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The 2nd Annual Conference of the
Society of Pharmacometrics and Health Analytics (SOPHAS)
(Formerly PAGIN)

International Conference on Pharmacometrics, India

ICOP 2026
INDIA

THEME

Quantitative Approaches in Drug Development: A Path Forward

Organized by:

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

Workshops
January 28 and 31, 2026

Conference
January 29 & 30, 2026

Venue
Fortune Valley View, Manipal

QS WORLD UNIVERSITY RANKINGS 2025

101-150 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

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ABSTRACT BOOK

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MESSAGE

Principal, MCOPS

Dr. Srinivas Mutalik

Dear Delegates, It is a privilege to welcome you to ICoP India 2026, being held on 29–30 January 2026. This conference reflects the growing maturity and momentum of pharmacometrics and Model-Informed Drug Development (MIDD) in India and globally, where quantitative thinking is no longer "supporting science," but a central driver of better, faster, and more confident decisions across discovery, development, and life-cycle management.

The program has been designed to be both rigorous and practical. Over two days, we will discuss how quantitative methods shape decision-making in modern drug development, with sessions spanning MIDD in oncology, biomarkers and surrogate endpoints, and mechanistic perspectives that strengthen translation. We also focus on real-world applications in generic and small-molecule development, including PBPK/PBBM, IVIVC for complex formulations (including long-acting injectables), and emerging modeling strategies that address exposure limitations and formulation performance questions. Day 2 extends this scope to biologics, biosimilars, and new modalities, while also investing intentionally in the future of the field through student and young professional sessions, podium presentations, and an Open House on industry perspectives and opportunities in pharmacometrics in India. With poster exhibitions and informal networking, ICoP India 2026 is built not only to share knowledge, but to create connections that endure beyond the conference.

I encourage every participant to engage fully and use this platform to build collaborations that advance patient-centric and evidence-driven development.
With best wishes for an inspiring and impactful meeting.

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 continuing its exciting journey in hosting the second International Conference on Pharmacometrics India 2026. Our society was 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 taking its proud steps with initiatives like courses on pharmacometrics and AI in drug development apart from short course in Bioequivalence and drug development. We are proudly graduating the first cohort of pharmacometrics students and looking forward to their career progression as future leaders.

SOPHAS is actively collaborating with various stakeholders like industry, academia, regulatory agencies and global societies in furthering the profession, nurturing talent and shaping the regulatory landscape and contributing to the precision therapy for the benefit of patients.

We are grateful for our speakers, sponsors, participants and our well-wishers for their support in every step of ICOP India 2026. We are indebted to the International Society of Pharmacometrics (ISOP) for their continued support. Center for Pharmacometrics at the Manipal College of Pharmaceutical Sciences has taken the lead again to host ICOP India 2026 at Manipal. This year's conference will provide a great platform for all the participants to deliberate on the theme of "Quantitative Approaches in Drug Development: A Path Forward". There are also excellent plans for social events and a Gala Dinner.

I welcome all the participants of ICOP India 2026 for the important event on pharmacometrics and quantitative sciences and enjoy the flavors of local hospitality arranged by local organizing committee.

Dr. Surulivelrajan Mallayasamy

The President, SOPHAS.

LETTER FROM THE ISOP LEADERSHIP

Dr. Vijay Ivaturi

Dear ICOP India Attendees, Colleagues, and Friends,

It is a distinct honor to welcome you to Manipal for the Second ICOP Conference in India. As we gather here from January 28th to 31st, I am filled with pride seeing how far this initiative has come since our inaugural meeting.

I would like to extend my deepest gratitude to ISoP for their continued support, and offer a special congratulations to SOPHAS for their perseverance and commitment to this mission. Your dedication aligns perfectly with ISoP's vision, and it is clear that the community here in India is not just growing—it is rapidly becoming the next generational hub for quantitative sciences. We are incredibly excited to partner with you in fostering this evolution.

Witnessing the growth from last year to this year has been truly remarkable, particularly the infectious enthusiasm I see amongst the students. You represent the future of our field, and your energy is the driving force behind these gatherings.

I hope you all have fun, learn from one another, and build lasting connections over these few days. Please remember that ISoP is always here to support you, to advance the science, and to strengthen the network of quantitative sciences around the world.

Warm regards,

Dr. Vijay Ivaturi
Past-President, ISoP

ABOUT

Centre for Pharmacometrics

The Department of Pharmacy Practice, MCOPS, MAHE has been actively working in the field of pharmacometrics for over a decade. The Centre for Pharmacometrics, managed by Dr. Surulivelrajan, is actively involved in training and research on quantitative methods. Nationally important institutions such as ACTREC, Mumbai, and PGIMER, Chandigarh, are collaborators of the Centre. The Centre also works closely with the Society of Pharmacometrics and Health Analytics (SOPHAS).

The Centre supports the conduct of the DMPK Certificate Course of SSX, India. It regularly conducts workshops, training programs, and certificate courses in pharmacometrics, pharmacokinetics, and data analytics using new-age tools.

Currently, the Centre has a team of nearly half a dozen scientists working on industry consultancy projects, along with an equal number of doctoral candidates pursuing research on various projects supported by MAHE, central government agencies, and industry grants.
The Centre cherishes the privilege of conducting the 2nd Annual Conference of ICoP India 2026 and warmly welcomes all SOPHAS council members, sponsors, and participants to Manipal.

Dr. Surulivelrajan Mallayasamy

Co-ordinator
Centre for Pharmacometrics,
Dept of Pharmacy Practice, MCOPS, MAHE.


