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The First Annual Conference of the
Society of Pharmacometrics and Health Analytics (SOPHAS)
(Formerly PAGIN)

Supported by
Endowed Chair, MAHE and ISoP

International Conference on Pharmacometrics, India

ICOP 2025
INDIA

THEME
Quantitative Methods for 505(b)(2) and Generic Drug Development

Workshop
January 31, 2025

Conference
February 1 and 2, 2025

Venue
Fortune Valley View, Manipal

Organized by:

Center for Pharmacometrics
Department of Pharmacy Practice
Manipal College of Pharmaceutical Sciences
MAHE, Manipal

QS WORLD UNIVERSITY RANKINGS 2024
151-200 range
By subject Pharmacy and Pharmacology

nirf
National Institutional Ranking Framework (NIRF)
Ministry of Education, Govt. of India
India Rankings 2024

Ranked 8th among Pharmacy Institutions in India

https://sophas.net

ABSTRACT BOOK

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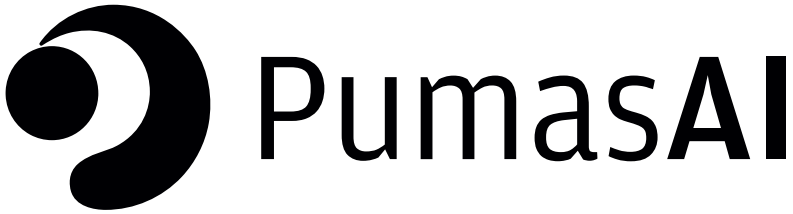

GOLD SPONSORS

Message

Principal of MCOPS

Dr Srinivas Mutalik

With immense pride and enthusiasm, I extend my warm greetings to all the participants of ICOP 2025, the First Annual Conference of the Society of Pharmacometrics and Health Analytics which is being organized by Centre for Pharmacometrics, Department of Pharmacy Practice, Manipal College of Pharmaceutical Sciences, Manipal and supported by endowed Chair, MAHE, Manipal. This prestigious conference is a testament to our shared commitment to advancing pharmaceutical sciences and it underscores our dedication to leveraging quantitative methods and clinical pharmacometrics to address contemporary challenges in drug development and patient care.

As we convene for this significant gathering, we embark on a journey of exploration and innovation that promises to unlock new possibilities across diverse areas of drug discovery, development, and regulatory science. ICOP 2025 provides an exceptional platform for exchanging ideas, sharing research, and fostering interdisciplinary collaborations that will shape the future of our field.

I extend my heartfelt gratitude to the organizing committee, sponsoring and supporting agencies, and collaborators, whose unwavering dedication and concerted efforts have made this conference possible. It is through your vision and determination that we can bring together such a diverse and accomplished group of minds united by a shared passion for scientific progress.

Let this conference be a space for meaningful dialogue, thought-provoking discussions, and the exploration of groundbreaking methodologies. Together, may we cultivate new perspectives, strengthen partnerships, and drive impactful innovation that will leave a lasting legacy.

Wishing you all an enriching and inspiring experience at ICOP India 2025.

Dr Srinivas Mutalik
Professor and Principal
Manipal College of Pharmaceutical Sciences
Manipal Academy of Higher Education, INDIA

Message

President - SOPHAS

Dr. Surulivelrajan Mallayasamy

Greetings from the office of SOPHAS!!

SOPHAS is reaching an exciting milestone with the initiation of the first international conference on Pharmacometrics India 2025. Our society founded in 2008 by Late Dr Ramalingam Sankaran as Population Approach group in India (PAGIN). Over the year, the society dedicated itself to training and educating students, academics and industry in pharmacometrics.

SOPHAS is looking at the future with great enthusiasm, hope and confidence that it will be able to adapt to the ever-changing landscape of pharmacometrics and health analytics. With the infusion of new talent and expertise, society is looking to develop and deliver courses on pharmacometrics, clinical pharmacology, drug development and delving into novel domains like machine learning and their application in pharmacometrics. SOPHAS is partnering with industry, academia, regulatory agencies and other stakeholders both nationally and internationally to expand our horizons for the benefit of all our stakeholders. SOPHAS is young, agile and supported by a dynamic group of office bearers, advisors, volunteers and well-wishers from across the world.

The first annual conference of the SOPHAS christened as International Conference on Pharmacometrics India 2025, supported by the International Society of Pharmacometrics (ISOP) with its global community program. This is the first such conference supported by ISOP. Center for Pharmacometrics at the Manipal College of Pharmaceutical Sciences has taken the lead to bring the ICOP India 2025 to Manipal. Manipal Academy of Higher Education (MAHE) and its Endowed chair professor Dr. Vijay Ivaturi is a key benefactor of this conference. SOPHAS thanks all the supporters along with the key sponsors for their great support to make ICOP India 2025, a reality.

ICOP India 2025 will provide a great platform to deliberate on the theme of quantitative sciences on 505(B)(2) submissions and generic drug development. The scientific committee has identified curated an impressive array of speakers and topics. These topics are vital for the generic drug landscape of India and help companies with their efforts on model informed formulation development and generic drug development. Clinical pharmacometrics section is going to be a great learning opportunity for the clinical pharmacology members in our audience to apply this science in precise and individualized therapy in their mission to serve patients.

I welcome all the participants of ICOP India 2025 for learning, deliberating, networking and enjoying the hospitality arranged by local organizing committee.

Dr. Surulivelrajan Mallayasamy
The President,
SOPHAS

Message

President - ISOP

Dr. Vijay Ivaturi

Dear Colleagues and Friends,

On behalf of the International Society of Pharmacometrics (ISoP), it is my great pleasure to welcome you to the first-ever International Conference on Pharmacometrics – India, organized by the Society of Pharmacometrics and Health Analytics (Sophas), here in beautiful Manipal. This milestone event represents an exciting new chapter for the pharmacometrics community in India that showcases our collective commitment to advancing the science and application of quantitative approaches in drug development and healthcare.

For many years, India has been recognized as a powerhouse of talent, contributing significantly to the global pharmacometrics landscape. With an ever-growing pool of highly skilled scientists, researchers, and clinicians, India's role in shaping the future of pharmacometrics is poised to increase exponentially. This conference marks a crucial step forward in bringing together the Indian pharmacometrics community—building stronger networks, supporting collaborative research, and inspiring new generations of scientists to explore the exciting opportunities in model-informed drug development (MIDD).

Beyond uniting the community, this event also creates momentum for broader adoption of MIDD strategies in India's pharmaceutical and healthcare industries. As more companies embrace modeling and simulation to guide R&D, we can expect a surge in scientific innovation and greater efficiency in bringing life-saving therapies to patients. Indeed, by investing in training and development here in India, we have the opportunity not only to cultivate homegrown expertise but also to retain this valuable talent to drive long-term growth and excellence.

I would like to extend my gratitude to the leadership and members of Sophas, along with the Conference Planning Committee, whose dedication and efforts have brought this inaugural event to life. Their hard work has laid a strong foundation for future gatherings and collaborations in the region. In addition, we are grateful to Manipal Academy of Higher Education for graciously hosting us and creating an environment that promotes scientific exchange and community-building. Finally, I personally thank the ISoP leadership to promote the internationalization of pharmacometrics through their Global Community Program that promotes events such as ICoP.

Let us take this time to celebrate our collective achievements and continue working together toward the continued success of pharmacometrics in India and around the world. I hope you enjoy the conference and leave inspired by new ideas, enriched with fresh collaborations, and motivated to further expand the frontiers of our field.

Thank you for joining us, and I wish you a productive and memorable conference in Manipal.

Warm regards,

Dr. Vijay Ivaturi
President,
International Society of Pharmacometrics (ISoP)

About Center for Pharmacometrics

Department of Pharmacy Practice, MCOPS, MAHE has a history of working in pharmacometrics projects for more than a decade. Population pharmacokinetic studies of anti-epileptic drugs were the focus on the initial days. Lately the research is focused on the pharmacometrics studies of anti-infectives in special populations like neonates and immunosuppressants in organ transplant patients. In the year 2022, the Centre for Pharmacometrics was formally recognized and Dr. Surulivelrajan M has been approved as a Coordinator of the Centre along with Dr. Mahadev Rao and Dr.Rajesh V from the department of Pharmacy Practice.

The centre is actively collaborating with eminent institutions like ACTREC, Mumbai and PGIMER, Chandigarh at the national level. The centre is working in close collaboration with the Society of Pharmacometrics and Health Analytics (SOPHAS). The Centre is supporting the conduct of the DMPK certificate course of SSX, India. The centre is conducting workshops and training programs and certificate courses in pharmacometrics, pharmacokinetics and data analytics using new age tools. Recently, Dr. Vijay Ivaturi from the Pumas-AI Inc., USA has been appointed as an endowed chair to advise and enhance the research in pharmacometrics at the centre.

The centre is aspiring to increase the breadth of research in pharmacometrics, data analytics, AI/ML and their applications in clinical pharmacometrics and translational research in the drug development programs. The Centre is consulting industries to support their drug development projects especially in implanting pharmacometric aspects in their program. The centre cherishes the moment of hosting the 1st annual conference of ICOP, India and welcomes all the SOPHAS council members, sponsors and participants to Manipal.

Dr. Surulivelrajan Mallayasamy
Co-ordinator
Centre for Pharmacometrics
at Dept of Pharmacy Practice, MCOPS, MAHE

CERTIFICATE COURSE ON PHARMACOMETRICS

Organized by

Society of Pharmacometrics and Health Analytics (SOPHAS)

COURSE HIGHLIGHTS

Pharmacometrics is an evolving discipline touching the whole gamut of drug discovery, development, and therapeutic use. Increased need for trained human resources is felt across the pharmaceutical industry and in clinical practice setting all over the world, and this course actively addresses that need.

At the end of the course, students are expected to

- Understand the Principles of pharmacokinetics, PK modeling, and Pharmacometrics
- Use appropriate tools for desicion-making in drug development and clinical practice scenarios using pharmacometrics skills
- Execute professionally relevant projects and gain relevant hands-on experience

Participants:

Students and professionals with scope to work in Pharmacokinetics and Pharmacometrics discipline

Duration:

Course-related work: 12 months
Project-related work: 4 months
Overall: 16 months

For applying to the course, scan here

For more information, visit

https://sophas.net

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ICOP-INDIA 2025 Conference Agenda

Pre-conference Organized by SOPHAS

31st January 2025 | Hall GD -KMC Interact lecture Hall, Manipal, India

Time	Session	Topic	Speaker
8:00-9:00	Registration & Breakfast (Interact building, MAHE,Manipal)		
9:00-10:30	Basics of Pharmacometrics and PBPK Models: A Practical Approach	Introduction to Pharmacometrics	**Surulivelrajan M,** MCOPS, MAHE
10.30-10.45		Introducing the activity	**Jaya Shree Dilli Batcha & Arun Prasath,** MCOPS, MAHE
10:45-11:00		Coffee/Tea Break	
11:00-1:00		Reading Population Pharmacokinetic papers and Presentation	**Jaya Shree Dilli Batcha & Arun Prasath,** MCOPS, MAHE, **Sivacharan Kollipara & Rajkumar Boddu,** DRL Hyderabad
1:00-2:00		Lunch Break	
2:00-5:00		Introduction to the concepts of PBPK and demonstrations and case studies	**Sivacharan Kollipara & Rajkumar Boddu,** DRL Hyderabad

