainedafter the analysisof adsorption will show if this new polymer is also suitable for pharmaceutical studies.If the results are relevant,this polymer will be kept as new material and a new liver model will be developed based on this TbP chip.

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Poster 15: Physiologically-based pharmacokinetic modelling of dendrimer nanoparticles to unravel structure – PK parameters relationships

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Background and Objectives:
Nanoparticles (NPs) have been developed for over two decades in order to improve the pharmacokinetic (PK) profile of drugs and to target specific tissues. The diversity of NPs in terms of structures and properties results in specific PK behaviors. Physiologically-based pharmacokinetic (PBPK) modeling is a powerful tool to predict PK of NPs by integrating parameters describing physiological and biological processes, as well as physicochemical parameters. This approach will allow to better understand the impact of NPs characteristics on the in vivo disposition. In the current work, a theoretical PBPK model was developed for gallium-68 radiolabeled-dendrimers to better understand the link between their physicochemical characteristics and their PK properties.

Methods:
A PBPK model tailored to NPs (nanoPBPK) was developed using R software (4.2.2), including a specific compartmental structure based on the current understanding1-3 of the PK of NPs. When available, parameter values from the literature were used in the equations. Experimental in vivo data previously obtained for seven formulations of dendrimers varying in the length of the alkyl chain, fluorination and presence of RGD, and developed by CINaM and CERIMED4, were used for model evaluation and refinement.
The data consisted in blood samples (n=6) and PET images (n=6) collected at 9 and 12 time points respectively after intravenous injection in healthy mice. A semi-mechanistic population PK analysis5 of the data allowed to decipher renal and hepatic clearances as well as partition coefficient values which were integrated in the PBPK model. NPs-specific parameters highly influencing concentrations of dendrimers over time in plasma and organs were identified, allowing to establish relationships between NPs properties and their PK.

Results:
A nanoPBPK model with both renal and hepatic clearance was built, which included mononuclear phagocyte system sub-compartments for organs such as lungs, spleen and liver. A permeability-limited model was used to describe distribution in tissues. The a priori nanoPBPK model well described the evolution of concentrations of dendrimers in plasma and tissues. Partition coefficient and permeability coefficient were found to be the most influential parameters. The parameters were refined in the PBPK model to obtain more accurate predictions, linking structural characteristics of dendrimers to their PK.

Conclusions:

The PBPK model provided a good description of the experimental data and a breakthrough mechanistic insight into the processes involved in the distribution and elimination of dendrimers. The current work allowed to bridge NPs structural properties with biological properties and in vivo behavior. The next step will be the extension of the PBPK model to nondendrimeric nanoparticle types, such as lipid nanocapsules, in order to provide a generic tool to guide the design of future innovative NPs.

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Poster 16 : Population pharmacokinetic model of cefotaxime encompassing time-varying physiopathology: exploration of intra-individual variability of the renal function

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Materials and methods:

In a prospective, observational study, adult ICU patients (October 2015 - May 2017) were treated with a loading dose (2-4g/0.5h) followed by a continuous infusion (1-24g/24h) of cefotaxime. Cefotaxime concentrations 30 minutes after the loading dose, during the continuous infusion at day 1, 4 and 7 after drug initiation, and 4 hours after the end of the infusion, were measured by a validated HPLC-UV method. Demographic, clinical and biological data were collected at inclusion and throughout the study. Data were analysed by nonlinear mixed-effects modeling using MONOLIX version 2023R1. Data below the limit of quantification were treated as left-censored. The impact of covariates values at baseline was evaluated using the stepwise covariate model procedure. Time-varying covariates reflecting the evolution of renal function during the course of treatment were first included in the model as a regressor, then as a biomarker model.

Results:

The study included 76 ICU hospitalized patients (31 females, 45 males, age 57.5 ± 17.6 years). 251 cefotaxime plasma concentrations were available for PK analysis. 597 serum creatinine levels were collected to monitor the renal function. A one-compartment model with linear elimination and proportional residual error best described the PK data. Inclusion of baseline serum creatinine concentration as a covariate on cefotaxime clearance significantly improved the model and reduced the unexplained interindividual variability of clearance from 54 to 31%. Inclusion of time-varying serum creatinine as a regressor further improved the model. Backward interpolation of the regressor performed better than forward interpolation. In order to anticipate changes in kidney function, particularly from normal kidney function to kidney injury, a joint model with a biomarker model of serum creatinine impacting the cefotaxime PK model was developed. A mono-exponential increase followed by a mono-exponential decrease best described kidney injury and recovery.

Conclusions:

A PopPK model of cefotaxime was developed, encompassing the variation of renal function over the treatment course. Serum creatinine concentration explained a significant part of the high inter- and intra-variability of cefotaxime PK in ICU patients. Since the impact of renal function might be similar for other β-lactams4, our approach might be applied to a common PopPK model for various β-lactams in order to optimize a priori dosing adjustment in the context of drug switches.