CERTIFICATE COURSE
PHARMACOMETRICS
ORGANIZED BY: SOCIETY OF PHARMACOMETRICS AND HEALTH ANALYTICS (SOPHAS), PSG INSTITUTE OF MEDICAL SCIENCES & RESEARCH
About the Program
Pharmacometrics is an evolving discipline impacting all stages of drug discovery, development, and clinical use. With growing demand for skilled professionals in this field, this course offers specialized training for students, academics, and industry professionals.
Scope of the Course
Understand principles of statistics pharmacokinetics and PKPD modeling for pharmacometrics
Use quantitative tools for decision-making in drug development and clinical practice
Execute professionally relevant projects with hands-on experience
Learning Experience
Live & recorded lectures
Group discussions & in-person applied sessions
Moodle (learn.sophas.net)
Pumas & PumasCP (Academic licenses provided)
Curriculum Overview
Statistics for Pharmacometrics
Covers core statistical concepts from descriptive stats and probability to regression, ANOVA, and clinical trial design.
Basics of Pharmacokinetics (PK)
Explores ADME processes through compartmental models, including IV bolus, absorption, elimination, multiple dosing, and clinical PK.
PK/PD Modeling & Simulation
Includes project-based model development and covers structural models, covariates, variability, mechanistic approaches, and simulation techniques.
Capstone Project
Learners apply their knowledge to design and execute full modeling workflows using real-world datasets.
Course Coordinator: Dr. Vijay Ivaturi
Intake for the 2026 batch begins in June 2026
Coimbatore, Tamil Nadu, India
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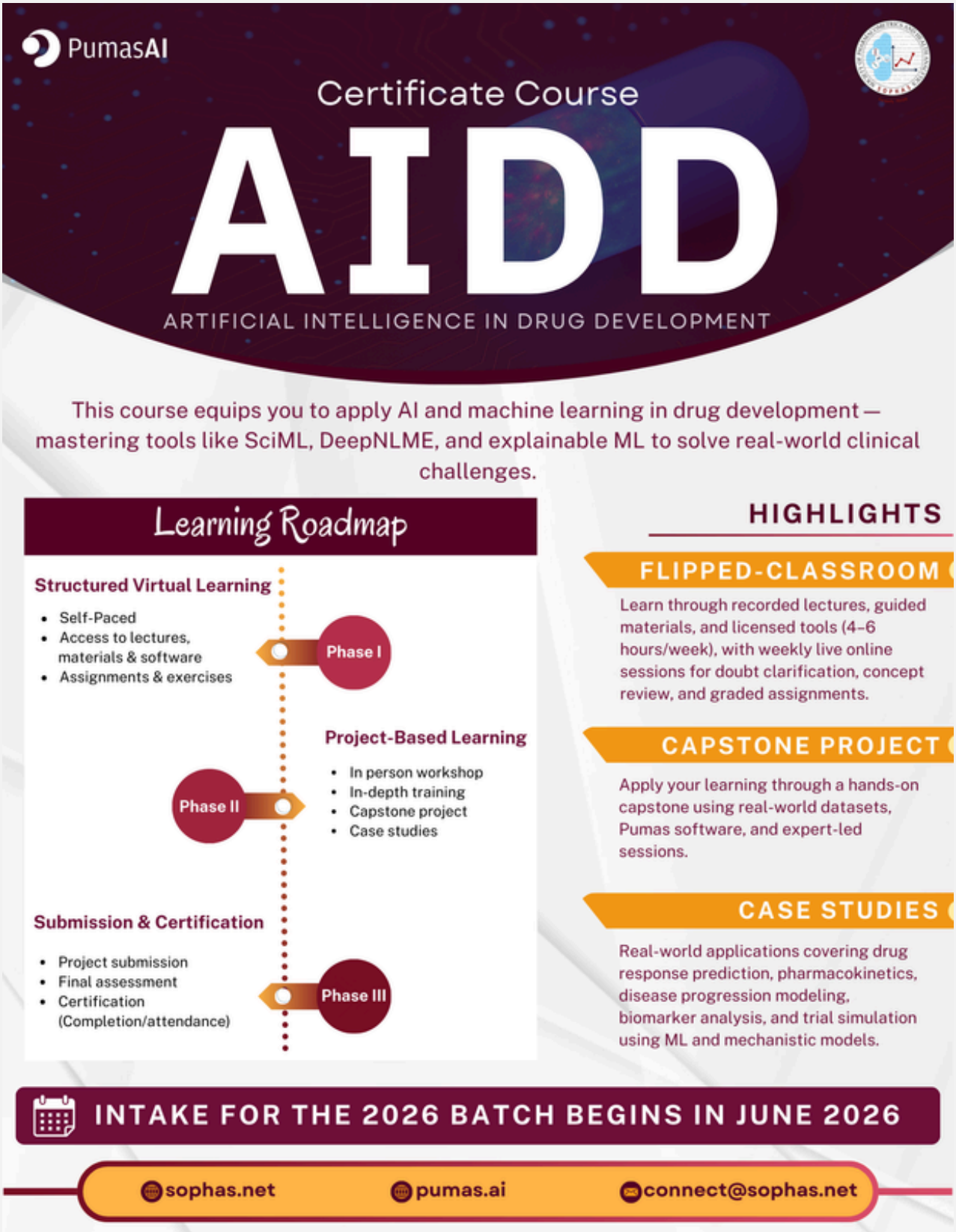
Know more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Access to lectures, materials & software
Assignments & exercises
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Project-Based Learning
In person workshop
In-depth training
Capstone project
Case studies
Phase II
Submission & Certification
Project submission
Final assessment
Certification (Completion/attendance)
Phase III
HIGHLIGHTS
FLIPPED-CLASSROOM
Learn through recorded lectures, guided materials, and licensed tools (4–6 hours/week), with weekly live online sessions for doubt clarification, concept review, and graded assignments.
CAPSTONE PROJECT
Apply your learning through a hands-on capstone using real-world datasets, Pumas software, and expert-led sessions.
CASE STUDIES
Real-world applications covering drug response prediction, pharmacokinetics, disease progression modeling, biomarker analysis, and trial simulation using ML and mechanistic models.
INTAKE FOR THE 2026 BATCH BEGINS IN JUNE 2026
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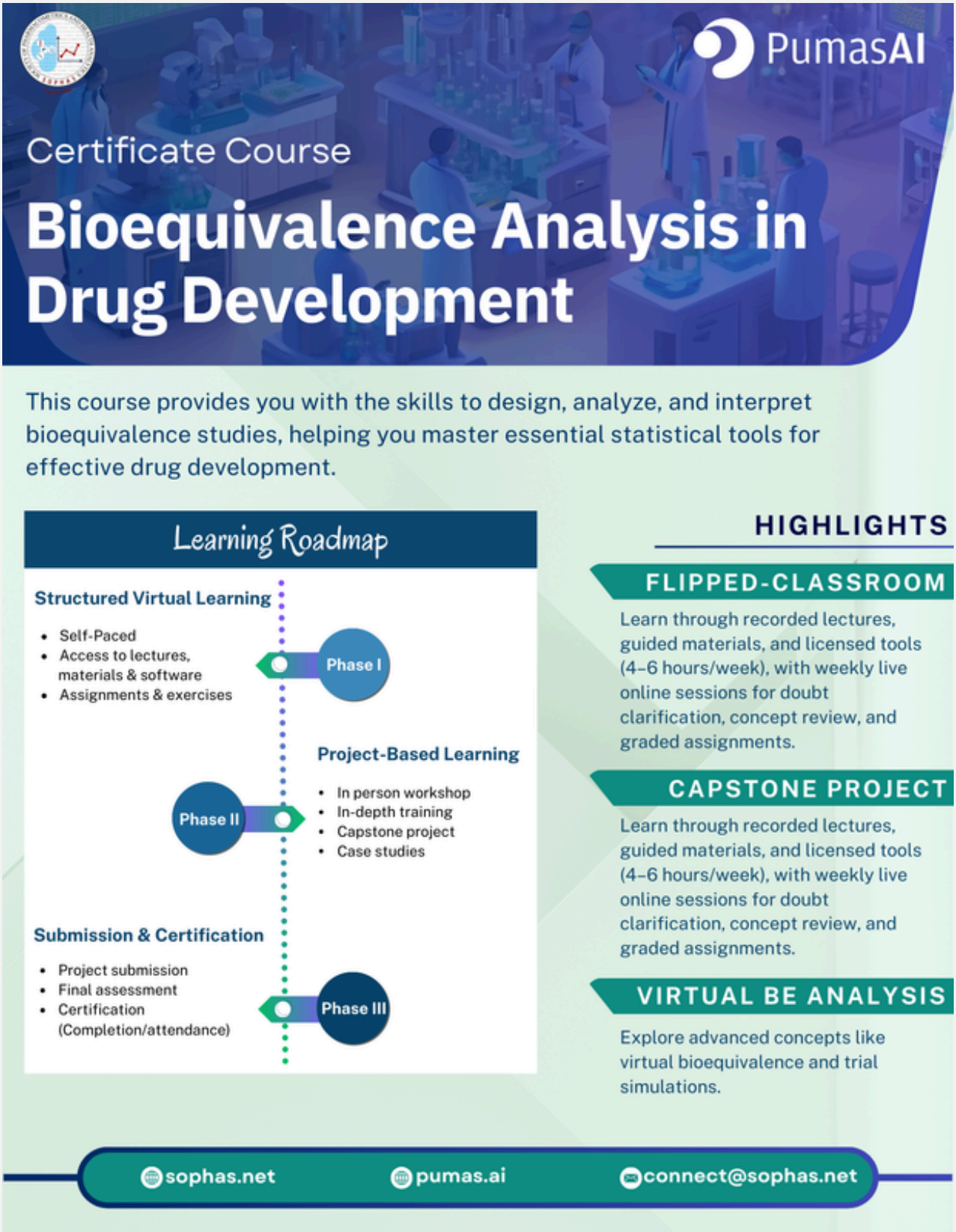
PumasAI
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This course provides you with the skills to design, analyze, and interpret bioequivalence studies, helping you master essential statistical tools for effective drug development.
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Self-Paced
Access to lectures, materials & software
Assignments & exercises
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Submission & Certification
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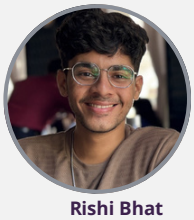