ICOP CONFERENCE

Day 1: Feb 1, 2025

Forenoon Session (9:00 - 13:00) Theme: Quantitative methods in 505(b)(2) submissions			
Time	**Topic**	**Speaker**	**Chair**
8:00-9:00	Power Breakfast	Mentoring session for students and Young scientists	**Dr. Yasvanth Ashokraj,** Cipla Ltd, Mumbai
9:00-9:30	Inauguration & Setting the agenda	**Dr. Surulivelrajan M,** President, SOPHAS and Convenor, ICOP-India 2025.	
9:30-10:30	**Dr. Ramalingam Sankaran Commemoration Lecture:** Strategic Integration of Model-Informed Approaches in 505(b)(2) Drug Development	**Dr. Mathangi Gopalakrishnan,** Associate Professor, University of Maryland, MD, USA	
10:30-11:00	Translational and MIDD approaches in 505(b)(2) submissions	**Dr. Rajendra Singh,** Senior Director, Head of Pharmacometrics, Teva, USA	
11:00-11:30	Coffee Break		
11:30-12:00	Applications of modeling and simulations in generic product development: Case studies and regulatory perspectives	**Mr. Sivacharan Kollipara,** Head, Biopharmaceutics, Dr. Reddy's Laboratories Ltd, Hyderabad, India	
12:00-12:45	Panel Discussion	**Dr. Vijay Ivaturi, Dr. Mathangi Gopalakrishnan, Mr. Sivacharan Kollipara**	
12:45-14:45	(Lunch, Exhibits, Poster sessions)		
Afternoon Session (14:45 - 17.00) **Theme: Clinical Pharmacometrics in Patient Care**			
Time	**Topic**	**Speaker**	**Chair**
14:45-15:05	Dose optimization in oncology	**Dr. Vikram Gota,** Professor, Advanced Centre for Treatment, Research and Education in Cancer (ACTREC), Mumbai	**Dr. Smita Patnaik,** PGIMER, Chandigarh
15:05-15:25	Pharmacometric approaches to assess ultra-short response-guided treatment in Hepatitis C	**Dr. Richard Hoglund,** Head, Pharmacometrics research group, Department of Clinical Pharmacology, Mahidol-Oxford Research Unit, Bangkok, Thailand.	
15:25-15:45	A pharmacometrics approach to assess drug exposures in lactating women and breastfed infants	**Dr. Thanaporn Wattanakul,** Scientist & Deputy Head of Pharmacometrics at Mahidol Oxford Tropical Medicine Research Unit, Bangkok, Thailand	

Time	Topic	Speaker	Chair
15:45-16:00	Coffee Break		Dr. Smita Patnaik, PGIMER, Chandigarh
16:00-16:20	Intravenous doxycycline, azithromycin, or both for severe scrub typhus	Dr. Blessed Winston Arul Dhas, Professor, Christian Medical College, Vellore	
16:20-16:40	Pre-referral rectal artesunate in children with severe malaria: any benefit?	Dr. Ayorinde Adehin, Scientist in Pharmacometrics, MORU, University of Oxford	
16:40-17:00	Pharmacometrics approach for dose optimization of anti-bacterial in special populations	Dr. Nusrat Shafiq, Professor, Clinical Pharmacology Unit, Department of Pharmacology, Postgraduate Institute of Medical Education and Research, Chandigarh	
18:30-19:30	Cultural Program		
19:30-21:00	Gala Dinner		

Day 2: Feb 2, 2025

Forenoon Session (9:00 - 13:00)
Theme: Quantitative methods in Generic drug development

Time	Topic	Speaker	Chair
8:15-9:15	Power Breakfast	Mentoring session for students and Young scientists	Mr. Sivacharan Kollipara, Dr. Reddy's Laboratories Limited (DRL), Hyderabad
9:15-9:30	Overview for the forthcoming activities of SOPHAS	Mr. Sivacharan Kollipara, Head, Biopharmaceutics, Dr. Reddy's Laboratories Ltd.	
09:30-10:30	**Keynote Speech:** Leveraging Model Integrated Evidence for Drug Development and Approval	Dr. Liang Zhao, Professor, University of California San Francisco, CA, USA Former Director, Division of Quantitative methods and Modeling, USFDA	
10:30-11:00	Application of Model based Bioequivalence: A perspective for Generic Drug Industry	Dr. Yasvanth Ashokraj, Director, Biopharmaceutics and Pharmacokinetics, CIPLA, Mumbai	
11:00-11:30	Coffee Break		
11:30-12:00	Modeling and Simulation: Ek Soch hai	Dr. Joga Gobburu, Centre for Translational Medicine, University of Maryland, MD, USA	
12:00-12:45	Panel Discussion	**Panel members:** Dr. Liang Zhao, Dr. Joga Gobburu, Dr. Yasvanth Ashokraj	
12:45-14:45	(Lunch, Exhibits, Poster sessions)		

Afternoon Session (14.45 - 17.00) Theme: Students/ Young Professional Sessions (Podium presentations and Tutorial Session)			
Time	**Topic**	**Speaker**	**Chair/Moderator**
14:45-15:45	Podium Presentations	Students/Young Scientists	**Dr. Smita Patnaik,** PGIMER, Chandigarh
15:45-16:00	Coffee Break		
16:00-16:45	Tutorial Sessions for Young scientists and students	**Dr. Vijay Ivaturi, Mr. Sivacharan Kollipara, Dr. Smita Patnaik, Dr. Mathangi Gopalakrishnan** **Moderator: Dr. Natasha Nayak**	
16:45-17:00	Closing session		

Post Conference for Students and Trainees Organized by **SOPHAS**

3rd February 2025 | CCEID Hall, Health Science Library, Manipal, India

Time	Session	Topic	Speaker
8:00-9:00	Registration & Breakfast (Interact building, MAHE, Manipal)		
9:00-9:30	Designing Safe and Effective First in Human Dose Strategies in Pumas	Welcome	**Vijay Ivaturi,** Pumas AI
9:30-10:30		Navigating the Landscape of First-In-Human Trials	**Nikita Ramwani,** Pumas AI
10.30-10.45		Deep Roots and Decision Trees: The Logic Behind Dose Selection	**Tejashree Pasumarthi,** MCOPS, MAHE
10:45-11:00		Coffee/Tea Break	
11:00-1:00		Discussion on real-world case studies	**Tejashree Pasumarthi,** MCOPS, MAHE **&** **Teshini Suthahar,** MCOPS, MAHE
1:00-2:00		Lunch Break	
2:00-4:00		Hands on with Quarto Markdown Document	**H. Sharath Kumar,** Pumas AI **& Architha Aithal,** Pumas AI

Speakers Abstracts

Dr. Mathangi Gopalakrishnan
University of Maryland, Baltimore, MD, USA

Dr. Mathangi Gopalakrishnan is Associate Professor at the Center for Translational Medicine, University of Maryland School of Pharmacy. Dr. Gopalakrishnan is a quantitative clinical pharmacologist and biostatistician by training with more than 12 years' experience using innovative quantitative approaches to guide precision therapeutics in pediatric, maternal and critically-ill patient populations. She is experienced in clinical trial design and drug development strategy including 505b(2) and generic applications. Dr. Gopalakrishnan is currently involved in several drug development projects including the development of an artificial blood product and medical countermeasures. Dr. Gopalakrishnan is also a co-investigator in multiple grants involved in design and analysis of pharmacokinetic-pharmacodynamic studies for nutritional supplements and low-calorie artificial sweeteners in pregnant and postpartum women. She has authored about 60 peer-reviewed publications and is the recipient of American College of Clinical Pharmacy's Best teacher award in 2018. She is also the program director for the online Masters program in Pharmacometrics at University of Maryland, Baltimore. She obtained her Bachelors and Masters in Pharmacy from Birla Institute of Technology and Science, Pilani, India and her Ph.D in statistics from University of Maryland, Baltimore County.

Model-informed drug development (MIDD) strategies are increasingly employed to improve the efficiency of drug development processes. MIDD involves leveraging a variety of quantitative models to optimize clinical trial designs, guide dosing strategies, and inform regulatory decisions. The 505(b)(2) drug approval pathway, positioned between new drug approvals and generic drug approvals, allows changes in characteristics of previously approved drugs—such as changes in dosage forms, strengths, regimens, or routes of administration—while avoiding unnecessary duplication of studies. By strategically incorporating MIDD approaches into 505(b)(2) regulatory submissions, the drug approval process can be further accelerated. This presentation will provide an overview of MIDD strategies relevant to 505(b)(2) development, illustrated through various case studies.

Dr Rajendra Singh

Senior Director, Head of Pharmacometrics, Teva, USA

Rajendra Singh is currently working as Senior Director and Global Head of Pharmacometrics within Quantitative Clinical Pharmacology and Biosimilar Sciences Department at Teva Pharmaceuticals, based in West Chester, PA, USA. He lead a group of pharmacometricians responsible for integrating pharmacokinetic/pharmacodynamic data to assist in quantitative decision-making. Dr. Singh received his B. Pharm, M. Pharm, and Ph.D. (Specialization in Pharmacokinetics of Antimalarial drugs) from India. Before joining Teva, he worked as a Lecturer at BBD University, a Research Scientist at Ranbaxy Research Laboratories, a Group Leader at Cadila Pharmaceutical Ltd. in India, and Director of Clinical Pharmacology at GSK USA. He also completed three years of post-doctoral training at the University of Florida.

Dr Rajendra Singh will enlighten the audience on the topic translational and MIDD approaches in 505(b)(2) submissions and highlight the pertinent issues with appropriate case studies

Mr. Sivacharan Kollipara
Dr. Reddy's Laboratories Limited (DRL), Hyderabad

Mr. Sivacharan Kollipara is currently working as Head, Biopharmaceutics department in the Global Clinical Management group, IPDO at Dr. Reddy's Laboratories Limited (DRL), Hyderabad. He is responsible for biopharmaceutics evaluation, bioequivalence risk assessment, and bioequivalence prediction for conventional as well as complex generic products at DRL. He is also involved in PK modeling and simulations activities supporting generic drug development of various immediate release, modified release, and complex products at DRL and involved in utilizing novel PBPK and PBBM modeling approaches for regulatory justifications for various markets. Prior to joining DRL, Mr. Kollipara was Principal Scientist (Global Pharmaceutical Development) at Novartis Healthcare Pvt Ltd., Hyderabad. Previously he also has been associated with Ranbaxy Research Laboratories, Gurgaon (Metabolism and Pharmacokinetics). He obtained Masters in Pharmaceutical Sciences from BITS, Pilani, Rajasthan, India and currently pursuing Ph.D. Mr. Kollipara is also Chair Person, Scientific Planning Committee for SOPHAS (Society of Pharmacometrics & Health Analytics). Overall Mr. Kollipara has an experience of 17 years in the field of drug discovery, development and generic product development, bioanalytical method development and validation, PK data modelling and simulations. He has authored/co-authored ~40 peer-reviewed publications. His research interests include PBPK/PBBM modeling, virtual bioequivalence simulations, IVIVC/R, drug-drug interactions, dissolution/bioequivalence safe space, bio-predictive dissolution methodologies, biowaivers, novel statistical tools for dissolution similarity analysis and food effect evaluations.