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Industry and Academic Posters

Poster 17: Validation of PBPK-Based Translation to Predict Monoclonal Antibody Pharmacokinetics in Pediatric Populations

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Background and objectives: Accurate prediction of pediatric dose is a necessity before conducting a clinical trial or using a drug product in standard clinical practices. For the pediatric population, both safety and efficacy need to be considered due to ethical reasons**.**

1 The recommended doses of most of the therapeutic proteins, including monoclonal antibodies (mAbs), are extrapolated to pediatrics from adult doses based on body weight. However, this approach does not consider physiological and biochemical differences between children and adults. Therefore, this could lead to mAbs' underexposure, limiting its efficacy in this population. Other methods are necessary to mechanistically predict pediatric doses.

For small molecules, physiologically based pharmacokinetic (PBPK) models have been long used to predict pediatric dose based on age-related changes in the physiology and enzymes/transporters ontogeny.

2 The aim of this study is to evaluate the ability of the PBPK model to predict pediatric exposure for mAbs.

Material and methods: Two immunoglobulin G1 (IgG1) mAbs were used for model development and validation: infliximab (anti-TNF-alpha) and bevacizumab (anti-VGEF). The PBPK models were built using the Biologics module within GastroPlus©. Average concentration profiles in adult and pediatric populations were extracted from the literature. Simulations were conducted with specific doses, dose schedules, and subject demographic information matching specific clinical trials. For each mAb, the PBPK model was calibrated based on observed data in healthy and patient adults. Then, the physiological parameters were scaled to match the pediatric physiology to predict exposure in the pediatric population. Predicted plasma concentration-time courses were compared with reported observed data to assess the ability of the PBPK model to predict pediatric exposure. Accurate clinical predictions were defined as predicted error (PE) ratios within 0.8 to 1.25-fold and acceptable predictions within the range of 0.67 to 1.5-fold of the observed data.

Results: The final PBPK models in healthy adults described well the observed plasma concentration-time courses for the two mAbs. For infliximab, the vascular and lymphatic reflection coefficients were adjusted to 0.99 and 0.60, respectively, and the elimination rate constant (Kdeg) was fitted to 1.34 E+04 (1/day). For bevacizumab, the parameter values for the vascular reflection coefficient, the lymphatic reflection coefficient, and the Kdeg were 0.99, 0.63, and 1.24 E+04 (1/day), respectively. Using adult patients' observed data and literature information, infliximab kdeg was increased by 1.5-fold to account for inflammation effect on mAbs clearance. In a similar fashion, VGEF circulating concentration was increased by 100% to account for the cancer effect. These final PBPK models could then accurately predict infliximab and bevacizumab exposure in pediatric population. PE ratios for Cmax and AUC at steady state for infliximab were 1.22 and 1.30 respectively, and PE ratios for bevacizumab were between 1.09 and 1.12 for Cmax and 1.23 and 1.32 for AUC.

Conclusions: PBPK models allowed an accurate prediction of the observed data in the pediatric population for two mAbs. For both mAbs, one of the PBPK model parameters was adjusted to account for disease conditions prior to informing the pediatric extrapolation (endosomal clearance for infliximab and circulating VGEF concentration for bevacizumab). More case studies will be needed for other mAbs to confirm this study's results. Nevertheless, the accurate pediatric extrapolation outcomes for these mAbs represent an important step in the validation process of the extrapolation method used to predict biologics exposure in this population using a PBPK model.

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Poster 18: In vitro – in vivo correlation of antisense-oligonucleotide metabolite profiles in rat

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Background and objectives: Over the past decades, interest towards oligonucleotide-based therapies has been strongly increasing among the pharmaceutical industry. Several generations of antisense oligonucleotides (ASOs) have been introduced as drug candidates, with structures containing modifications in their RNA backbone and ribose units aiming to optimize their affinity towards the target, as well as their distribution, metabolism, and pharmacokinetics.

Antisense oligonucleotides are generally metabolized to shorter oligomers by various exo- and endonucleases, which are present in several tissues. As the modern backbone-modified ASOs typically have high tissue distribution, especially to liver and kidney, the metabolism occurring in these organs plays a large role in their elimination. Biotransformation data is typically needed for regulatory health agencies in early clinical stage development, and in the lack of widely accepted in vitro models for ASO metabolism studies, the data is most often collected by analysis of samples from general toxicity studies [1]. The aim of this work was to investigate metabolite profiles of two antisense oligonucleotide compounds, using various liver and kidney derived in vitro and rat in vivo systems, for comparing the in vitro – in vivo correlation. The investigated ASOs were alicaforsen and volanesorsen, both containing phosphorothioate backbone modification, and the latter containing also 2-methoxyethyl (2-MOE) modification in the five first ribose unites from both 3' – and 5' – terminals of the sequence.

Material and methods: The ASOs were incubated at 10 µM test concentration for 24h with rat and human liver and kidney S9 fractions and rat liver and kidney homogenates and for 72h with plated rat and human hepatocytes. The incubations were quenched using 2% NH4OH, followed by extraction with phenol: chloroform: isoamyl-alcohol (25:24:1). The ASOs were administered subcutaneously (6 mg/kg) to two male rats three times every 24 h (alicaforsen) or 48 h (volanesorsen).