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CONFERENCE SCHEDULE

Day 1: 29 Jan 2026

Forenoon Session
Chairpersons: Dr. Rama Sivasubramanian, Director R&D, Teva pharma, Maharashtra, India
Theme: Quantitative Methods for Drug Development Decision

No	Time (IST)	Topic	Speaker
	7:00 - 9:00	**Power Breakfast • Poster Exhibitions**	
	9:00 - 9:15	**Inauguration**	
1	9:15 - 10:00	Keynote Speech: Impact of MIDD in Oncology	**Dr. Amit Roy** VP, Scientific & Strategic Consulting, PumasAI DE, USA,
2	10:00 - 10:30	A Quantitative Framework to Assess Biomarkers as Surrogate Endpoints: Applications in Drug Development	**Dr.Mathangi Gopalakrishnan** Associate Professor, Center for Translational Medicine, University of Maryland school of Pharmacy Baltimore, MD, USA
	10:30 - 11:00	**Coffee Break**	
3	11:00 - 11:30	Modeling How Early Treatment Initiation Improves Post-Treatment Control of HIV Infection	**Prof. Narendra Dixit** Professor, Department of Chemical Engineering & Bioengineering, IISc Bengaluru, Karnataka, India
4	11:30 - 11:45	Reimagining Pharmacometrics: From Analysis to Decision-Making	**Dr. Dhanashri Gudi** Vice President, Business Development & Strategy, Pumas-AI, Inc., USA
5	11:45 - 12:15	Panel Discussion	All Forenoon Speakers & Select Experts
	12:15 - 13:45	**Lunch, Exhibits, Poster sessions**	

Afternoon Session
Chairpersons: Dr. Sivacharan Kollipara, Head, Biopharmaceutics, Global Clinical Management, Dr. Reddy's Laboratories Ltd, Hyderabad, Telangana, India; & Dr. Suraj Bhansali, R&D Data Science & Head of India Country Operations, Certara, Hyderabad, Telangana, India
Theme: Quantitative Science in Generic & New Drug Development (Small Molecules)