Applications of modeling and simulations in generic product development: Case studies and regulatory perspectives

In recent years, modeling and simulation approaches have transformed the development of generic product development. Approaches such as physiologically based pharmacokinetic (PBPK) and physiologically based biopharmaceutics (PBBM) modeling can speed up the generic product development by obtaining confidence into the bioequivalence studies and facilitating the biowaivers. Such approaches are encouraged by regulatory agencies to reduce human bioequivalence testing and to bring products as early as possible into the market. In this context, this talk will highlight the use of PBPK and PBBM in generic product development. A general workflow for the development of physiological models with incorporation of model inputs will be discussed. Integration of critical model input, i.e. biopredictive dissolution in the context of in vivo prediction will be discussed in detail. Further, various case examples wherein PBPK and PBBM were used to obtain waiver of bioequivalence studies will be discussed in detail. Successful biowaivers in case of f2 similarity factor mismatch and waiver of fed bioequivalence study with help of PBBM will be discussed with case examples. Application of PBBM to justify dissolution specifications for an extended release product will be discussed in detail. Evaluation of impact of critical bioavailability attributes (CBA) through PBBM will be portrayed. Various approaches for establishing in vitro in vivo correlation (IVIVC) for extended release products for establishing dissolution safe space will be discussed with case examples. Overall, this presentation aims to summarize current understanding of PBPK and PBBM approaches to speed up the generic product development in the regulatory context.

Keywords: PBBM, PBPK, Dissolution, Bioequivalence, Generic product development

Dr. Vikram Gota

Advanced Centre for Treatment, Research and Education in Cancer (ACTREC), Tata Memorial Centre, Mumbai

Dr. Vikram Gota completed his MD in pharmacology from Christian Medical College, Vellore, following which he briefly worked as a Clinical Investigator in bioavailability and bioequivalence studies. Thereafter, he joined the INDO-Oxford (INDOX) Cancer Trials Network at Tata Memorial Centre (TMC), Mumbai, where he received training in the design and conduct of phase I clinical trials. During this time he also obtained the post graduate diploma in clinical trials from the London School of Hygiene and Tropical Medicine, University of London. He is presently the officer-in-charge of the department of clinical pharmacology at the Advanced Centre for Treatment, Research and Education in Cancer (ACTREC), Tata Memorial Centre.

His research interests include early clinical development of drugs and pharmacokinetics driven optimization of drugs used in cancer. Specifically, he is interested in understanding the factors affecting the variability of pharmacokinetics and toxicity of cytotoxic chemotherapy in pediatric cancer patients with malnutrition.

Application of Pharmacometrics in the clinics

Pharmacometrics, the science of interpreting and modeling drug behavior quantitatively, plays a pivotal role in advancing cancer patient care. By integrating pharmacokinetics (PK), pharmacodynamics (PD), and clinical data, pharmacometric approaches enable personalized therapy, optimizing drug efficacy while minimizing toxicity. It facilitates broader advancements in oncology, such as dose individualization and combination therapy design. Models like those used for carboplatin dosing based on glomerular filtration rate (GFR) and therapeutic drug monitoring of tyrosine kinase inhibitors (TKIs) help achieve optimal therapeutic windows. Additionally, pharmacometric models enhance clinical trial design, accelerating drug development and enabling adaptive dosing strategies.

Contributions from the Department of Clinical Pharmacology at ACTREC in this field exemplify the practical application of pharmacometrics in oncology. In one study, we investigated the pharmacokinetics and clinical outcomes of low-dose nivolumab in cancer patients. Patients received either a 40 mg flat dose or a 3 mg/kg dose based on affordability, and blood samples were analyzed to measure plasma drug levels. This work demonstrated the feasibility of cost-effective dosing strategies, making immunotherapy more accessible without compromising efficacy.

In another study, we are planning to develop a mathematical model that will link nutritional status, biochemical markers (the metabolome), pharmacokinetics, toxicity and efficacy so that toxicity/efficacy can be predicted from baseline nutrition parameters in children with solid tumours. The integrative pharmacokinetic, pharmacodynamic and metabolomic approach will be used for precision dosing of anticancer drugs in this population as we aim to develop/test nutritional interventions that can improve cancer outcomes in undernourished children.

Our interdisciplinary approach, combining quantitative pharmacology and clinical application, highlights the transformative potential of pharmacometrics in optimizing cancer treatment and advancing personalized medicine.

Dr. Richard Hoglund
Mahidol Oxford Tropical Medicine Research Unit, Bangkok, Thailand.

Dr. Richard Hoglund heads the pharmacometrics research group at the department of Clinical Pharmacology which is a part of the Mahidol-Oxford Research Unit located in Bangkok, Thailand. He received a master in chemical engineering from Uppsala University and his PhD from the University of Gothenburg. His thesis used pharmacometric techniques to investigate the pharmacokinetic and pharmacodynamic properties of piperaquine and he also investigated potential drug-drug interactions between antimalarial and antiretroviral drugs. His current research is mainly focused on pharmacokinetics, pharmacodynamics and utilizing pharmacometric methodologies in neglected tropical diseases to optimise current and future therapies. He leads a group of around 10 students and scientist working in the pharmacometric field, the group has a diverse scientific output and has for example published papers on evaluation of adherence in clinical studies, dose optimization of antimalarial drugs, repurposing drugs for COVID-19 and modelling of distribution of drug to breast milk.

Pharmacometric approaches to assess ultra-short response-guided treatment in Hepatitis C

Elimination of Hepatitis C is hampered by a high cost of treatment which can partly be attributed to long treatment regimens. Response-guided therapy is a promising alternative, in which early virologic response decides the treatment length. In this pharmacometric study, data from two studies of Hepatitis C patients in Vietnam were analysed. The first study included patients with mild liver disease and utilized response guided treatment. In this study, the patients received either a 4-week or an 8-week treatment with sofosbuvir and daclatasvir, based on their day 2 virologic response. The second study was in patients with severe liver disease and used a standard treatment length. Drug levels of sofosbuvir, its metabolite GS-331007, and daclatasvir were quantified, after either dense or sparse sampling. A pharmacometric approach was used to successfully evaluate the pharmacokinetic properties of these drugs and a preliminary pharmacokinetic-pharmacodynamic model was developed.

Dr. Thanaporn Wattanakul
Mahidol Oxford Tropical Medicine Research Unit, Bangkok, Thailand.

Dr. Wattanakul is an experienced pharmacometrician and licensed pharmacist specializing in tropical diseases, particularly malaria. Currently, she serves as the Deputy Head of the Pharmacometrics Group in the Department of Clinical Pharmacology at the Mahidol Oxford Tropical Medicine Research Unit, Bangkok, Thailand.

Dr. Wattanakul earned a DPhil in Clinical Medicine from the University of Oxford in 2020. Her research focuses on malaria and aim to optimize treatments for special populations, including children, lactating women, and pregnant women, through pharmacokinetic/pharmacodynamic (PK/PD) modelling. These groups are often underrepresented in clinical trials despite their unique physiological characteristics, which can substantially affect drug exposure and therapeutic response. Recently, she began developing a new research theme in pharmacoeconomic modelling, aiming to integrate PK/PD modelling into cost-effectiveness analysis. This approach examines the relationship between drug dosing and treatment response, offering valuable insights into cost-effective treatments, which are important for policy decision-makers, especially in low- and middle-income countries. Dr. Wattanakul has been recognized with the ISoP Emerging Scientist Award (2024) and the JITMM Young Investigator Award (2023).

Population Pharmacokinetics of Primaquine in Lactating Women and Breastfed Infants

Current guidelines recommend avoiding primaquine treatment for lactating women to avoid potential haemolysis in infants with glucose-6-phosphate dehydrogenase (G6PD) deficiency. To assess the risk of haemolysis in infants, it is essential to understand the amount of the drug transferred through breast milk and the infant's resulting drug exposure. A pharmacokinetic model was developed to describe drug concentrations in lactating women using venous, capillary, and breast milk data. Additionally, a mother-to-infant model was developed to mimic the infant feeding pattern and used to predict drug exposures in infants. The exposures of primaquine and its metabolite, carboxyprimaquine, in infants are less than 1% of the exposure in the mothers. As a result, even in infants with the most severe G6PD deficiency variants, it is highly unlikely that standard primaquine doses (0.25-1 mg base/kg once daily for 1-14 days) would lead to significant haemolysis. After the neonatal period, primaquine should not be restricted for lactating women.

Dr. Blessed Winston Arul Dhas
Christian Medical College, Vellore

Blessed Winston Arul Dhas is a clinical pharmacologist and pharmacometrician with extensive experience in therapeutic drug monitoring (TDM). He completed his MBBS and MD in Pharmacology from Christian Medical College, Vellore, and further honed his expertise with a postdoctoral fellowship in Disease and Therapeutic Response Modeling at the Indiana University School of Medicine.

Blessed's primary focus lies in pharmacometrics, where he has made significant contributions through population pharmacokinetic modeling and PK-PD modeling of various drugs, including methadone, oxycodone, and buprenorphine. His work aims to optimize drug dosing and improve clinical outcomes, particularly in pediatric and surgical pain management. One of his notable early works includes the population pharmacokinetic study on tuberculosis in children, which demonstrated the need for an increased dose of rifampicin, which has now been adopted into regular clinical care. He is presently working on developing various PK-PD models to optimize the dosing of antibiotics in populations with rapidly changing pharmacokinetics in a critical care setting.

Blessed is deeply passionate about TDM and has successfully implemented model-informed precision dosing in his practice. This approach has enabled him to tailor drug therapies to individual patient needs, enhancing the efficacy and safety of treatments. He has been actively involved in teaching, research, and clinical practice, contributing to numerous publications in esteemed journals. His work has been recognized with several awards, including the Dr. Paul Stephen Memorial Award and the SENATUS Award for the best paper.

Intravenous doxycycline, azithromycin, or both for severe scrub typhus.

Severe scrub typhus, a rickettsial disease associated with multi-organ failure and a high fatality rate, remains a significant health concern. While intravenous doxycycline, azithromycin, or their combination are commonly used in the treatment, their comparative efficacy is not well established. This study aimed to describe the pharmacokinetics (PK) and pharmacodynamics (PD) of these drugs—evaluating microbiological cure as monotherapy and in combination using combinatorial pharmacodynamic modeling. could potentially provide valuable insights for optimizing drug regimens and improving the treatment outcomes of severe scrub typhus. A total of 744 patients with severe scrub typhus were enrolled, and plasma concentrations of azithromycin (n=2462) and doxycycline (n=2420), as well as bacterial copy numbers (n=2029), were measured. Blood samples for measuring azithromycin and doxycycline concentrations were taken at trough, and randomly later to cover the entire inter-dose interval. For some participants, additional samples were collected within a single inter-dose period to aid a combination of rich and sparse data. Additional PK samples were collected after the last dose to match the drugs' very long half-life. A population PK-PD model was developed to describe the effect of individual monotherapies and combination therapy in causing microbiological cures. The general pharmacodynamic interaction (GPDI) model was employed to describe the combinatorial pharmacodynamics of both these drugs. Covariate analysis revealed that eGFR, neutrophil%, and serum albumin concentrations are associated with baseline bacterial copy numbers. Simulations using the PD model indicated that azithromycin is more effective than doxycycline, while combination therapy offers only marginal additional benefit for microbiological cure.

Dr. Ayorinde Adehin

Mahidol Oxford Tropical Medicine Research Unit, Bangkok, Thailand.

Dr Ayorinde Adehin is a Scientist at the Department of Clinical Pharmacology at the Mahidol Oxford Tropical Medicine Research Unit (MORU) in Bangkok, Thailand. He holds a bachelor's degree in Biochemistry and a doctoral degree in Pharmaceutical Chemistry. Ayorinde's research focuses on using pharmacometrics to enhance decision making in preclinical and clinical settings.

Currently, he works in areas of infectious and neglected tropical diseases, developing mathematical models that expand the understanding of pathogen dynamics and optimize drug-use.

Pre-referral rectal artesunate in children with severe malaria: any benefit?