Plasma and urine samples were collected 0 - 24h after the last dose, while kidney and liver were harvested at 24h time points and homogenized 1: 4 in PBS. Plasma, urine, and tissue homogenates were then extracted as above.

All extracted samples were analyzed by LC/HR-MS (Waters Acquity LC and Thermo Orbitrap Exploris 120 mass spectrometer) with Waters BEH C18-column (2.1 × 50 mm, 1.7 µm particle size) and gradient elution with acetonitrile and 100 mM HFIP / 15 mM DIPEA. The acquired data was processed for metabolite profiles using Thermo BiopharmaFinder software.

Results: A high number of metabolites were detected for both ASOs, their number and relative abundances being generally highest in the in vivo liver and kidney samples and the lowest in the in vitro samples. No clear differences between rat and human in vitro experiments were found, but slightly different metabolite profiles were observed between in vitro hepatic and renal models. The in vitro experiments predicted the most abundant in vivo plasma, liver and kidney metabolites, formed via deletions from 3' n-terminal, better for alicaforsen than for 2'- MOE-modified volanesorsen. For both ASOs, the most abundant metabolites in urine were shorter 5 – 8 -mers and were underpredicted by the in vitro models. However, many of the metabolites detected from in vivo samples were not observed in the in vitro samples.

Conclusions: The hepatic and renal in vitro models show variable correlation to rat in vivo metabolite profiles, especially for 2'- MOE-modified volanesorsen. To reduce the use of animals in research and to enable better early-stage prediction of oligonucleotide therapeutics in vivo metabolism, novel hepatic and renal in vitro assays are needed.

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Poster 19: Old battles and new horizons for urine PK analysis in early drug development

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Background and objectives

GULLIVER-2 Part 2 was the repeat dose, randomized, placebo-controlled Phase 2a component of an early phase study investigating the safety, tolerability, and pharmacokinetics of GB1211 (a Gal-3 inhibitor) in participants with moderate (Child-Pugh B) hepatic impairment.

This presentation describes a fit-for-purpose approach for handling urine PK assessments when facing the well-known battles with regards to urine bioanalytical methods at early stages of clinical development.

Material and methods

Urine samples from part 2 of GULLIVER-2 study were analysed using a fully validated LC-MS/MS assay. Urine pharmacokinetic parameters were derived using WinNonlin and SAS.

Results

LC-MS/MS bioanalytical method for determination of GB1211 in urine was validated at the initial calibration range: 0.5 – 500 ng/mL based on first-in-human study data. The analysis of GULLIVER-2 study samples showed greater concentrations than anticipated. Three additional dilution factors were validated (concentration 2000 ng/mL, dilution factor 50; concentration 21 000 ng/mL, dilution factor 50; and concentration 40 000 ng/mL, dilution factor 100) and 304 out of 345 study samples were analyzed with dilutions. However, some study samples from 5 patients required adjustment in the concentration range to be accurately analyzed. Therefore, changes in the concentration range (100 ng/mL to 28 000 ng/mL) and partial validation experiments were performed.

As the change in calibration range may result in within-subject bias , notably in the interpretation of PK parameters tables with concentrations obtained using a method with exactly one calibration range per patient and separate tables with concentrations obtained using a method with two calibration ranges for a set of patients were generated. Additionally, some of the PK parameters were flagged and therefore two more tables were generated with inclusion and exclusion of a set of justifiably flagged parameters.

Conclusions

This strategy, which was adopted in collaboration with PK and bioanalytical scientists, proved to be a flexible solution for urine PK assessments by taking into account both the regulatory framework and the bioanalytical challenges.

Poster 20: Predicting drug-drug interactions of belumosidil using a physiologically based pharmacokinetic model

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Background and objectives: Belumosudil is a selective inhibitor of Rho-associated protein kinase 2 (ROCK2) approved for treating chronic graft-versus-host disease (cGVHD) in adult and pediatric patients. In vitro incubations with human liver microsomes indicated that the metabolism of belumosudil involves various cytochrome P450 (CYP) isoforms with CYP3A4 responsible for 41.9% of belumosudil metabolism, with contributions from CYP2D6 (21.7%), CYP2C8 (14.2%), CYP1A2 (<5%), CYP2C19 (<5%) and uridine diphosphate glucuronosyltransferase (UGT)1A9 [1].

In a clinical study on drug-drug interactions (DDIs) [1], it was observed that a strong CYP3A4 inhibitor itraconazole (ITZ) led to a 25% increase in belumosudil exposure (AUC0-t), while a strong CYP3A4 and CYP2C8 inducer rifampicin (RIF) resulted in a 72% decrease in AUC0-t, compared to the exposure levels when belumosudil was administered alone.

The primary objective of this study is to use previously published belumosudil data to develop a Physiologically Based Pharmacokinetic (PBPK) model that predict the clinically observed DDI of ITZ and RIF on belumosudil pharmacokinetics.