1	13:45 - 14:05	Harnessing PBBM & PBPK Modeling for Next-Generation Generic Drug Development	**Dr. Rajkumar Boddu** Team Lead, Biopharmaceutics, Global Clinical Management, Dr. Reddy's Laboratories Ltd Hyderabad, Telangana, India
2	14:05 - 14:25	Optimising & Enhancing Drug Development Using Simcyp PBPK Simulator	**Ms. Maitri Sanghavi** Research Scientist, SIMCYP, Certara Hyderabad, Telangana, India
3	14:25 - 14:45	Hypothesis Generation With PBPK to Identify Mechanisms Limiting Exposure of Orally Administered Drugs	**Dr. Sheila Annie Peters** Executive Director, Boehringer Ingelheim Germany
	14:45 - 15:15	**Coffee Break**	
4	15:15 - 15:35	Physiologically-Based Pharmacokinetic Modelling: An Integral Component of Model-Informed Drug Development	**Dr. Samarth Thakore** Principal Scientist II, PK Sciences, NIBR, Novartis Hyderabad, Telangana, India
5	15:35 - 15:55	Physiologically Based IVIVC for Complex Formulations: Focus on Long-Acting Injectables	**Dr. Anant Ketkar** Principal Scientist & Scientific Lead - India, Simulations Plus, Inc India
6	15:55 - 16:15	Panel Discussion	All Afternoon Speakers & Select Experts
	18:00 - 21:00	**Gala Night**	

CONFERENCE SCHEDULE

Day 2: 30 Jan 2026

Forenoon Session

Chairpersons: Dr. Bhairav Paleja, Principal Scientist, Vantage Research, Chennai, Tamil Nadu, India; & Dr. Balaji Agoram, Senior Vice President, Arcus Biosciences, Brisbane, CA, USA

Theme: Quantitative Sciences in Biologics, Biosimilars & New modalities (Large Molecules)

No	Time (IST)	Topic	Speaker
1	9:00 - 9:45	Dr. Ramalingam Sankaran Commemoration Lecture: From Sheiner to Systems: Evolving Personalized Dosing in the Era of Precision Medicine	**Prof. Krishna Devarakonda** Visiting & Adjunct Professor, Thomas J. Long School of Pharmacy - University of the Pacific Richmond, TX, USA
2	9:45 - 10:30	**Scientific Briefing & Pharmacometrics Certificate Graduation Ceremony**	
3	10:30 - 11:00	Does Progressive Disease Justify Discontinuation: A Simulation Analysis	**Dr. Kannan Thiagarajan** Principal Scientist, Vantage Research Chennai, Tamil Nadu, India
	11:00 - 11:30	**Coffee Break**	
4	11:30 - 12:00	The Role of Mechanistic Models to Complement Pharmacometrics in Model-Informed Drug Development	**Dr. Khamir Mehta** Senior Director in Clinical Pharmacology Modeling & Simulation Department San Francisco, CA, USA
5	12:00 - 12:30	Novel Modeling Approaches Towards Dose Optimization of TCEs	**Dr. Karthick Vishwanathan** Executive Director, Head of CPQP Oncology, AstraZeneca Waltham Site Head Waltham, MA, USA
6	12:30 - 13:00	Panel Discussion	All Forenoon Speakers & Select Experts
	13:00 - 14:00	**Lunch, Exhibits, Poster sessions**	

Afternoon Session

Chairpersons: Dr. Sivacharan Kollipara, Head, Biopharmaceutics, Global Clinical Management, Dr. Reddy's Laboratories Ltd, Hyderabad, Telangana, India; & Dr. Vijay Ivaturi, Co-Founder & CEO, Pumas-AI Inc, DE, USA; Endowed Chair, Center for Pharmacometrics, Manipal, Karnataka, India; Past President, ISoP, Branchburg, NJ, USA

Theme: Students/Young Professional Sessions

1	14:00 - 15:15	**Student Podium Presentations & Roller Coaster Sessions**	
	15:15 - 15:30	**Coffee Break**	
2	15:30 - 16:30	Open House: Industry Perspectives, Opportunities, Future in Pharmacometrics in India	**Dr. Vijay Ivaturi** Co-Founder & CEO, Pumas-AI Inc, DE, USA; Endowed Chair, Center for Pharmacometrics, Manipal, Karnataka, India; Past President, ISoP, Branchburg, NJ, USA **Dr.Mathangi Gopalakrishnan** Associate Professor, Center for Translational Medicine, University of Maryland school of Pharmacy Baltimore, MD, USA Industry Experts from Various Companies
	16:30 - 17:00	**Closure**	

ABOUT THE SPEAKERS

Dr. Amit Roy

VP, Scientific & Strategic Consulting, PumasAI DE,USA

An engineer by training, Dr. Roy brings more than 25 years of experience in drug development and advanced pharmacometrics. He has extensive experience integrating MIDD into drug development across several therapeutic areas, including cardiovascular diseases, hematology, immunology, oncology, and virology. He has extensive experience in interacting with global regulatory agencies such as US FDA, EMA, PMDA, not only for regular submissions, but also for innovative topics such as Project Optimus.
Dr. Roy served as the Executive Director and Head of Pharmacometrics at Bristol-Myers Squibb (BMS) for 18 years prior to joining PumasAI. He is well published and recognized as one of the world leaders in the field of Pharmacometrics. He obtained BS from University of Michigan, PhD in Chemical and Biochemical Engineering from Rutgers University.

Keynote Speaker

Impact of MIDD in Oncology

Oncology drug development is notoriously challenging — less than 5% of Phase 1 investigational drugs are ultimately approved. Moreover, the dosage regimens of approved drugs are often sub-optimal — hence the FDA Project Optimus.
This talk will discuss some of the major challenges in oncology drug development, and present case studies in which innovative MIDD approaches enabled impactful enhancements of the oncology drug development paradigm.

ABOUT THE SPEAKERS

Dr. Mathangi Gopalakrishnan

Associate Professor, Center for Translational Medicine,
University of Maryland school of Pharmacy
Baltimore,MD, USA

Dr. Mathangi Gopalakrishnan is an Associate Professor at the Center for Translational Medicine, University of Maryland School of Pharmacy. She is a quantitative clinical pharmacologist and biostatistician with over 12 years of experience applying innovative model-informed approaches to advance precision therapeutics in pediatric, maternal, and critically ill populations. Her expertise spans clinical trial design and drug development strategy, including 505(b)(2), generic, and model-informed drug development (MIDD) applications.