Parenteral artesunate is the initial regimen of choice in the treatment of severe malaria in children. However, the use of pre-referral rectal artesunate suppository (RAS) has been proposed in instances where parenteral doses are inaccessible. At this time, the World Health Organization advises a cautious use of RAS in response to a published report where increased fatality was associated with its field deployment. Here, we examined the disposition of intravenous artesunate and RAS at recommended doses in children with severe malaria and compared the derivable malaria parasite clearance. Rectal bioavailability of artesunate was low and quite variable. Plasma exposure of dihydroartemisinin, the major and bioactive metabolite of artesunate, was comparable for RAS and intravenous artesunate, and so were simulated parasite-reduction, 12 h after dosing. These findings are consistent with previously reported clinical benefits of RAS. Hence, the use of RAS as a pre-referral intervention, where relevant, should be encouraged.

Prof Nusrat Shafiq
PGIMER, Chandigarh

Prof Nusrat Shafiq is working as a Professor in Clinical Pharmacology Unit of Department of Pharmacology, PGIMER, Chandigarh since 2008 after finishing her DM in Clinical Pharmacology from PGIMER, Chandigarh in December, 2005. She is also member-secretary, IEC, PGIMER, adjunct faculty in telemedicine center of PGIMER and Faculty of Cochrane India Evidence Synthesis Unit. Her main domain of work is therapeutics for infections with a special focus on therapeutics for Multidrug Resistant Organisms. She is PI for ICMR network of Phase I Clinical trials at PGIMER and India Hub for International Network for Antimicrobial Optimization (CAMO Net, Wellcome Trust) She was past president of Society of Antimicrobial Stewardship PractIses in India and is currently heading their training and guidelines committee. She is reviewer and assessor for some prestigious International Grants. In her career spanning nearly two decades she has been earnestly working in the domains of training, research and patient care. She is one of the founder members of Consortium for Dose Optimization where in she works with ACTREC , Mumbai and MAHE, Manipal for pharmacometrics n the domain of infections. She has publications in high impact journals with considerable citations. Currently my team of research fellows, MD and DM residents are undertaking several key studies. Her publications can be looked up at : https://pubmed.ncbi.nlm.nih.gov/?term=shafiq+N&sort=date&size=200

Pharmacometrics approach for dose optimization of antibacterials in special population

Special populations such as pediatric, critically ill patients, patients with compromised renal and or hepatic functions are sparingly evaluated during the drug development process and often thereafter. Evidence based approach for right dose in such populations remains a challenge for most practicing clinicians. There is thus an imminent need to generate evidence for such situations using pharmacometrics approach. Importantly, in the recent years infections due to drug resistant organisms have become a big challenge in the space of infections. These infections very frequently lead to sepsis or are difficult to treat primarily because of very few therapeutic options and a dearth of information on right dose of the antimicrobials in such situations. The evaluation of covariates in pharmacokinetic-pharmacodynamic models in these populations may require different considerations too. In the current presentation, I will walk through some of our studies in this domain and try to look at the way they have attempted to answer critical practice related questions. We shall also explore how some of the ongoing studies are looking into questions which are hitherto sparingly answered for infections in special populations using pharmacometrics approach.

Dr. Liang Zhao
University of California San Francisco (UCSF)

Dr. Liang Zhao is currently a professor and establishing the Center for Global Regulatory Science and Innovation at the School of Pharmacy, University of California San Francisco (UCSF). Prior to joining UCSF, he had served as the Director of Division of Quantitative Methods and Modeling (DQMM), ORS/OGD/CDER/FDA between 2015 and 2024. He has demonstrated excellence and leadership in drug development and regulatory science for new and generic drugs during his 20-year professional tenure including in Pharsight (acquired by Certara) as an associate consultant, BMS as a research investigator, MedImmune (now AstraZeneca) as an Associate Director, and FDA as Clinical Pharmacology reviewer, Pharmacometrics Team Leader for new drug development, and Division Director. Dr. Zhao and his team have introduced a broad array of innovative tools in the realm of drug deliveries, bioequivalence assessment, and big data tools including machine learning to pharmacometrics. During his tenure in FDA, his team had also implemented the Model Integrated Evidence (MIE) Industry Meeting Pilot to support regulatory communications between generic applicants and the FDA and proposed a regulatory mechanism of using Model Master File to support regulatory submissions. Liang had served as the Chair of the FDA ModSim WG for the Modeling & Simulation community. He has published over 120 peer reviewed publications and 8 book chapters. He received the 2023 Gary Neil Prize for Innovation in Drug Development from ASCPT in recognition to his contribution to clinical pharmacology and pharmacometrics.

Using Model Integrated Evidence for Bioequivalence Assessment

The presentation will focus on how we can leverage advanced pharmacometric models to bridge the gap between clinical data and regulatory decisions, particularly in the areas of bioequivalence assessment, drug delivery models, and products with novel formulations.

The presentation will discuss the growing importance of MIE in streamlining drug development pipelines, as a further step from Model Informed Drug Development. Using examples from bioequivalence studies, the presentation will highlight how in silico and pharmacometric models are transforming the evaluation of complex generic drugs, enabling more efficient pathways for regulatory approval while maintaining rigorous safety and efficacy standards.

The presentation will focus on two types of models, conventional pharmacometrics models and mechanistic drug delivery models, showcasing how modeling is helping us understand and predict drug delivery as well as reducing burdens from in vivo clinical study. These models are proving especially crucial for developing innovative formulations, including long-acting injectables and modified-release systems, which require precise, data-driven strategies for characterization and optimization.

At the end, the talk illustrates how model-integrated evidence is not only reshaping the drug development landscape but also opening doors for cost-effective, patient-centered innovation.

Dr. Joga Gobburu
University of Maryland, Baltimore, MD, USA

Dr. Gobburu is Professor with the School of Pharmacy and the School of Medicine, University of Maryland, Baltimore, MD, USA. He held various positions at the US FDA between 1998 and 2011. He has experience with overseeing the review of 1000s of Investigational New Drug Applications (INDs), over 250 New Drug and Biological Licensing Applications, numerous FDA Guidances and policies pertaining to drug approval and labeling. He received numerous awards from FDA and other professional organizations. He has published over 180 papers and book chapters. He is co-founder of PumasAI Inc., and Vivpro Corporation.

Pharmacometrics Ek Soch Hai!

Pharmacometrics in pharmaceutical generic drug development transcends mere number-crunching; it represents a transformative mindset essential for addressing complex challenges in formulation, bioequivalence, and regulatory strategy. Both pharmaceutical companies and regulatory bodies must adjust their mindsets to fully harness the potential of pharmacometrics. This talk explores how pharmacometrics enables informed decision-making by integrating data, predicting outcomes, and optimizing processes. By embracing pharmacometrics as a holistic framework, stakeholders can enhance efficiency, reduce development timelines, and ensure quality. Real-world examples will illustrate how this paradigm shift fosters innovation and aligns with evolving regulatory expectations, driving impactful results.

Dr. Yasvanth Ashokraj
Cipla Ltd, Mumbai.

Dr. Yasvanth Ashokraj is currently Director, Biopharmaceutics and Pharmacokinetics (BioPK)at Cipla Ltd, Mumbai. Prior to Cipla worked in Sandoz India, Dr. Reddy's Laboratories, Sun Pharmaceuticals (formerly Ranbaxy laboratories) and Nicholas Piramal India Ltd in similar role for past 20 years. His is currently responsible to lead the BioPK function to support various generic and 505b2 development and submissions for various markets. He was instrumental in establishing pharmacokinetic modelling and simulation capabilities both PBPK and POPPK in Cipla and other companies. He also served as adjunct professor Shri Ramachandra Institute of Higher Education and Research, Chennai. He graduated from NIPER, Mohali and authored/coauthored 24 research and review publications.

Model-based bioequivalence (MBBE) an evolving concept has been endeavored to resolve certain critical challenges in generic drug product development especially, patient-based BE studies with limited sampling option or long duration studies. This presentation focusses to comprehensively enlist the challenges in BE studies conducted for generic drug product development and provide the overview of application of MBBE for resolving them, with some case studies.

Oral & Poster presentation abstracts

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Quantitative analysis of antibody decay in Chagas disease: a novel approach for an old disease

OP-01

Cintia V. Cruz[a,b], Junjie Ding[a,b], Jaime Altcheh[c], Richard M. Hoglunda[b], Joel Tarninga[b]

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This study aimed to quantify antibody decay as a biomarker for treatment response in Chagas disease, offering a novel approach compared to the traditional "time-to-event" analysis, which typically estimates the time until antibody disappearance. Chagas disease, caused by the protozoan *Trypanosoma cruzi*, is a neglected disease endemic to Latin America but prevalent globally due to migration. It is characterized by two phases: an acute phase with high parasitemia, followed by a chronic phase that is asymptomatic for most patients but that leads to severe cardiac and gastrointestinal disease in 20% of cases. The present analysis is based on individual-level data from the Hospital de Niños Ricardo Gutierrez (HNRG) Chagas & Parasitology Department. Initial exploratory analyses were performed using R, enabling quantification and visualization of antibody decay patterns. Nonlinear mixed-effects modelling was performed in NONMEM, using a SPLINE function to characterize the bi-phasic antibody decay kinetics. This quantitative approach provides a deeper insight into the antibody decay dynamics and treatment effects, potentially improving biomarker utility in monitoring therapeutic outcomes. The results of this study are expected to enhance the accuracy of treatment response assessments in Chagas disease, ultimately providing better patient management and therapeutic decisions.

Evaluating the impact of codon usage, GC Content, and secondary structure on *in vitro* mRNA protein expression using non-linear mixed modeling

OP-02

Sharath Kumar[1], Saugandhika Minnikanti[1], Niklas Korsbo[1], Ajay Singh[2], Rohan Gurjar[2], Tejas Borwankar[2], Swarnendu Kaviraj[2], Vijay Ivaturi[1]

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Background: Messenger RNA (mRNA) design challenges are increasingly addressed through the optimization of chemical stability and codon usage. However, the relationship between upstream optimized construct parameters (including codon usage, GC content, and mRNA secondary structure) and *in vitro* protein expression is unknown. Hence, the aim of the study was to leverage the *in vitro* data from literature and develop a model to predict protein expression. Methods: An extensive literature review was conducted to gather studies optimizing the gene of interest, untranslated regions (UTRs), and PolyA tail lengths, published between January 1, 2019, and December 1, 2024. Sequences from these studies were digitized and extracted, and parameters including Minimum Free Energy (MFE), Codon Adaptation Index (CAI), %GC content, and Mean Ribosome Load (MRL) were predicted using available web tools. Furthermore, univariate and multivariate analysis followed by non-linear mixed-effects modeling of observed protein expression across different mRNA constructs was performed using Pumas 2.5.1. Results: Data from nine published studies were collected, most of which employed reporter proteins. The observed *in vitro* protein expression data were modelled using a gamma-distributed delay model (due to insufficient literature data to capture the full mRNA translation process), with shape and scale parameters estimated to be 2.69 and 0.02, respectively. To address the wide variation in reported protein expression levels, largely attributable to differences in assay types, a scaling factor for each assay type was incorporated (range = 0.63 - 9000), significantly improving model fit and demonstrating the model's potential to predict expression of different proteins. The shape and scale parameter estimates across studies were comparable, indicating similar protein dynamics, while only the scaling factor varied between studies. Although, no statistically significant covariate relationship with scaling factor was observed, trends in PolyA tail length, 5'UTR MFE, CAI, and %GC content aligned with findings in existing literature. Variability in transfection methods, cell lines, and protein measurement assays was noted across the studies. Conclusion: A protein expression model was developed using the data extracted from existing literature, incorporating covariate analysis with parameters such as MFE, CAI, %GC content, and MRL. Further studies are required to validate these findings.