Methods: A whole body PBPK model for belumosudil was developed in GastroPlus™ v9.7 (SimulationsPlus, Inc.). The ACAT™ model was used to describe the intestinal dissolution, precipitation and absorption of belumosudil. The model incorporates physicochemical parameters predicted from structure using ADMET Predictor™ (v9.5) along with published solubility and in-vitro metabolism data [1]. Permeability and clearance terms were refined using PK data from 2 separate clinical studies in which PK following IV (0.1 mg) and oral (200mg tablet) dosing (with and without ITZ and RIF) were evaluated in healthy male subjects [1,2]. In DDI simulations study design and dosing regimen was matched with the clinical study design [1]. The default ITZ and RIF models from the GastroPlus™ DDI database (version 9.7) were used.
Results: The PBPK model accurately predicted the exposures of belumosudil following the intravenous (IV) microtracer infusion (100 µg) (%PE was 4% and 0% for Cmax and AUC0-t, respectively) and oral administration of a single 200 mg tablet in fasted conditions (%PE was -23% and 8% for Cmax and AUC0-t, respectively) in healthy male subjects. The model accurately predicted the increase in exposure resulting from co-administration of ITZ (200 mg once daily for 9 days with concomitantly with belumosidil on Day 1); predicted DDI ratio; Cmax 1.12, AUC0-t 1.25, observed DDI ratio; Cmax : 1.2 (1.11-1.31), AUC0-t 1.25 (1.17-1.33). Moreover the greater (likely to be clinically relevant) negative interaction observed following RIF dosing (600 mg once daily for 9 days before belumosidil dosing) was also predicted by the model; predicted DDI ratio; Cmax 0.58, AUC0-t: 0.37, observed DDI ratio; Cmax 0.41 (0.37-0.44), AUC0-t 0.28 (0.26-0.30).
Conclusions: A PBPK model has been developed using GastroPlus™ v9.7 to successfully predict the clinical DDIs of belumosudil with ITZ and RIF in healthy male subjects. The model holds potential for additional exploration, specifically exploring the DDI interactions of belumosudil with other potential perpetrator drugs.

Poster 21: Development and application of a full LC-MS workflow for the analysis of interchain cysteine-conjugated ADCs

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Background and objectives

The development of new analytical workflows is essential to characterize in vivo behavior of next generation biotherapeutics, such as Antibody-Drug Conjugates (ADCs) that are complex molecules designed to target and kill cancer cells and composed of a biologically active agent covalently attached to a mAb via a chemical linker1,2.
These last years, the conjugation strategy has evolved from stochastic conjugation on lysine residues to more controlled approaches, allowing to get more homogeneous Drug-to-Antibody Ratio (DAR) profiles3.
To support the development and the optimization of ADCs, it is essential to understand their pharmacokinetics behaviors (stability, antigen binding, clearance, biodistribution), by assessing the DAR in vivo. Therefore, the objective of this work was to develop a full LC-MS workflow for the bioanalysis of an interchain cysteine-conjugated ADC, in vivo, to quantify the conjugated drug, to quantify the total antibody species and to determine the DAR profile.

All together, these approaches allow to obtain the PK profiles of all individual circulating DAR species and to determine PK parameters.

Material and methods

We have developed a full LC-MS workflow for the bioanalysis of Adcetris® (Brentuximab vedotin, Takeda) used in the treatment of Hodgkin lymphoma. This ADC is an interchain cysteine-conjugated ADC (DAR 4) consisting of a mixture of covalent and non-covalent species. An in vivo study has been conducted using CD1 mice and an injection dose of 10 mg/kg of Adcetris®. The resulting samples have been used for the LC-MS workflow described hereafter.

The conjugated drug (MMAE) has been deconjugated through the cleavage of the Val-Cit linker with papain. Then its quantification has been performed using LC-MS/MS with an ACQUITY UPLC I-Class (Waters) coupled to a 6500 triple quad (Sciex). In parallel, a middle-up MS approach combining immuno-enrichment and LC-MS analysis of LC and HC subunits after disulfide bond reduction has been set up using a Synapt G2-Si HRMS QToF (Waters). Finally, bottom-up MS was used to quantify the total antibody species on an ACQUITY UPLC I-Class (Waters) coupled to a 6500 triple quad (Sciex).

Results

The DAR obtained for the in vivo study was 3.7 at 5 min and decreased to 0.8 at 336h. The quantification of the antibody by ELISA and LC-MS/MS showed similar profiles of the kinetics for both techniques with an averaged difference of 15%. Moreover, the calculated Total Conjugated Drug (TCD) based on DAR and LC-MS/MS results fitted well with the calculated TCD based on DAR and ELISA results with an averaged difference of 11%. Finally, the quantification of conjugated MMAE by LC-MS/MS after papain cleavage was done giving the measured TCD. This measured TCD had a general profile close to the calculated TCD whatever the technique considered (DAR combined to ELISA or DAR combined to LC-MS/MS). Therefore, this in vivo study with Adcetris® enabled us to validate the methodology combining various LC-MS/MS approaches for the determination of PK profiles.