Dr. Gopalakrishnan currently leads and collaborates on several drug development programs, including the development of artificial blood products and medical countermeasures, and serves as a co-investigator on multiple grants focused on pharmacokinetic–pharmacodynamic modeling of nutritional supplements and non nutritive sweeteners in pregnant and postpartum women. She has authored more than 65 peer-reviewed publications, is the recipient of the 2018 American College of Clinical Pharmacy Best Teacher Award, and serves as Program Director for the Online MS in Pharmacometrics at the University of Maryland, Baltimore. Dr. Gopalakrishnan earned her BPharm and MPharm from the Birla Institute of Technology and Science (BITS), Pilani, India, and her PhD in Statistics from the University of Maryland, Baltimore County.

ABOUT THE SPEAKERS

A Quantitative Framework to Assess Biomarkers as Surrogate Endpoints: Applications in Drug Development

The use of biomarkers as surrogate endpoints offers significant potential to streamline clinical trials and accelerate drug development, yet rigorous quantitative evaluation is essential to ensure their validity and regulatory acceptability. This presentation will describe the quantitative framework for evaluating biomarkers as surrogate endpoints to support efficient, evidence-based drug development. Key analytical and model-informed methodologies for assessing biomarker–outcome relationships and determining surrogate validity will be outlined. Case studies will illustrate practical applications, highlighting how this framework can inform clinical development strategies, strengthen decision-making, and enhance regulatory confidence in the use of surrogate endpoints.

ABOUT THE SPEAKERS

Prof. Narendra M Dixit

Professor, Department of Chemical Engineering &
Bioengineering, IISc
Bengaluru, Karnataka, India

Narendra Dixit is a professor in the Departments of Chemical Engineering and Bioengineering at IISc. He got his BTech from IIT Bombay, MS and PhD from the University of Illinois at Urbana-Champaign and did postdoctoral studies at the Los Alamos National Lab before joining IISc in 2005, where he has been since. His interests are in computational biology, focusing on infectious diseases and microbiomes. He has been a senior fellow of the DBT Wellcome Trust India Alliance and is a fellow of the Indian Academy of Sciences and the Indian National Academy of Engineering. He serves on the editorial boards of CPT:PSP, PLoS Computational Biology, and mBio.

Modeling How Early Treatment Initiation Improves Post-Treatment Control of HIV Infection

TREATMENT CONTROL OF HIV INFECTION

Antiretroviral therapy (ART) for HIV-1 infection is not curative. Treatment interruption typically results in viral rebound and progressive disease, necessitating lifelong ART. However, a small fraction of people living with HIV under ART, termed post-treatment controllers (PTCs), achieve long-term virus control after treatment interruption. Studies on PTCs are driving efforts to develop novel therapeutics aimed at eliciting such long-term control in the majority who fail to achieve post-treatment control. Both human and primate studies have shown that early ART initiation is associated with a higher chance of post-treatment control, driven by superior CD8 T cell responses. However, the underpinning mechanisms are unclear. We developed a within-host mathematical model for analyzing the influence of ART initiation time on the occurrence of post-treatment control. We hypothesized that upon infection, virus-specific CD8 T cells accumulate 'antigenic experience' through continual exposure to the antigen. Early ART initiation limits this experience, preserving memory CD8 T cells and thereby,

Modeling How Early Treatment Initiation Improves Post-Treatment Control of HIV Infection

enabling better response to rebounding virus post-ART. We fit the model to longitudinal data from a recent macaque study using a nonlinear mixed effects approach. We then performed in silico trials with 10,000 virtual individuals to quantify the population-level variability in PTCs. The model exhibited bistability. One stable steady state had low viral load and high memory cell levels, and the other vice versa, recapitulating the post-treatment control and progressive disease states, respectively. Early treatment initiation made the control state more accessible. Our model provided good fits to the experimental data. Using the virtual population simulations, we predict the window of treatment initiation for maximal post-treatment control. Further, we estimate the memory CD8 T cell pool size and its quality necessary to achieve post-treatment control, setting quantitative targets for interventions.

ABOUT THE SPEAKERS

Dr. Rajkumar Boddu

Team Lead, Biopharmaceutics Group, Global Clinical Management, Dr. Reddy's Laboratories Ltd., Hyderabad, Telangana, India.

Dr. Rajkumar Boddu currently serves as Team Lead in the Biopharmaceutics Department within the Global Clinical Management group at IPDO, Dr. Reddy's Laboratories Limited (DRL), Hyderabad. He is responsible for biopharmaceutics evaluations through model-informed drug development, bioequivalence (BE) risk assessment, and BE predictions for both conventional and complex generic products. Prior to joining DRL, he worked with organizations such as AET Labs, Aizant Research Solutions, and Hetero Drugs. With over 15 years of experience in biopharmaceutics and formulation development, Dr. Boddu is an accomplished pharmaceutical scientist whose core expertise includes Physiologically Based Biopharmaceutics Modeling (PBBM) and Physiologically Based Pharmacokinetic Modeling (PBPK). These advanced modeling approaches are applied to oral solid dosage forms, long-acting injectables, topical formulations, and differentiated 505(b)(2) products. He has extensive experience in regulatory justifications, including biowaivers, dissolution specifications, and gender effect assessments, supported by advanced modeling techniques. Dr. Boddu has authored or co-authored more than 30 peer-reviewed publications and serves as a scientific reviewer for several journals. He is also a sought-after speaker at international conferences, where he has delivered numerous talks on PBPK/PBBM applications in new drug and generic product development.

Harnessing PBBM & PBPK Modeling for Next-Generation Generic Drug Development

The use of physiologically based biopharmaceutics modeling (PBBM) and physiologically based pharmacokinetic modeling (PBPK) has grown significantly in recent years. These simulation-based approaches offer substantial potential to streamline generic drug development by reducing both cost and timelines, and in certain cases, may support clinical study waivers. They are instrumental in defining dissolution safe spaces, justifying dissolution specifications, identifying critical bioavailability attributes, and demonstrating the absence of clinical impact

ABOUT THE SPEAKERS

Harnessing PBBM & PBPK Modeling for Next-Generation Generic Drug Development

when dissolution similarity cannot be achieved. Owing to their wide-ranging applications, PBPK and PBBM are increasingly integrated into generic product development strategies. This presentation provides an overview of the concepts and applications of PBPK and PBBM in the context of generics, along with a review of recent regulatory guidelines. It outlines various modeling approaches, workflows, and methodologies for developing physiological models, as well as techniques for integrating bio-predictive dissolution data with emerging trends. Case studies are presented to illustrate their role in bioequivalence predictions across dosage forms, dissolution specifications justifications and superseding traditional dissolution similarity, and demonstrating the discriminatory power of dissolution methods. Use of modeling tools in the context of recent ICH bioequivalence guidances is also discussed in detail. Collectively, these examples and regulatory insights underscore the significant impact of physiological modeling approaches in accelerating generic drug development and enabling earlier market entry.