Population Pharmacokinetic and Pharmacodynamic model of Propofol in patients with Renal Impairment

OP-03

Dr. Rachna Rohilla[1], Dr. Jaya Shree Dilli Batcha[2], Dr. Preethy Mathew[3], Dr. Goverdhan Dutt Puri[4], Dr. Surulivelrajan Mallayasamy[5], Sumit Dey[6], Dr. Ravimohan Mavuduru[7], Dr. Arup Kumar Mandal[8], Dr. Smita Pattanaik[9]

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[5]Professor and Head, Department of Pharmacy Practice, Manipal College of Pharmaceutical Sciences, India
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[9]Professor, Department of Pharmacology, Postgraduate Institute of Medical Education and Research, Chandigarh, India.

Background: Propofol is a commonly used intravenous anaesthetic agent with kidney playing a minor role in elimination but the pharmacokinetics (PK) have been found to significantly affected in end stage renal disease patients. Aim: To study PK-PD of propofol in patients with various stages of renal impairment and compare with normal renal function. Methods: The study was prospective, single centre in renally impaired patients undergoing surgery under general anaesthesia. A total of 10 blood samples were collected from each patient as per prespecified sampling time points from 38 patients for propofol estimation. Time to loss of consciousness, time to eye opening were recorded along with Bi-spectral index (BIS) as PD end points. Results: The concentration time profile (287 blood samples) and BIS data from 35 patients were used for analysis and model development. Creatinine clearance was found to be an important co-variate affecting the PK model. The stage 3 and 4 patients achieved higher plasma concentrations at the same induction and maintenance doses of propofol and tend to achieve lower BIS. The propofol C_{max} was higher in stage 4 as compared to stage 1 or 2 patients. The average concentration at LOC was significantly higher in stage 4 (6.61±6.28 µg/ml) as compared to stages 1 (2.06±1.69 µg/ml) or stage 2 (1.64±1.77 µg/ml). Average time to eye opening was also higher in stage 3 and 4 (12.9±4.7 and 9.5±3.1 minutes respectively) as compared to stage 1 and stage 2 (7±3.2 and 7.9±2.4 minutes respectively). Conclusion: The moderate-severe renal impairment patients required lower dose of propofol to achieve the same level of anaesthesia as with normal creatinine clearance. The model can help optimize propofol dose after validation.

OP-04

Power of integrating PBPK with PBBM (PBPK-BM): a single model predicting food effect, gender impact, drug-drug interactions and bioequivalence in fasting & fed conditions

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Lately, PBPK (Physiologically Based Pharmacokinetic) and PBBM (Physiologically Based Biopharmaceutics Modeling) have demonstrated their significance in both innovator and generic drug development. Traditionally, PBPK modeling is employed to predict drug-drug interactions and drug exposures in special populations, while PBBM modeling is utilized for various biopharmaceutics applications. Due to these differing utilities, PBPK and PBBM models are often developed separately. However, when combined, they can serve multiple purposes through a unified model, enhancing their overall utility. In this case, we developed an integrated PBPK-PBBM model for a DRL IR product. This model has been applied for bioequivalence assessment under fasting and fed conditions, evaluating gender impact and food effect, and also predicting drug-drug interactions. The model was constructed using physicochemical properties, enzyme and transporter kinetics, and bio-predictive dissolution data. It was validated with both passing and failed pilot bioequivalence (BE) studies, ensuring its robustness and reliability. The validated model accurately predicted pivotal bioequivalence outcomes in both fasting and fed conditions. It also successfully predicted gender impact and food effect, aligning with existing literature. Additionally, the model accurately accounted for drug-drug interactions arising from transporters and metabolizing enzymes, demonstrating its comprehensive applicability. Overall, this work highlights the utility of combining PBPK and PBBM models to create a single, integrated model. This unified model can be used for multiple purposes, including regulatory justifications, and has the potential to reduce regulatory review timelines. By leveraging the strengths of both PBPK and PBBM modeling, we can achieve more accurate and reliable predictions, ultimately enhancing the drug development process and ensuring better therapeutic outcomes.

Probability of Target Attainment Analysis for Antibiotic Therapy in a Virtual Population of Soldiers with Battlefield Injuries

PP-01

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Background: Soldiers with battlefield injuries often have elevated creatinine clearance (CrCL) and decreased serum albumin (ALB). Antibiotic therapy has not been optimized for this population despite likely alterations in pharmacokinetics, which may result in a failure to control infections in the field hospital environment. Objectives: Our objective was to assess the probability of target attainment (PTA) for various antibiotics (e.g. cefazolin, ceftriaxone, ertapenem) and pathogens (e.g. *S. aureus*, *E. Coli, K. pneumoniae*) in virtual populations representative of critical care patients with recent battlefield injuries. Methods: Published population pharmacokinetic (popPK) models of 9 antibiotics were implemented in Pumas software. Minimum inhibitory concentrations (MIC) for common pathogens were extracted from the EUCAST database. Stochastic simulations were performed to assess PTA based on established targets for each antibiotic, e.g. percent time that free concentrations are over the MIC (%fT>MIC) or the ratio of free area under the concentration-time curve to MIC (fAUC/MIC ratio). Virtual populations were examined with CrCL of 125, (normal) 150 (mildly elevated), 200 (moderately elevated), and 250 (highly elevated) mL/min and ALB of 2 (hypoalbuminemia), 4 (low normal), and 6 (high normal) g/dL. Results: Pathophysiological changes in CrCl and Alb were predicted to significantly lower the PTA for specific combinations of pathogens and antibiotics. For example, an increase in CrCL from 125 to 250 mL/min was predicted to decrease the PTA of cefazolin (1000 mg IV q6h) against *S. aureus* from 47% to 5% and ceftriaxone (1000 mg IV q24h) against *E. coli* from 95% to 89%. Similarly, a decrease in Alb from 40 to 20 g/dL was predicted to decrease the PTA of cefazolin against *S. aureus* from 65% to 40%. Conclusion: This analysis demonstrates that pathophysiological changes following battlefield trauma are likely to affect the PK of certain antibiotics and decrease their PTA. Further analysis should be performed to optimize antibiotic therapy in this population.

External Evaluation of Published Population Pharmacokinetic Models of Imatinib in CML patients with Multicentre Data

PP-02

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Background: CML is a hematological cancer caused by a translocation in the BCR-ABL gene, which results in the development of the Philadelphia chromosome. Tyrosine kinase inhibitors are used to treat it; these drugs prevent tyrosine kinase enzymes from binding to the BCR-ABL gene. Imatinib is a TKI used as the first-line therapy for CML patients. PopPK models for imatinib in CML patients show that it has a higher inter-individual variability. The main objective of this study was to externally evaluate the published PopPK of imatinib in adult CML patients using the combination of clinical data from western and southern Indian populations. Methodology: The PopPK studies for imatinib identified through systematic review were used for external evaluation. The prediction ability of model was calculated based on the observed and model predicted concentration for the clinical data from both centres. Result: A total 89 patients were used for external validation of PopPK models. The model by Menon et al was able to predict well for the given population with lower individual relative mean prediction error, individual relative median absolute prediction error and individual relative room mean squared error. Conclusion: The dosing nomogram proposed in our previous publication from the Menon et al. model, which was one compartment with first-order elimination and zero-order absorption with weight as a covariate on clearance and volume of distribution, can be used to determine the appropriate dose for patients in order to maintain target trough concentration.

Pharmacometrics for Dose Optimization of Meropenem in Critically Ill Patients

PP-03

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Background: Meropenem is an injectable, broad spectrum-beta-lactum antibiotic used to treat infections in critically ill patients and also considered as a last resort against extended spectrum beta lactamase producing bacilli in intensive care settings. Objective: To develop and qualify a population pharmacokinetic model for Meropenem in South Indian patients. Methods: A Prospective open label study was conducted to gather concentration data from 110 critically ill adult patients who received meropenem of 500mg or 1g over 30mins or 3-hour infusion every 8h or 12h. Meropenem plasma concentration was quantified by high-performance liquid chromatography. Meropenem population pharmacokinetics was performed by using PUMAS® v.2.5.0. The final PK model was created and used to simulate how the dosage regimen affects the probability of target attainment (PTA). The simulated dosage regimen was assessed through the MIC range of 0.125 to 16 mg/L and was conducted using R studio (v.4.3.2). Results: The Concentration–time courses were best described by a two-compartment model with first-order elimination. Among the pharmacokinetic parameters estimated, only the central compartment clearance showed a clinically significant variance (39%). The most significant covariate was creatinine clearance on CL. The total clearance (Cl), volume of distribution in the central compartment (Vc), inter-compartmental clearance (Q), and volume of the peripheral compartment (Vp) of Meropenem are 11.3 L/hr, 32.4 L, 45 L/hr, and 19.3 L respectively. The additive error was 0.010051 mg/ml and the proportional error was 0.25955%. Model was qualified by internal validation, simulation-based diagnostics such as visual predictive checks (VPCs), and methods for investigating the confidence intervals (CI) of the parameters such as bootstrap and log-likelihood profiling. The covariate model significantly reduced the inter individual variability (variance) to about 21 % from 53%. The simulations showed that the 94% of concentrations were above MIC in 1 gram twice or thrice daily compared to 24% of concentrations in 500mg twice or thrice daily doses. Conclusion: Population pharmacokinetic parameters were estimated. Simulations using the developed data showed that 1 gram twice or thrice daily dose was better than 500 mg twice or thrice daily dose in achieving desired concentrations above MIC.

Assessment of target attainment with vancomycin therapy in critically ill patients: A pharmacometric approach

PP-04

Nikhil Aravind, Ritika Kondel Bhandari, Avaneesh Pandey, Surulivel Rajan, Sharath Kumar, Samir Malhotra, Yashwant Raj Sakaray, Neeru Sahni, Navneet Sharma, Nusrat Shafiq

PGIMER, Chandigarh.

Background: Sepsis management requires urgent and optimized antimicrobial use. In sepsis, there is alteration of the pharmacokinetics of the drugs on account of several pathophysiological changes. So, pharmacokinetic studies to optimize antimicrobial dose and improve probability of target attainment need to be conducted. Vancomycin is a key component of empiric and/or lab-based use in patients with sepsis. The aim of present study was to compare two intravenous dosing regimens 1000 mg bid and 500 mg qid in critically ill patients with sepsis and to validate nomogram generated from pop-pk-pd modeling in a sample cohort. Methods: The study was conducted by Department of Pharmacology in collaboration with critical care units in a tertiary care center of North India after obtaining approval from IEC (No. INT/IEC/SPL-480) and registration with CTRI (CTRI/2023/02/049473). Eligible patients were randomly assigned to receive either the vancomycin dose routinely administered 1000 mg iv twice daily or 500 mg iv four times daily. Relevant covariate data were collected. Sparse sampling methodology with capture of trough concentrations was carried out. Structural model followed by covariate model was built using PUMAS software. Model diagnostics conducted include goodness-of-fit, visual predictive check and 1000 bootstraps to validate the model. Data simulation for 1000 mg bid and 500 mg qid were carried out for different weight and creatinine clearance combinations ranging from 45-80 kg and 50-100 ml/min. Key primary endpoint was an increased probability of target attainment. Results: A total of 26 patients were randomized to the two treatment arms. A 2-compartment combined error model with the covariates creatinine clearance and body weight explained the data adequately. The pharmacokinetic parameters were V_c– 5.9L, V_p– 11.9L, Cl – 2.5L/h, Q – 15.8L/h. AUC_{0-24}/MIC estimation from simulated data showed that number of individuals attaining the target was significantly higher in the 500 mg qid group as compared to 1000 mg bid group. The trough concentrations in the therapeutic range of 15-20 mg/L was observed for a higher proportion of patients in 500 mg qid as compared to 1000 mg bid across all creatinine clearance and weight ranges tested. This dosing regimen was further validated in prospective precision dosing cohort of 3 patients. Conclusion: The results of the study indicate that a higher proportion of patients achieve the required target in 500 mg iv qid group and it may be used in therapeutics to increase clinical efficacy.