Conclusions

Lately, the conjugation strategy of ADCs has evolved from stochastic conjugation on lysine residues to more controlled approaches, in order to get more homogeneous Drug-to-Antibody Ratio (DAR) profiles. This is the case of interchain cysteine-conjugated ADCs. To support the development of these new types of ADCs, it is essential to develop innovative workflows. Here, a full LC-MS workflow has been developed for the characterization of in vivo evolution of Adcetris®. It enables us to quantify the conjugated drug (MMAE) after the cleavage of the drug using papain, to quantify the total antibody by LC-MS and to determine the DAR profile by HRMS. The total conjugated drug has then been determined giving PK profiles of all individual circulating DAR species.

Poster 22: Interactions of organophosphate flame retardants with human drug transporters

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Background and objectives:

Organophosphate flame retardants (OPFRs) are widely distributed in the environment and exert possible deleterious effects towards the human health. As a consequence, these pollutants are of increasing interest. The present study investigates in vitro their possible interactions with human SLC and ABC drug transporters, which contribute to xenobiotic toxico- and pharmacokinetics.

Material and methods:

This study focused on 7 OPFRs (TDCPP, TCEP, TCPP, TNBP, TBOEP, TPHP and TOCP). To study ABC transporters, P-gp-positive MCF7R cells, hepatoma HuH-7 cells, expressing human multidrug resistance-associated protein (MRP) 2 and MRP4 and human breast cancer resistance protein (BCRP)-transfected HEK-293 cells were used. As for SLC transporters, human HEK-293 cells expressing human SLC transporters, i.e., organic cation transporter (OCT) 1, OCT2, MATE1, MATE2-K, organic anion transporter (OAT) 1, OAT3, organic anion transporting polypeptide (OATP) 1B1 or OATP1B3, as well as control HEK-MOCK cells, human hepatoma HepaRG cells and fresh or cryopreserved primary human hepatocytes were used. OPFR effects on the activity of ABC and SLC transporters were investigated through the measure of cellular uptake or retention of reference substrates for transporters, in the presence or absence of reference inhibitors. mRNA regulation was studied by RT-qPCR.

Results:

4 of tested OPFRs, i.e., TBOEP, TDCPP, TOCP and TPHP, were found to inhibit activities of some transporters, such as OAT3, OATP1B1, OATP1B3, OCT2 or BCRP. These inhibition were concentration-dependent, with IC50 values ranging from 6.1 µM (for TDCPP-mediated inhibition of OCT2) to 51.4 µM (for TOCP-mediated inhibition of BCRP). OPFRs also blocked the transporter-dependent membrane passage of endogenous substrates, notably that of hormones. Indeed, OAT3-mediated transport of estrone-3-sulfate (E3S) was blocked by TBOEP and TPHP in a concentration-dependent manner. OAT3 however failed to transport TBOEP and TPHP. In the same way, the OATP1B3-mediated transport of cholecystokinin octapeptide (CCK-8) was reduced by TDCPP in a concentration-dependent manner and TDCPP also decreased the OCT2-mediated accumulation of dopamine in HEK-OCT2 cells. OPFRs additionally repressed mRNA expressions of some transporters in cultured human hepatic HepaRG cells, especially those of OAT2 and OCT1 in response to TOCP, with IC50 values of 2.3 µM and 2.5 µM, respectively.

Conclusion:

These data therefore add OPFRs to the expanding list of pollutants interacting with drug transporters, even if OPFR concentrations required to impact transporters, in the 2-50 µM range, are rather higher than those observed in humans environmentally or dietarily exposed to these chemicals.

Poster 23: Detailed comparison of three major PBPK software: PK-sim, Simcyp and Gastroplus

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Background:

Physiologically-based pharmacokinetic (PBPK) modeling revolutionizes drug development by simulating drug-body interactions, yet a significant gap remains: a comprehensive comparative analysis of PBPK software. Literature on this topic is limited. In 2016, Sjeogren et al. compared oral absorption models in Simcyp, GastroPlus, and unpublicized GI-Sim, highlighting differences in absolute average fold error (AAFE) [1]. Despite distinctions, all aided formulation development by capturing dose and particle size dependencies. In 2017, the Innovative Medicines Initiative's Oral Biopharmaceutical Tools project assessed PBPK models' oral absorption accuracy, including Simcyp, GastroPlus, and GI-Sim [2;3]. A 2020 follow-up with updated data revealed disparities in simulation outputs, despite identical input parameters [4]. In 2022, Garcia et al. compared PK-Sim and Simcyp for simvastatin pharmacokinetics, finding similar performance with variations in absorption and elimination models [5].

To address this knowledge gap, we undertake a comprehensive PBPK platform comparison, focusing on distribution and elimination, and considering the latest software releases, including the increasingly influential open-source PK-Sim.