ABOUT THE SPEAKERS

Ms. Maitri Sanghavi

Research Scientist, SIMCYP, Certara Hyderabad, Telangana, India

Maitri Sanghavi holds a Master of Science degree in Pharmaceutical Sciences from the National Institute of Pharmaceutical Education and Research (NIPER), Mohali. With more than eleven years of experience in modelling and simulation—spanning platforms such as Simcyp, GastroPlus, and PK-SIM—she has developed strong expertise in biopharmaceutics, mechanistic modelling, and clinical development. She has worked with leading organisations including Dr. Reddy's and Zydus Lifesciences, where her experience strengthened her interest in physiologically based biopharmaceutics modelling. At Certara UK (Simcyp Division), she continues to pursue her passion for advanced mechanistic approaches applied to drug development.

Her expertise includes predictive in vitro assessment, formulation optimisation, bioequivalence evaluations, IVIVC/IVIVR, virtual bioequivalence, and food-effect assessment, along with contributions to PBPK modelling in regulatory submissions. She has published research in this domain and guided multiple PBPK/PBBM applications, supporting improved decision-making across development stages. Her experience also extends to clinical execution of BABE studies, responding to regulatory queries, proposing alternative bioequivalence strategies, biowaiver pathways, animal healthcare product development, and 505(b)(2) projects. She is also invited as a speaker and panellist at international regulatory and scientific conferences, contributing to technical discussions on the advancement of modelling science.

ABOUT THE SPEAKERS

Optimising & Enhancing Drug Development Using Simcyp PBPK Simulator

This session will explore how population-based mechanistic PBPK models as implemented within the Simcyp Simulator can significantly improve drug development and regulatory interactions. Drawing on real-world case studies and practical project experiences, the talk will highlight how physiologically based biopharmaceutic and pharmacokinetic modelling can de-risk development, optimise formulation strategy, guide clinical study design, and support regulatory interactions.

Attendees will gain a good understanding of how mechanistic modelling can be integrated into development workflows to enhance efficiency, reduce costs, and support more predictable outcomes in both generic and innovative drug programmes.

ABOUT THE SPEAKERS

Dr. Sheila Annie Peters

Executive Director, Boehringer Ingelheim
Germany

Dr. Sheila Annie Peters is the Executive Director of Translational Medicine and Clinical Pharmacology, and Early Asset Lead in Oncology at Boehringer Ingelheim, Germany.
Dr. Peters earned her Ph.D. in Chemistry from IIT, Chennai, followed by a post-doctoral fellowship at the Indian Institute of Science, Bengaluru. Her illustrious career spans over two decades of global leadership across major pharmaceutical hubs, including senior roles at Merck Healthcare KGaA and AstraZeneca across India, UK, Sweden, and Germany.

A globally recognized authority in drug development, she has led high-impact teams in Clinical Pharmacology and Translational Medicine across therapeutic areas such as cardiovascular, metabolic, and oncology. Notably, she serves as the Topic Leader for the European Federation of Pharmaceutical Industries and Associations (EFPIA) within the ICH M12 group, driving the international harmonization of drug-drug interaction guidelines.

Dr Peters is a world-renowned expert in PBPK modelling and Model-Informed Drug Development and author of a textbook on PBPK modelling and simulation, published by John Wiley & Sons.

Dr. Peters is also the Recipient of the 2013 AstraZeneca Innovative Medicines Science Award for the “Design and Development of LungSim Simulation tool for Inhalation PK Modelling”.

ABOUT THE SPEAKERS

Hypothesis Generation with PBPK to Identify Mechanisms Limiting Exposure of Orally Administered Drugs

Oral route is the preferred route of drug administration because of its convenience, cost-effectiveness, and non-invasiveness. It allows for flexibility in dosage forms and ensures high patient compliance. PBPK models incorporating drug properties and in-vitro parameters can predict the oral bioavailability of drugs, if the mechanisms limiting the oral exposure of a drug such as poor solubility, delayed gastric emptying, gut metabolism, etc. are known ahead of model development. Model parameterization of these mechanisms is then achieved with bottom-up and/or top-down approaches. However, there are difficulties with both approaches. In the bottom-up approach, conditions in in-vitro assays may not accurately mimic the in-vivo conditions leading to an in-vitro – in-vivo (IVIV) disconnect. Model parameterization by the top-down approach when clinical PK data becomes available is challenged by parameter non-identifiability.

This presentation describes how PBPK models can be used for hypothesis generation to identify mechanisms limiting drug exposure in preclinical species. When the generated hypothesis supporting mechanisms underlying PK profiles are confirmed with clinical PK, the conduct of unnecessary studies can be averted.

ABOUT THE SPEAKERS

Dr. Samarth Thakore

Principal Scientist II, PK Sciences, NIBR, Novartis
Hyderabad, Telangana, India

Samarth D. Thakore, Ph.D., is a Principal Scientist at Biomedical Research, Novartis. His research expertise encompasses solid-state pharmaceutics, biopharmaceutics, and Physiologically Based Pharmacokinetic Modelling. He specializes in applying model-informed drug development strategies to facilitate First-in-Human transitions and support clinical pharmacology studies. He earned his Ph.D. from NIPER, S.A.S. Nagar, and has authored 11 publications in the fields of pharmaceutical crystallization, enabling formulations, and absorption modelling.