Population pharmacokinetic properties of arterolane when co-administered with piperaquine in healthy volunteers

PP-05

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Malaria is an infectious disease, caused by five different plasmodium species, afflicting people primarily in developing countries. The World Health Organisation estimates a total of 249 million estimated clinical cases and 608,000 estimated deaths in 2022. The treatment of malaria is threatened by artemisinin and partner-drug resistance in Southeast Asia and Africa, thus limiting the efficacy of current antimalarial combination therapies. This resistance development is one of the most important obstacles to malaria eradication and mimic historical patterns in which antimalarial drug resistance is first observed in Southeast Asia and spread globally. Therefore, new drugs and drug combinations are needed urgently. One new treatment is the fixed-dose combination of arterolane maleate and piperaquine phosphate which has been developed for the treatment uncomplicated *P. falciparum* malaria. Arterolane, a synthetic non-artemisinin trioxolane peroxide antimalarial compounds, has shown a rapid parasiticidal activity with an extended elimination half-life. This study aimed to characterise the population pharmacokinetics properties of arterolane in healthy male volunteers when administered alone and with piperaquine, using nonlinear mixed-effects population modelling to explore potential drug-drug and food-drug interactions. The disposition pharmacokinetic properties of arterolane were best described by a one-compartment model with one transit absorption compartment, displaying secondary absorption peaks likely due to post-dose meals. The developed model incorporated body weight as an allometric function. The concomitant administration of piperaquine resulted in increased exposure to arterolane. No impact of food was identified in the model. The population pharmacokinetic model of arterolane demonstrated adequate model diagnostics and good predictive performance.

Predictive Performance of Population Pharmacokinetic Model of Vancomycin in a cohort of patients: a retrospective pilot analysis of anonymised data

PP-06

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Background: Vancomycin is a glycopeptide antibiotic widely used to treat serious gram-positive infections, including methicillin-resistant *Staphylococcus aureus* (MRSA). Due to its narrow therapeutic index and significant interpatient variability, therapeutic drug monitoring (TDM) is essential to optimize dosing and minimize toxicity. This study aimed to evaluate the predictive performance of a in house developed population pharmacokinetic model for vancomycin using TDM data. Methods: An analysis of anonymised database of patients (5-17 years of age) with disseminated staphylococcal sepsis, whose therapeutic drug monitoring was carried out for the purpose of dose modification was used. An inhouse model developed in patients with sepsis showed that a two-compartment model with body weight and creatinine clearance as significant covariate respectively on Volume of Distribution and Creatinine clearance had explained the data well in the previous cohort. Predictive performance was assessed using mean prediction error (MPE) to evaluate bias and mean absolute prediction error (MAPE) to measure accuracy. A scatter plot comparing observed and model-predicted vancomycin trough concentrations was generated. Results: The model demonstrated a mean prediction error (MPE) of -21%, indicating a slight underestimation of predicted concentrations. The mean absolute prediction error (MAPE) was 25%, reflecting acceptable predictive accuracy for this population. Scatter plot analysis showed a good correlation between predicted and observed concentrations. Conclusion: The vancomycin pharmacokinetic model evaluated in this study predicted TDM trough concentrations in, with reasonable accuracy and acceptable bias. These findings suggest that the model fits the observed data and can serve as a valuable tool for guiding vancomycin dosing in pediatric populations. Further studies with larger datasets may refine the model to improve its predictive performance.

Application of population pharmacokinetics to improve bioequivalence study design: a case with a long half-life and highly variable drug product.

PP-07

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Objective: To optimize the washout period in a BE study for a highly variable drug product with a long half-life. Introduction: Traditionally, the washout period is based on the half-life of the drug where >5half-life of moieties of interest is considered sufficient. Subjects with pre-dose concentration >5%of the C_{max} need to be dropped from all BE study evaluations. An optimal wash out period is essential for any long half-life drug, else the pre-dose concentrations in subsequent periods would lead to loss of that subject data, or the duration of study would be lengthy affecting the project timelines significantly. Method: To quantitatively assess the impact of washout period on likelihood of percentage of pre-dose concentration >5% of C_{max}, the population pharmacokinetic model of a model drug was recreated in PumasAI® and simulated for various sampling times i.e., theoretical 3, 4, and 5 half-lives on triplicates of 100 subjects. Results: The washout period of 3, 4 and 5 half-lives resulted in 42, 89 and 99% of subjects free of pre-dose concentration > 5% of C_{max}. Conclusion: Instead of traditional way of calculation of washout period based on half-lives, the model-based evaluation allows for quantification of risk and efficient study design, therefore, balancing the cost Vs time on the product development.

A Semi-Mechanistic PBBM to Describe Complex and Saturable Absorption of Metformin: Application to dissolution specification Justification of ER formulation

PP-08

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Physiologically based pharmacokinetic (PBPK) or physiologically based biopharmaceutics models (PBBM) are modeling approaches that demonstrated significant applications in in both new drugs and generic product development. In generic product development, justification of dissolution specifications and establishment of dissolution safe space have important applications. For molecules exhibiting saturable absorption behavior, justification of dissolution specifications requires development of a model that incorporates effects of transporters is critical to simulate *in vivo* scenario. In the present case, semi-mechanistic PBBM was developed to describe the non-linearity of BCS class III molecule metformin. Subsequently, this model was utilized to justify dissolution specifications of ER formulation of metformin manufactured at 500mg and 1000mg doses. Semi-mechanistic PBBM was built using physicochemical properties, dissolution and non-linearity was incorporated through kinetics of multiple transporter kinetics at absorption level. The model was initially validated using literature data and further validated using in-house bioequivalence data in fasting and fed conditions. Further, virtual bioequivalence trials predicted the bioequivalence outcome that matched with clinical study data. Virtual dissolution profiles at lower and upper specifications were generated to justify the dissolution specifications. The model predicted bioequivalence between lower and upper specifications against pivotal test formulations thereby justifying dissolution specifications. Overall, complex and saturable absorption pathway of metformin was successfully simulated and this work was utilized for regulatory justification wherein manufacturing flexibility has been obtained through establishment of clinically relevant dissolution specifications.

Exploring Challenges to Support Advanced Bioequivalence Approach for Complex Generics

PP-09

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The challenges of complex generics impact both the pharmaceutical and healthcare industry. Developing physiologically-based pharmacokinetic modeling (PBPK) can provide optimal solutions by minimizing the requirement for *in vivo* evidence during regulatory review. By establishing risk-based predictive *in vitro* dissolution models, the PBPK model is also a practical approach for advancing patient-oriented quality goals. Aim: Our study was aimed to explore the challenges from the perspective of industrial professionals to identify critical issues encountered during the development and analytical process. Method: A qualitative research approach (In depth-interview) was employed, with semi-structured questionnaire among various stakeholders in India. A total of 10 formulation-analytical scientists with more than five years of experience participated in the study. The questionnaire had items related to challenges in development stage, formulation, optimization, replication of performance, critical quality and process attributes, analytical technologies and ends with the opinion about the current regulations. Thematic analysis was used to classify the challenges into distinct categories based on the experiences and insights shared by the interviewees. Atlas. Ti 9 was used to analyze the findings. Results: The study identified five key challenges such as formulation issues, analytical difficulties, regulatory barriers, cost and time constraints, miscellaneous scale-up problems, and lack of trained professionals.

Classes of complex generic	Challenges	Method to overcome (Suggestion)
Complex Injectables	Physicochemical challenges; degree of polymerization of the PLGA polymer, Variation in pharmacokinetic parameters;	PBPK modeling • To establish IVIVC • As a biowaiver (for *in vivo* studies recommended by product specific guidelines) • To explore relationships between systemic and local drug exposure PKPD model, E-R model, or QSP model : To waive clinical endpoint BE study
Complex API	Source of raw material, excipients related challenges, scale up challenge, physicochemical properties	
Complex nanotechnological	Solvent & solubility related issue, technology employed, Cost, reconstitution time, moisture content	
Complex ophthalmic	Alteration in drug retention time; drug content	

Conclusion: This exploratory research provided a detailed understanding of the challenges highlights the need to address these issues to achieve regulatory compliance.

Delineate: A Literature Co-Pilot for Quantitative Systems Pharmacology; AI-Assisted Literature Mining and Data Digitization

PP-10

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Delineate is a powerful tool for model-based meta-analysis (MBMA), producing NONMEM compatible datasets that integrate trial arm covariates, dosing schedules and digitized observations for efficient scalable workflows. Thus, the platform was developed to address the primary issues of data extraction and curation from scientific literature for quantitative systems pharmacology (QSP) and model informed drug development (MIDD). To achieve this, Delineate combines fine-tuned Large Language Models with custom computer vision algorithms within an agent architecture, taking advantage of modularity in handling complex tasks to achieve robustness and accuracy. This architecture enables plot digitization, dosing extraction, covariate extraction, meta data organization, etc. The platform also has a 'Chat with Paper' feature for users, which allows them to query and extract information of interest from uploaded literature. Delineate platform enables 70% faster digitization of plots than other tools such as Web Plot Digitizer. Furthermore, the Delineate platform can autofill user-defined fields related to the plot, such as the experimental and clinical conditions under which the data was collected, achieving 92% accuracy when tested on a dataset of 100 clinical trial papers. Additionally, our LLM agent increased accuracy on a QSP-related benchmark set to 95% from 22% with GPT-4. Using advanced AI methods and expert quality control, Delineate guarantees high accuracy and reliability that enables usage in MBMA and QSP work flows. Its capabilities allow efficient literature mining, model replication and dataset creation for model validation and parameter fitting. It represents an epic based transformative approach, freeing up researchers from dealing with the integration of literature-based insights into pharmacometric model building.

ADaM.jl: Clinical Data Preparation, Visualization and Validation tool in Pumas

PP-11

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Pharmaceutical investigators must adhere to a specific set of procedures and standards for clinical trial submissions to the regulatory agencies. CDISC is an organization which sets specific standards for clinical data collection and analysis which includes SDTM (Study Data Tabulation model) and ADaM (Analysis Data Model). ADaM.jl is a Julia-based package that works with Pumas ecosystem of tools that facilitates the creation, validation, and visualization of ADaM datasets from SDTM datasets. Methodology: Population pharmacokinetic datasets were prepared using ADaM.jl. SDTM datasets that consisted of trial information split across multiple datasets such as concentration, dosing, demographics, lab, vital signs etc, were combined in stages to derive the ADaM datasets. In the process, certain steps were performed such as derivation of date and time variables, expansion and compression of doses, flagging exclusions. After performing these operations and deriving the analysis dataset, the time variables, the biomarker and vital signs information were validated. Then, a dashboard that visualized the results consisting of plots and tables was developed. Results: ADaM.jl simplified the data preparation by handling error-prone and time-consuming steps efficiently. The tool could also handle the potential ambiguity in the source data effectively. Due to abstraction of complex functionalities and adherence to a derivation structure, the current tool demonstrated a significant reduction in dataset preparation times. Conclusion: ADaM.jl is a data analysis package written in Julia language that is available within the ecosystem of Pumas tools. It helped to reduce complex data preparation steps and minimize errors. Future releases will focus on more robust visualization and validation methods of the derived datasets.