Method:

In this comprehensive study, we selected eight highly diverse compounds, namely Metoprolol, Lorazepam, Dabigatran, Lamotrigine, Haloperidol, Valproic Acid, Cefuroxime, and Trimethoprim, categorized into four distinct groups based on their elimination pathways: CYP substrates, UGT substrates, CYP/UGT mixed substrates, and those primarily eliminated through renal excretion. For each of these compounds, we developed three distinct PBPK bottom-up models on PK-Sim, GastroPlus and Smcyp, all constructed using identical input parameters obtained from the existing literature. Our focus was exclusively on intravenous administration to enable a precise comparison of distribution and elimination-related parameters.

To assess the accuracy of these models, virtual populations were generated, and concentration-time profiles, as well as clearance (CL) and volume of distribution (Vss), were predicted and compared across all three software platforms. Statistical analysis, including an ANOVA test, was conducted to rigorously evaluate the significance of any observed differences.

Results:

For compounds primarily eliminated by CYP enzymes, such as metoprolol and trimethoprim, the ANOVA test revealed significant differences (with p-values of 0.05 and 0.1) in CL and Vss predictions among all three software platforms, except for Vss predictions between PK-Sim and Simcyp. In the case of compounds predominantly eliminated by UGT enzymes, including Lorazepam, Dabigatran, and Lamotrigine, as well as compounds with mixed CYP/UGT elimination like Haloperidol and Valproic Acid, the ANOVA test (with p-values of 0.05 and 0.1) demonstrated significant variations in CL and Vss predictions across all three software tools.

However, for cefuroxime, which undergoes renal excretion as its primary elimination pathway, the ANOVA test (with a p-value of 0.01) indicated significant differences in CL and Vss predictions between all software platforms, except for Vss predictions between Simcyp and PK-Sim. These findings provide valuable insights into the software-specific performance variations when modeling the pharmacokinetics of compounds with different elimination pathways, contributing to a more informed approach in drug development.

Conclusion:

Our study offers an initial exploration of the variabilities in PBPK modeling due to different software platforms, emphasizing their impact on predicted pharmacokinetic (PK) parameters. These distinctions warrant further investigation by the scientific community to enhance confidence in PBPK modeling. Future research should dissect software equations, examining partition coefficients (Kp), population file differences, and scaling parameters. It's essential to note our study's focus on healthy volunteers; future work should expand to encompass diverse PBPK modeling dimensions, including various administration routes, drug formulations, and populations. This comprehensive approach will advance our understanding of PBPK modeling, enhancing its reliability in drug development.

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Sponsor Guide

Profiles for sponsors , listed alphabetically by sponsor grade.

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sanofi

GOLD SPONSOR

The first step towards a molecule becoming a drug is to be accepted as a clinical candidate. Before that, series of compounds are tested thoroughly to ensure that the right molecule is chosen. ADME-Tox research is a crucial part of this path and that's why leading pharma and biotech companies have made us part of their team.

Admescope offers a broad portfolio of tailor-made ADME-Tox assays both in vitro and in vivo. Admescope's expertise lies in drug metabolism, including metabolite profiling & identification, drug–drug interactions, early pharmacokinetics, and quantitative bioanalysis. The right assays are available, regardless of phase, whether it is discovery, lead optimization, or preclinical development. The level of data interpretation can be customized according to the client's needs. In addition to small molecules and peptides, Admescope provides services for oligonucleotides and larger biologics.

As part of Symeres, we aim to have real, positive impact on people's lives. We make molecules matter. Together

Admescope
A SYMERES COMPANY

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WHO WE ARE

As a mid-sized global biopharmaceutical company, Ipsen improves patients' lives through research, innovation and the development of transformative medicines in Oncology, Rare Disease and Neuroscience.

WHAT WE DO

Improving people's lives and health outcomes by focusing on areas of high unmet medical need, we are accelerating our momentum and rapidly boosting our pipeline to bring the full potential of our innovative medicines to patients.

IPSEN
Innovation for patient care

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We are a growing pharmaceutical company and a dedicated ally to healthcare providers treating patients with critical conditions.
Our portfolio of products, many of them lifesaving, is focused on emergency care and rare diseases. Our expertise lies in mastering complex products, navigating complicated regulatory pathways, and serving niche patient populations.

SERB Pharmaceuticals

Since **SOLVO's** inception in 1999, our commitment to transporter research is still going strong, while our portfolio has since then grown to cover a wider range of in vitro ADME/Tox assays. This development has been supported by our dedicated R&D team and resulted in 100+ peer reviewed publications to date.
This scientific approach extends to all our offers. For all inquiries, our expert team can support one-to-one consultative discussions to find the best assay solutions for any project. We work with small and large companies worldwide, at any step in the drug development journey. Solutions are offered from simplified screen-type setups to studies for regulatory submission, including custom assay development or tailored assay setups. As part of Charles River Discovery, we also provide access to end-to-end DMPK solutions. We invite you to meet our experts and see how we can contribute to the success of your company!

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BioIVT enables smarter science and accelerates medical breakthroughs by delivering high-quality personalized biospecimen solutions and research services to life science and diagnostic industries. Recognized as an industry leader, we specialize in control and disease state samples including human and animal tissues or preparations, cell and gene therapy products, blood, and other biofluids, as well as ADME contract research services from standalone bioanalytical support through tiered in vitro studies with submission-ready reports to customized consulting.
By combining our technical expertise, exceptional customer service, and unmatched access to biological specimens, BioIVT serves the research community as a trusted partner in ELEVATING SCIENCE®.