Physiologically-Based Pharmacokinetic Modelling: An Integral Component of Model-Informed Drug Development

Physiologically based pharmacokinetic (PBPK) modeling enables quantitative translation from preclinical data to humans, supports first-in-human (FIH) dose selection, informs clinical trial design, and characterizes drug–drug interactions (DDI), food effects, and formulation changes.

Translation of pharmacokinetics (PK) from animals to humans is a major application of PBPK, wherein physicochemical properties and in-vitro as well as preclinical in-vivo data are leveraged to inform the potential fate of a development candidate in humans. Predicted PK informs safety margins and enables dose-escalation design for single- and multiple-ascending dose cohorts in FIH. Internal analyses on low-molecular-weight compounds suggest good PK prediction, with more than 70% of cases within a two-fold error range for area under the curve (AUC) versus observed PK. PBPK modeling follows a “predict–

ABOUT THE SPEAKERS

Physiologically-Based Pharmacokinetic Modelling: An Integral Component of Model-Informed Drug Development

learn–confirm" paradigm, where availability of FIH PK provides an opportunity to refine the model and understand missing information at the time of initial prediction. Understanding mechanistic pathways for potential drug molecules provides insights into drug–drug interactions, supports relative bioavailability assessments, informs inclusion/exclusion criteria, and anticipates PK changes in special populations, including pediatrics and organ impairment. PBPK modelling can also be leveraged to inform drug labels, where major application is around DDI predictions with expansion across clinical pharmacology studies. These examples underscore PBPK as an evolving tool across the pipeline and its growing role as an integral component of model-informed drug discovery and development (MIDD).

ABOUT THE SPEAKERS

Dr. Anant Ketkar, Ph.D.

Principal Scientist and Scientific Lead - India
Simulations Plus, Inc.

Anant Ketkar is working with Simulations Plus, Inc., as a Principal Scientist in the role of 'Scientific Lead – India'. He is involved in the application of PBPK/PBBM modelling and simulation to meet the objectives of various client projects. He also provides scientific input both in terms of software applications and project proposals to Indian distributors to support their marketing and sales efforts.

In partnership with Indian distributors, Electrolab and Molecular Solutions, he supports Simulations Plus's many customers in India and serves as a thought leader to increase awareness and adoption of PBBM/PBPK modelling throughout the country. He delivers modelling and simulation projects to address client objectives and inform regulatory interactions.

Dr. Ketkar earned his doctorate in Pharmaceutical Sciences from Poona College of Pharmacy, Pune, India. He carries around 25 years of experience in formulation research, including around 10 years of experience in PBPK-PBBM modelling for immediate release and extended-release solid orals of NCEs and generic compounds, and subcutaneous extended-release formulations. His expertise covers IVIVR and IVIVC, virtual bioequivalence (VBE), defining clinically relevant drug-product specifications (CRDPS) and helping formulation research scientists in gaining model-based insights for designing the drug-product and bio-predictive in-vitro dissolution methods. Prior to joining Simulations Plus in 2022, Dr. Ketkar was Head of Technical Services at IQGEN-X Pharma, where he led a team of formulation team leaders and scientists for development of solid and liquid orals, and injectables for the global market. Prior to that he worked in positions of increasing seniority with pharmaceutical research companies, including Bioved Pharmaceuticals Inc., Ranbaxy (now Sun Pharma), Pfizer Animal Health (now Zoetis), Sandoz and Sun Pharma Advanced Research Company (SPARC).

He has also served as a PBPK/PBBM modelling consultant for one of the leading Indian multinational pharma companies and worked as a freelance PBPK modeller for Indian generic pharma client on US-FDA submission of a PBPK modelling project.

ABOUT THE SPEAKERS

PHYSIOLOGICALLY BASED IVIVC FOR COMPLEX FORMULATIONS: FOCUS ON LONG-ACTING INJECTABLES

Model-Informed Drug Development (MIDD) has become indispensable in modern pharmaceutical product development. Regulatory agencies worldwide increasingly recognize and encourage the use of advanced modelling tools such as Physiologically Based Pharmacokinetic (PBPK) modelling and simulation and Physiologically Based Biopharmaceutics Modelling (PBBM). These approaches support decision-making in innovative and generic drug product research across the entire drug development spectrum, from early discovery through clinical phases and often play a critical role in regulatory submissions.

For complex drug-products, particularly extended-release formulations, achieving the desired drug-release profile is essential. Having a robust In-Vitro – In-Vivo Correlation (IVIVC) significantly enhances drug-product development efficiency. Physiologically Based IVIVC (PB-IVIVC) offers a mechanistic framework that integrates biopharmaceutical and physiological factors, enabling more accurate predictions and informed formulation design.

This presentation will showcase strategies for establishing IVIVC in complex drug-products, covering both oral and non-oral dosage forms. Special emphasis will be placed on bespoke approaches for developing PB-IVIVC for long-acting injectables, illustrated through a case study.

ABOUT THE SPEAKERS

Prof. Krishna R. Devarakonda

Visiting & Adjunct Professor, Thomas J. Long School of Pharmacy - University of the Pacific Richmond, TX, USA

Prof. Krishna R. Devarakonda serves as an Adjunct Professor, Pharmaceutical Sciences at the University of the Pacific, USA, and is the Founder and Chief Scientific Officer at 6-S Pharma Incorporated. He earned his Ph.D. in Clinical Pharmacology from Kakatiya University, Telangana and completed his Post-Doctoral fellowships at the Dr. Margarete Fischer-Bosch Institute of Clinical Pharmacology, Germany.

Prof. Deverakonda is a distinguished clinical pharmacologist with over 45 years of combined experience in industry and academia. Throughout his career, Prof. Devarakonda has held executive leadership roles, including Vice President of Clinical Development at Mallinckrodt Pharmaceuticals and President of ARCay Scientific, and Professor of Pharmacology at Kakatiya University.
His research focuses on Model-Based Drug Development, precision medicine, and the development of gastro-retentive formulations. He has authored more than 200 publications and book chapters and holds over 10 patents in the pharmaceutical sciences.

Prof. Devarakonda is a Fellow of the American College of Clinical Pharmacology and an Alexander von Humboldt Fellow. He has been honored with numerous prestigious accolades, including the Prof. M.L. Khorana Memorial Award and multiple Innovation Awards for his outstanding contributions to intellectual property and pharmaceutical research.