Improving Oral Bioavailability of Acalabrutinib using Polymer Lipid Hybrid Nanoparticles: Design, Optimization, and *in vivo* Pharmacokinetic Evaluation.

PP-12

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Acalabrutinib (ACP) is a first-line treatment for hematological malignancies, but its low bioavailability, due to poor solubility and interactions with CYP3A4/P-gp, limits its efficacy. This research aims to enhance oral bioavailability of ACP by designing ACP loaded polymer-lipid hybrid nanoparticles (ACP-PLHNs). The ACP-PLHNs were prepared using an emulsification solvent-evaporation method with a high-shear homogenizer and optimized via a spherical, rotatable circumscribed central composite design (axial point value of 2). Four critical factors—polymer-lipid ratio, Tween 80 concentration, homogenization speed, and homogenization duration—were found to influence particle size (PS), polydispersity index (PDI), and loading efficiency (LE). PS followed a reduced two-factor interaction model with natural logarithmic transformation, while PDI and LE followed reduced quadratic models with inverse square root and square root transformations, respectively. The model F-values (12.26 for PS, 7.16 for PDI, and 6.44 for LE) indicated the models were significant with < 0.06% chance of error. The optimized ACP-PLHNs exhibited a PS of ~150.2 nm, PDI of ~0.284, and LE of ~20.79%. *In vitro* dissolution studies in buffer solutions mimicking upper-intestinal and plasma pH showed 43-55% ACP release by 8 hours, with sustained release over 2 days. ACP release followed Higuchi square root kinetics ($R^2 > 0.986$). The Korsmeyer-Peppas model yielded an 'n' value of ~0.811, suggesting that release is governed by both diffusion and swelling. *In vivo* pharmacokinetic studies in male Wistar rats revealed that ACP-PLHNs nanosuspension enhanced bioavailability by 3.72-fold ($p < 0.001$) compared to conventional ACP suspension, with > 2-fold increase in drug distribution to the spleen ($p < 0.001$), a key site for B-cell accumulation. Additionally, ACP-PLHNs increased $MRT_{0-tlast}$ to ~5.90 h and decreased clearance to ~785.40 mL/h, compared to conventional ACP suspension ($MRT_{0-tlast}$ ~3.86 h, clearance ~2479.85 mL/h). These findings suggest that PLHN technology could enhance the clinical efficacy of ACP and similar therapeutics.

Optimization and Pharmacokinetic Assessment of Curcumin Loaded Solid Lipid Nanoparticles

PP-13

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Curcumin (diferuloylmethane) is a potent phytomolecule which possesses very low bioavailability because of its poor absorption, undergoes first pass metabolism. The present study focussed to develop curcumin loaded solid lipid nanoparticles (SLN) using Sterotex HM (SHM), sterotex NF (SNF) and Gelucire 33/01 as lipids and different composition of surfactant and cosurfactant have been utilized for the development of SLN. The developed curcumin solid lipid nanoparticle are characterized for size, morphology, encapsulation efficiency, stability and release pattern. The particle size was in the range of 80-200 nm. The drug content and %entrapment was found to be in the range of 40-60%. The poly dispersity index suggest the good uniformity of the sizes in the formulation prepared with SHM, Tween 80 and PG. The stability studies indicate the formulation were stable till a period of one year. The optimized formulation has been subjected to pharmacokinetic studies in rabbit model. Blood sample was withdrawn in different time intervals upto 24hrs. The plasma samples were analysed in the validated HPLC method. The results are indicative that the formulation prepared using SHM (Cu5b) found to have dose dependent increase in the bioavailability. The SLN loaded with curcumin was found to have enhanced bioavailability. To conclude, the curcumin bioavailability can be enhanced significantly through SLN delivery, and the dose can be reduced by one fourth.

Factors Affecting Pharmacokinetics of Sunitinib and its Metabolite, SU012662: A Systematic Review of Population Pharmacokinetic Studies

PP-14

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Background: Sunitinib Malate is used across geographies to treat advanced renal cell carcinoma, gastrointestinal stromal and pancreatic tumors in imatinib resistant patients. Objective: A wide variability in drug exposure is reported for both sunitinib and its active metabolite (SU012662). The systematic review aimed to summarize reported population pharmacokinetics (PopPK) studies of sunitinib and to identify the factors affecting the pharmacokinetics of sunitinib and SU012662. Methodology: A systematic search was undertaken using Scopus, Web of Science and PubMed databases. Studies were included in the review if population pharmacokinetic modelling approach was used for sunitinib and/or SU012662 in adult and/ or paediatric population. Results: A total of thirteen PopPK studies were included in the systematic review. Most of the studies reported two-compartment model with first-order absorption and elimination to describe sunitinib and SU012662. Body surface area (BSA), age, sex, ethnicity, tumor type, ABCB1 and ABCG2 genotype were the main covariates that affected the pharmacokinetics of sunitinib and SU012662. Discussion: The variability in the covariates alters sunitinib and SU012662 exposure and thus has the potential to influence the clinical outcome of sunitinib treatment. This necessitates the implementation of a generalizable PopPK model which can be used for precision dosing in patient population. Predictive performance assessment of these published models should be performed before implementing them during the routine clinical practice. Conclusions: PopPK models for sunitinib and SU012662 was explained using two-compartment structural model with first order absorption and elimination. Covariates such as BSA, age, sex, ethnicity, tumor type, ABCB1 and ABCG2 genotype are reported to affect the disposition of sunitinib and SU012662. All these co-variates must be considered while addressing the pharmacokinetic variability of sunitinib and SU012662 to ascertain the generalizability of the model to other populations.

Efficacy of Different Treatment Class Drugs on Endpoints of Interest in Amyotrophic Lateral Sclerosis (ALS): A Meta-Analysis

PP-15

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Objective: To perform meta-analysis to evaluate the efficacy of drugs from various treatment classes currently in pipeline on the key endpoints of interest in Amyotrophic Lateral Sclerosis (ALS). Methods: A systematic literature search was conducted using interventional randomized placebo-controlled trials from clinical databases such as Biosis, OVID Medline, Embase, Cortellis, and Trialtrove, covering data from 2000 to 2023. The studies focused on Revised Amyotrophic Lateral Sclerosis Functional rating scale (ALSFRS-R) scores and Percentage predicted Slow vital capacity (SVC% predicted) at 12-24 weeks for drugs currently in the ALS pipeline. The mean change from baseline for both the drug and placebo was calculated, with missing standard deviation (SD) values imputed using the median imputation method. The treatment difference between the drug and placebo was computed, and a meta-analysis was performed using the meta package in R version 4.1.3 and presented through forest plots. Results: The search identified 24 studies and meta-analysis on the endpoint ALSFRS-R, showed mean treatment difference at 12 weeks and 24 weeks as 0.26 [95% CI -0.34;0.85] and 1.33 [95% CI 0.35; 2.31] respectively. For SVC% predicted, the overall mean difference was 0.39 [95% CI -2.35; 3.14] and 0.74 [95% CI -0.12; 1.6] at 12 and 24 weeks available for the limited studies and drug classes. Ropinirole, acetyl-L-cartine;riluzole, olesoxime:riluzole and RNS60 showed improvement in ALSFRS-R scores from 12 to 24 weeks. Reldesemtiv did show a small positive effect on ALSFRS-R scores and SVC% predicted based on the mean treatment effect though not quite significant. Inference: The meta-analysis did not find significant differences in treatment effects across the various drug classes for ALS. Continued research is essential to identify effective therapies for ALS and improve patient outcomes.

Monoclonal antibodies for patients with Neuromyelitis Optica Spectrum Disorder (NMOSD) - Systematic Review and Meta-analysis

PP-16

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Objective: This systematic review and meta-analysis aim to evaluate the efficacy of current or in pipeline monoclonal antibodies on key measures of NMOSD and will inform benchmark estimates for future drug development. Methods: A comprehensive literature search was conducted across multiple databases to identify randomized controlled trials (RCTs) assessing the impact of monoclonal antibodies on Vascular Acuity Score (VAS) and Expanded Disability Status Scale (EDSS) score in NMOSD patients from 1998 to 2023. Studies were included if they reported change in baseline with an assessment of variability. Systematic review of literature was performed by a clinical team for the treatments of Eculizumab, Satralizumab and Inebilizumab, followed by data curation. Primary timepoints for each study ranged from 24-48 weeks. A random effects model with weighted average was employed for the analysis using the *"meta"* package in R Version 4.1.0. Data was visualized as forest plots. Results: Four RCTs, including 554 patients, met the inclusion criteria. For the VAS endpoint (24-28 weeks), a large effect size 2.57 with wide 95%CI [-2.15; 7.30] was observed across the studies. For EDSS scores, Eculizumab demonstrated slightly superior performance with a mean difference of -0.17 [-0.44; 0.10] compared to Satralizumab which had a mean difference of -0.11 [-0.37; 0.15] after 24 weeks. By the 48-week mark, Eculizumab maintained its consistent treatment effect. In contrast, Satralizumab showed slight improvement, resulting in a mean difference of -0.19 [-0.42; 0.04]. Conclusion: This systematic review and meta-analysis suggest that monoclonal antibodies are effective in reducing disability in NMOSD patients, as evidenced by improvements in EDSS scores. However, the uncertainty in the VAS analysis suggests a need for further research with larger sample sizes to validate these results. The consistent results across studies, indicated by low heterogeneity, underscore the potential of monoclonal antibodies as a viable treatment option for NMOSD.

Timing of gemcitabine administration and effect on its metabolism and elimination kinetics in metastatic cancer patients

PP-17

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Background and objective: Time of administration of chemotherapy varies, however, evaluation of effect of time of drug administration on drug kinetics remains much less explored. The objective of this study was to estimate differential effect of chrono-modulated therapy on gemcitabine elimination kinetics and its metabolism. Methods: The study included 14 participants. Gemcitabine (1000 mg m^{-2} infusion over 30 minutes) was administered as a part of chemotherapy regimen in day-care center at 9:00 hours or 15:00 hours. Plasma concentration of gemcitabine and cytidine deaminase enzyme activity was determined for each participant. Results: Chrono-modulation does not have a significant effect on gemcitabine elimination kinetics. However, an increase in adverse effects was reported by the evening group participants. There was no significant difference in CDA activity between groups. Evening group participants reported an increase in adverse drug reactions. Conclusion: Gemcitabine can be infused at any time of the day without any significant alterations in its elimination kinetics.

Enhancing formononetin absorption by integrating natural bioenhancers within a phospholipid matrix

PP-18

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The practical use of Formononetin (FMN) is hindered by its low solubility in water and significant phase II metabolic processes. In this study, we developed a phospholipid complex (PLPCX) formulation comprising FMN and the UDP-glucuronosyltransferase (UGT1A1) inhibitor piperine (PIP) to address the limitations associated with FMN. We conducted a detailed characterization and comparative analysis of the FMN-PIP-PLPCX. Our findings revealed that both formulations enhanced the water solubility of FMN and its oil-water partition coefficient. NMR, DSC and SEM analysis were conducted to elucidate the interactions and structural characteristics of the complex. Comparative analysis revealed that FMN-PIP-PLPCX exhibited significantly higher FMN release during *in vitro* studies and greater permeation across the Caco-2 monolayer compared to FMN-PIP-PLPCX. The *in vitro* findings with the *in vivo* pharmacokinetic results, demonstrating that FMN-PIP-PLPCX significantly enhanced C_{max} and $AUC_{(0-24)}$ by 7.16 and 23.33 fold at 5 mg/kg, and by 29.64 and 23.33 fold at 10 mg/kg, respectively, compared to pure FMN. Furthermore, the combined treatment of PIP and FMN enhanced the *in vitro* pharmacological efficacy against dexamethasone-induced osteoporosis. This study revealed that the integration of PIP into the FMN-PLPCX markedly improved FMN's water solubility, safeguarded it from phase II metabolic degradation, and consequently enhanced its bioavailability and therapeutic effectiveness.