BIOIVT
ELEVATING SCIENCE®

Comac Medical is focused on providing innovative and flexible solutions of the highest quality to meet pharmaceutical industry needs. Founded in 1997, we are CRO and SMO managing the full spectrum of clinical trial services from Phase I - IV across 33 European countries, the US and APAC. In 2005 Comac Medical started its state-of-the-art Clinical Research Unit for Phase I, BA/BE studies with 42 hospital beds, a highly qualified medical and operational team, a large patient/healthy volunteers database, an extensive referral physician network, and central laboratory/pharmacy services.
Comac Medical possesses a broad experience in PK modeling, PK analysis, and PK sampling, all while maintaining the highest standards of quality and understanding of current regulatory expectations.
Comac Medical has extensive experience in PK modeling and PK analysis including but not limited to:
+ Single and multiple dose studies,
+ Studies with modified release formulations
+ PK in EPS and translational medicine
+ PK/PD and PBPK modeling
+ PK in special populations (hepatic and renal impairment, elderly)
To keep up to date with the latest news, follow Comac Medical on LinkedIn or visit https://comac-medical.com

COMAC MEDICAL
EXPERTS IN CLINICAL RESEARCH

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Established in 1999, **Cyprotex** Limited was acquired by Evotec (www.evotec.com) in 2016. Cyprotex, an Evotec company, has sites at Alderley Park near Macclesfield, UK and in Framingham near Boston, USA. The company has dedicated and highly qualified employees with proven experience in a wide range of specialist techniques acquired across diverse industries. The majority of our clients focus in pharmaceutical research, however, we also support clients in the chemical, cosmetics and personal care, agrichemical and tobacco industries. Cyprotex specialises in in vitro and in silico ADME-Tox services. This includes in vitro ADME and safety screening to support discovery projects, regulatory in vitro ADME and DDI studies during preclinical and clinical development, specialist techniques for assessing mechanisms of in vitro human and animal toxicity (e.g. transcriptomics, 3D models and MEA electrophysiology) and PBPK/QSAR modelling expertise. Further information on Cyprotex is available on our website at www.cyprotex.com.

cyprotex AN EVOTEC COMPANY

Debiopharm is an independent biopharmaceutical company based in Switzerland with an ongoing commitment to develop tomorrow's standard of care to cure cancer & infectious diseases and improve patient quality of life. Our main activities include drug development, drug manufacturing and digital health investment.

Debiopharm
WE DEVELOP FOR PATIENTS

LesqLABS is a biosimulation solutions company providing consulting and services for the development and utilization of PBPK and QSP modeling & simulation platforms using OPEN-SOURCE software as value-generating, holistic modeling & simulation tools to support our customers decision making process along the entire life cycle of pharmaceutical, chemical, or crop protection products.
esqLABS can offer custom-tailored, open-source solutions and actively contributes to the open systems pharmacology community through our involvement in the software development for the OSP Suite (www.open-systems-pharmacology.org with PK-Sim and MoBi and R tools), we further support the community by providing software and model qualification, and online and workshop-based training.

esQlabs
we empower life sciences

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L'Oréal has devoted itself to beauty for over 100 years. With its unique international portfolio of 35 diverse and complementary brands, the Group generated sales amounting to 27,99 billion euros in 2020 and employs 85,400 people worldwide. As the world's leading beauty company, L'Oréal is present across all distribution networks: mass market, department stores, pharmacies and drugstores, hair salons, travel retail, branded retail and e-commerce.
Research and Innovation, and a dedicated research team of 4,000+ people, are at the core of L'Oréal's strategy, working to meet beauty needs and aspirations all over the world. L'Oréal sets out ambitious sustainable development goals across the Group for 2030 and aims to empower its ecosystem for a more inclusive and sustainable society

L'ORÉAL
RESEARCH
& INNOVATION

Pierre Fabre Laboratories is the 2nd largest dermo-cosmetic player in the world and the 2nd largest private French pharmaceutical group. Its portfolio includes numerous medical franchises and international brands such as Pierre Fabre Oncologie, Pierre Fabre Dermatologie, Eau Thermale Avène, Ducray, Klorane, René Furterer, A-Derma, Même Cosmetics, Naturactive, Elgydium, Inava and Arthrodont.
In 2022, Pierre Fabre Laboratories recorded turnover of €2.7 billion, 69% of which was generated internationally in 120 countries, and invested more than €170 million in R&D.
Pierre Fabre Laboratories has always been based in the Occitanie region of France and manufactures 90% of its products in France. It employs nearly 9,600 people worldwide.
Pierre Fabre Laboratories is 86% owned by the Pierre Fabre Foundation, a foundation recognized as being of public interest since 1999, and secondarily by its employees through an employee shareholding plan.
In 2022, its CSR approach was assessed as "Exemplary" by the independent organization AFNOR Certification for the Engagé RSE (Committed to CSR) label (ISO 26000 standard for sustainable development). www.pierre-fabre.com @PierreFabre

Pierre Fabre

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Pharmetheus is a diversified Life Sciences consultancy partner at the forefront of the application of quantitative approaches to drug research, development, and usage. We operate in the area of biosimulation and biotech, using software to describe biological processes.
We offer consulting services focused on the application of quantitative approaches to support drug research, development, and life-cycle decisions. With our expertise in model-informed drug development, pharmacometrics, and PBPK-QSP, we support clients from strategy to design and analyses. At Pharmetheus, we are promoting a culture of innovation and collaboration where diversity and inclusivity are highly valued, and where everyone feels supported and empowered.