A QSP model to predict clinical PK/PD of siRNA therapeutics and learnings from model development

PP-19

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Aims: Small interfering RNA (siRNA) regulates gene expression by targeting and degrading specific mRNA, thus preventing protein synthesis. siRNAs are in development for correcting genetic disorders and managing chronic diseases. Better mechanistic understanding of the siRNA mechanism through modeling & simulation can enable prediction of PD durability from the clinical PK data and inform FIH dose prediction and dosing strategy. Objective: To develop a unified QSP model capturing the clinical PK/PD of approved siRNA molecules to support drug development decisions.

Methods:

- Expanded a published semi-mechanistic model and recalibrated it to capture PK/PD dynamics of five siRNAs: Fitusiran, Inclisiran, Olpasiran, Vutrisiran, and Lepodisiran.
- Developed a unified set of physiological parameters (volumes, flow rates) and certain drug-specific, and species-specific parameters for data fitting.
- Identified associations between siRNA chemical modifications and PK/PD-sensitive parameters.

Results and Discussion:

1. We have developed a robust model with sufficient elements that can capture 5 siRNA drugs' clinical PK/PD with different targets & varying PD durability, using a unified parameter set with changes in key drug-specific parameter, RISC degradation rate (kDR).
2. Development of modification score - We found significant correlation between RISC degradation (kDR) and chemical modification score proving that the chemical modification has a direct impact of stability that can be translated into a modeling parameter.

Conclusions:

The model effectively captures the clinical PK/PD of both short-acting and long-acting siRNA molecules. We are developing a translation protocol to go from preclinical cynomolgus monkey data and predict clinical doses and alternate dosing for novel siRNA drugs.

Development of QSP platform model for predicting clinical efficacy and CRS incidence of CD3 bispecifics in STEAP1 Prostate Cancer

PP-20

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Introduction: CD3 bispecifics are engineered antibodies that bind to CD3 on T cells and target antigens on cancer cells (TAAs), activating T cells to kill cancerous cells. However, they may induce adverse effects such as CRS (Cytokine Release Syndrome) from off-tumor toxicity, prompting research to investigate the optimal therapeutic window. Objectives: The aim of developing the CD3 bispecifics QSP platform model is to investigate the drivers of efficacy and adverse events and suggest an efficacious clinical dose, while proposing strategies to mitigate CRS. Recently we developed a QSP model to suggest an alternate dosing regimen and incremental dose for Xaluritamig (a STEAP TDB for prostate cancer). For the current effort, we focus on suggesting a clinical efficacious dose via translation from mouse Tumor Growth Inhibition (TGI) studies. Methods: A QSP platform model was developed for a 2+1 STEAP1 x CD3 bispecific antibody targeting prostate cancer, building on Hosseini et al. (2020). The original model incorporated drug interactions with CD3 and tumor-associated antigens, leading to dimer/trimer formation and T cell dynamics, highlighting the role of target receptor occupancy in efficacy and toxicity for Non-Hodgkin's lymphoma with a 1+1 CD3 bispecific antibody. We extended this model to a 1+2 bivalent bispecific antibody for prostate cancer, focusing on optimal dose priming. Clinical data were used to calibrate and validate the platform model. Results: The QSP model captured PBPK, clinical efficacy, and cytokine data for Xaluritamig, accurately predicting the clinical efficacious dose from mouse TGI studies. Conclusions: The model evaluates antigen expression, binding affinities, and T cell levels on efficacy and CRS. It supports early clinical development by guiding the therapeutic window of TCEs.

Mechanistic Modeling of GLP-1 Therapeutics Development for Obesity management

PP-21

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Incretin-based therapies targeting hormones such as glucagon-like peptide-1 (GLP-1) have emerged as effective strategies for managing type 2 diabetes (T2D) and obesity. These hormones play a crucial role in metabolic regulation by stimulating glucose-dependent insulin secretion, inhibiting glucagon release, slowing gastric emptying, and enhancing feelings of satiety. The development of weight loss therapies utilizing GLP-1 receptor agonists (GLP RA) hinges on a deep understanding of their mechanism of action, which involves receptor occupancy and target engagement in both target (e.g., pancreas, brain) and non-target tissues (e.g., gastrointestinal tract). In this overview, we propose the design of a mechanistic model integrating body weight dynamics, glucose regulation, meal metabolism, incretin pathways, drug pharmacokinetics, pharmacodynamics, and receptor pharmacodynamics. This framework is utilized to explore the effects of GLP-1 receptor drugs on glycemic control and weight loss and offers a powerful tool for predicting their efficacy and safety to optimize therapeutic outcomes. Receptor occupancy models are applied to characterize GLP-1 receptor engagement in target tissues and predict clinical efficacy. Additionally, leveraging published weight models, we differentiate fat mass loss from muscle mass retention, providing a comprehensive assessment of the drug's therapeutic impact. This model can be employed in understanding mechanisms underlying the superior efficacy of dual and triple receptor agonists with GLP1-RA. Safety profiles are proposed to be modeled with a focus on gastrointestinal adverse events, such as nausea, which are pivotal in determining the maximum tolerated dose and designing dosing schemes with high patient compliance. The model can be further calibrated to different dose and titration schemes of multiple GLP1 agonists to identify strategies that mitigate these adverse events, thus enhancing protocol adherence and reducing dropout rates in clinical trials. Insights derived from such mechanistic models might have significant implications for drug development. They can inform dose optimization, and design of dosing regimens that improve compliance and patient adherence, which is crucial in more effective long-term weight management therapies. This study aims to develop comprehensive strategies to improve GLP-1 RA interventions using model-driven insights to tailor obesity care and clinical decision-making, guided by patient profiles, co-morbidities, and therapeutic responses.

PP-22

Leveraging Latent Factor Modelling with Knowledge, Attitudes, and Practices in Anxiolytic & Antidepressant Resistance in patients with GAD and MDD.

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Introduction: Treatment-resistant depression (TRD) is a form of Major Depressive Disorder (MDD) unresponsive to at least two antidepressant trials, lacking consensus on staging. This study investigates how knowledge, attitudes, and practices influence personalized medicine for MDD. Objectives include identifying factors shaping treatment resistance, evaluating their impact on adherence, and developing a validated Knowledge, Attitude and Practice (KAP) model to improve outcomes through targeted clinical strategies. Statistical analysis and latent factor modelling guide these aims effectively. Methodology: This survey of 144 participants used a structured KAP questionnaire to assess understanding of antidepressants, adherence attitudes, and openness to genetic testing. Factor analysis with Varimax rotation identified key dimensions. Internal consistency was high (Cronbach's alpha), and descriptive statistics and regression analysis examined relationships between factors and treatment resistance outcomes using SAS studio version 9.4. Results: This study identified four latent factors explaining 90.11% of the variance in KAP regarding antidepressant therapy, with excellent reliability (Cronbach's alpha = 0.91). Factor 1 contributed 79.71% of the variance, highlighting public education's role in improving adherence and reducing misconceptions. Factor 2, focused on adherence and management, emphasized personalized strategies like reminders and telemedicine. Factor 3 addressed perceptions of genetic testing, advocating its role in precision medicine to minimize trial-and-error prescribing. Factor 4 emphasized trust and communication with healthcare providers, highlighting patient-centered interactions for sustained engagement. Regression analysis confirmed significant relationships between all factors and the final KAP score (R^2 = 0.9983, $p < 0.0001$). These findings offer a robust framework to advance precision psychiatry through education, adherence strategies, pharmacogenomics, and therapeutic alliances. Conclusion: This study reveals a transformative framework for tackling antidepressant treatment resistance, emphasizing public education, personalized adherence strategies, pharmacogenomics, and patient-provider collaboration. With robust reliability and model fit, the findings offer insights to optimize outcomes and revolutionize precision psychiatry.


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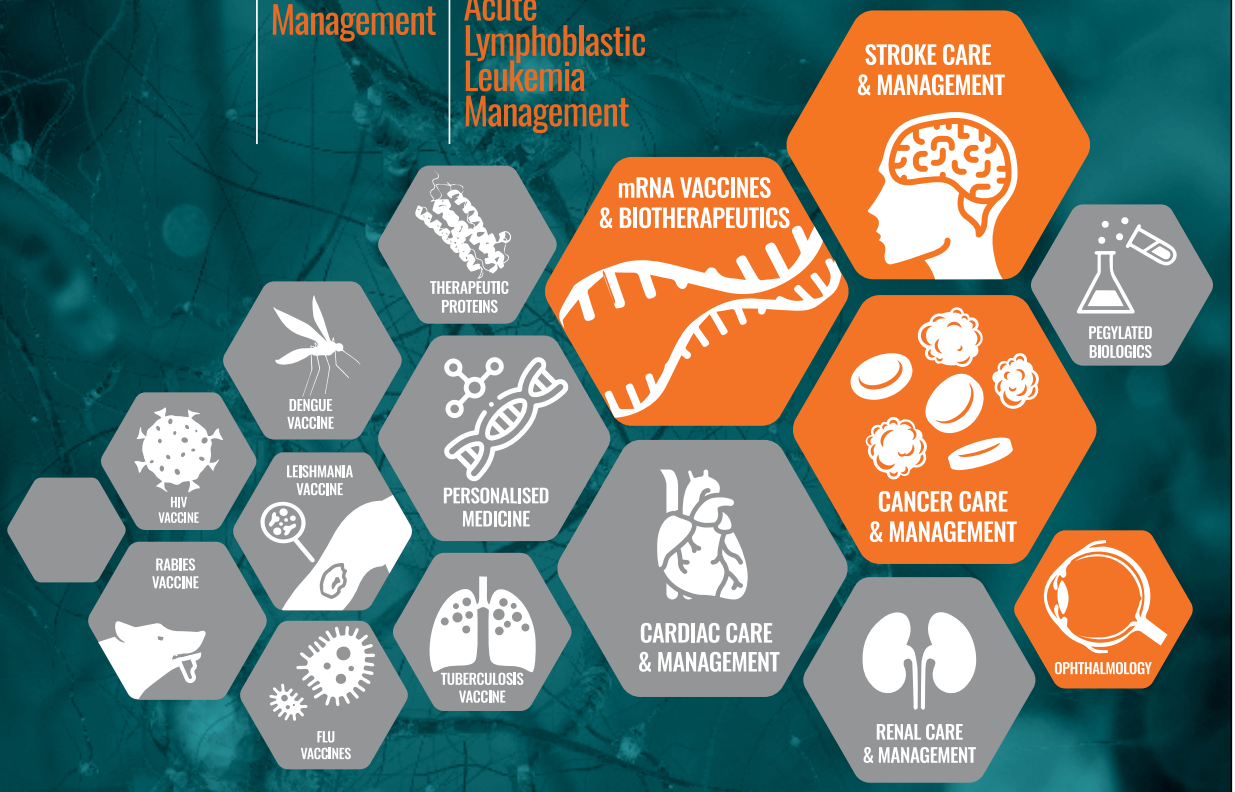

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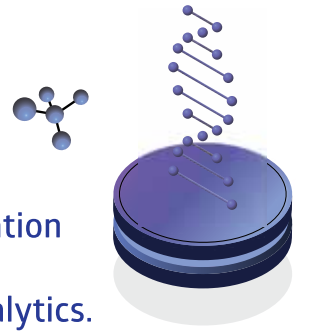

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