Pharmetheus®

Pharmidex is a UK-based CRO founded in 2002 providing high quality, cost-effective and rapid solutions to clients in in vitro ADME, Pharmacokinetics (DMPK), bioanalysis (non-GLP, GLP/GCP) and toxicology (non-GLP, GLP). Pharmidex also offer in silico modelling and efficacy models supporting oncology, CNS, respiratory, stroke and auto-immune disease programmes. The Pharmidex team are highly experienced in designing, executing, reporting and discussing results of studies to help advance client projects successfully. The client base includes medical charities, academic groups, biotech and pharma companies globally. In addition to fee-for-service offering, Pharmidex are always seeking opportunities to collaborate in grant funded projects. www.pharmidex.com/

pharmidex
world-leading translational research

PhinC Development is the expert partner for small to medium sized pharmaceutical or biotech companies, who need to move forward in early drug research.
Thanks to a multidisciplinary team with thorough field experience, PhinC Development helps to take the best decisions concerning drug development using all existing pharmacology and pharmacometrics modeling & simulation (M&S) tools
PhinC brings its expertise in pharmacometry, pharmacokinetics, pharmacology and biostatistics to develop innovative predictive models. Such models are extremely powerful tools, able to give Biotechs a decisive advantage in the race to develop drug candidates
The Model-Informed Drug Development (MIDD) approach allows us to have a global vision of your development program to be able to provide you with perfectly customized advice. At PhinC, we adapt to your way of working in order to be an integral part of your team to be able to advise you rationally. We offer personalized support throughout the development process, so you will have all the keys to make a decision with peace of mind.

PhinC Development

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About Servier

Founded to serve health, Servier is a global pharmaceutical group governed by a non-profit Foundation that aspires to have a meaningful social impact, both for patients and for a sustainable world. With its unique governance model, it can fully serve its vocation with a long-term vision: being committed to therapeutic progress to serve patient needs. The 21,400 employees of the Group are committed to this shared vocation, source of inspiration every day.

As a world leader in cardiology, Servier's ambition is to become a renowned, focused and innovative player in oncology by targeting hard-to-treat cancers. That is why the Group allocates over 50% of its R&D budget to developing targeted and innovative therapies in oncology.

Neuroscience and immuno-inflammatory diseases are the future growth drivers. In these areas, Servier is focused on a limited number of diseases in which accurate patient profiling makes it possible to offer a targeted therapeutic response through precision medicine.

To promote access to quality care for all at a lower cost, the Group also offers a range of quality generic drugs covering most pathologies, relying on strong brands in France, Eastern Europe, Brazil and Nigeria.

In all these areas, the Group includes the patient voice at each stage of the life cycle of a medicine.

Headquartered in France, Servier relies on a strong geographical footprint in over 150 countries and achieved a revenue of €4.9 billion in 2022.

More information on the new Group website: servier.com

SERVIER
moved by you

Simulations Plus, Inc. is a premier developer of modeling and simulation software and consulting services supporting drug discovery, development, research, and regulatory submissions. We partner with companies to provide a strategic, data-driven modeling methodology, starting in early discovery, continuing through preclinical/clinical development, and clinical trials/post approval. We offer #1-ranked, easy-to-use software (GastroPlus®, ADMET Predictor®, DILIsym®, NAFLDsym®, MonolixSuite® and more) to bridge data mining and compound library screening with QSAR models, PK/PD model development, and PBPK/TK modeling & simulation in animals and humans following administration around the body, and quantitative systems pharmacology approaches. Our technology and consulting services are utilized by major pharmaceutical, biotechnology, and regulatory agencies worldwide. For more information, visit our website at https://www.simulations-plus.com/

SimulationsPlus

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Our vision of helping to advance Life Sciences research every day, is embodied by providing a unique, holistic range of solutions to make life easier – easily and quickly accessible.
The full scope of your needs is at the centre of our attention. Our experts provide reliable, multimodal solutions, encompassing our extensive range of products, in-house laboratory platforms, and our practical administrative and logistics services. You'll find the right combination of answers to accelerate your daily work, in one place.
Enjoy local access to global solutions, always within easy reach at one of our 9 local offices in Europe.

tebubio
Facilitators of Life Sciences Research

Acknowledgement: The GMP board want to warmly thank Ikram Aribi, Rayane Boufalaas and Sara Salhi who prepared the present booklet