ABOUT THE SPEAKERS

Dr. Ramalingam Sankaran Commemoration Lecture

From Sheiner to Systems: Evolving Personalized Dosing in the Era of Precision Medicine

Late Dr. Ramalingam Sankaran (1960–2021) was an eminent Clinical Pharmacologist, Bioethicist, academic leader, a friend, and a great human being. He was one of the earliest scientists to contribute to establishing and popularizing the field of Pharmacometrics in India. He was instrumental in building the workforce necessary for pharmacometrics research in India. At PSG Institute of Medical Sciences and Research (PSGIMSR) in Coimbatore, while serving as the Principal and Dean, he had created an environment that fostered quantitative clinical research.

He co-founded PAGIN to promote the application of the population approach (PopPK) for data analysis in Indian clinical research. Demonstrating a continued commitment to the field's growth, Dr. Sankaran oversaw the evolution of PAGIN into a more formal organization: the Society of Pharmacometrics and Health Analytics (SOPHAS). I deem this presentation a fitting tribute to his dedication to the field of Clinical Pharmacology.

Personalized dosing, long envisioned by Lewis Sheiner, is the quantitative engine of precision medicine, uniting dose-exposure–response with adaptive learning to deliver the right regimen for each patient at the right time. Lewis Sheiner's pioneering work established the foundational paradigm that optimal drug dosing must account for individual patient variability. His development of nonlinear mixed-effects modeling (NONMEM) and advocacy for model-based drug development transformed how we approach dose individualization. Today, as precision medicine advances beyond genomics into integrated multi-omic approaches, we must revisit and extend Sheiner's principles to address contemporary challenges in personalized dosing.

His "learn-confirm" paradigm emphasized iterative model building using population data to identify covariates explaining variability, then prospectively validating dosing algorithms. However, traditional population pharmacokinetic

Dr. Ramalingam Sankaran Commemoration Lecture

From Sheiner to Systems: Evolving Personalized Dosing in the Era of Precision Medicine

approaches typically explain only 20-40% of observed variability, leaving substantial unexplained heterogeneity.

New directions in personalized dosing leverage emerging technologies that Sheiner anticipated but could not fully realize: Integration of multi-omic biomarkers, Real-time therapeutic drug monitoring with model-informed precision dosing (MIPD), Pharmacometric platforms for clinical decision support, and Real-world data from the electronic health records.

Sheiner's fundamental insight - that rational, individualized dosing requires quantitative models linking measurable patient characteristics to drug exposure and response - remains central. Modern precision medicine tools provide unprecedented opportunities to realize his vision of truly personalized pharmacotherapy.

ABOUT THE SPEAKERS

Dr. Kannan Thiagarajan

Principal Scientist, Vantage Research
Chennai, Tamil Nadu, India

Kannan Thiagarajan is a physicist turned modeling specialist with a PhD in Electronics from Mid Sweden University, Sweden and has deep expertise in mathematical and computational modeling. His work spans computational fluid dynamics, electron transport physics, and systems pharmacology, where he has developed models that improve prediction, analysis, and translational insights. With nearly a decade at Vantage, he now specializes in clinical pharmacology modeling in oncology, contributing directly to data-driven strategies across drug development portfolios.

Does Progressive Disease Justify Discontinuation: A Simulation Analysis

Background: With checkpoint inhibition becoming first-line therapy in several cancer indications, there is a growing number of patients that are refractory to PD1 therapy. It is unclear if these patients should remain on PD1 inhibitors while new therapies are added on top or if PD1 should be discontinued when new therapies are initiated. Here we simulate a randomized controlled study comparing pembrolizumab + Chemotherapy (P+C) to Chemotherapy (C) and pembrolizumab (P) in virtual patients that are refractory to PD1 therapy.

Methods: An IO QSP model was developed that includes intra-patient heterogeneity in tumor dynamics (target, non-target, and new metastatic lesions). The model was calibrated to individual lesion data from a large multi-centre, open-label phase Ib study (KEYNOTE-001) in patients with metastatic melanoma. A two-year phase III study comparing P+C, C and P was simulated with 312 virtual patients in each group. Virtual patients were removed from the trial at the time of RECISTv1.1 progression or dropout due to AE or loss to follow-up.

Does Progressive Disease Justify Discontinuation: A Simulation Analysis

Results: Virtual patients in the P+C arm displayed deeper (-27.6%) in comparison to C (11.7%) and P (-5.06%) arms The percent of virtual patients exhibiting growth in all of their target lesions was 2.2%, 11.8% and 4.2% for P+C, C and P arms, respectively. One year landmark progression free survival rate was higher in P+C arm (13.2% vs 9.6% and 4.4% in the C and P arms). Major cause of progression among the 3 arms during the refractory period was the appearance of new metastatic lesions.

Conclusions: Simulations presented here show that virtual patients that continued pembrolizumab treatment beyond RECISTv1.1 progression (as part of a combination) exhibited better response in target & non-target lesions compared to virtual patient that discontinue pembrolizumab (and switch to a new therapy).

ABOUT THE SPEAKERS

Dr. Khamir Mehta

Senior Director in Clinical Pharmacology
Modeling & Simulation Department
San Francisco, CA, USA

Dr. Khamir Mehta currently works with Amgen, San Francisco as a Senior Director in Clinical Pharmacology Modeling and Simulation department. He and his team develop statistical and/or mechanistic systems models, and various pharmacometric and data analytic models and methods to support drug development. Prior to joining Amgen, Dr.Mehta spent several years at Merck Research Laboratories as a modeler and data scientist in multiple groups (applied computer science, applied mathematics and quantitative pharmacology and pharmacometrics) and earlier with General Electric. He received his PhD in Chemical Engineering from University of Michigan and his masters degree from Indian Institute of Science.

THE ROLE OF MECHANISTIC MODELS TO COMPLEMENT PHARMACOMETRICS IN MODEL INFORMED DRUG DEVELOPMENT.

The realization of the promise of novel therapies depends critically on our ability to quantitatively understand and control the activation of intended target system components while limiting the adverse effects of undesired responses. Additionally, the need to understand and correlate the patient specific attributes to safety and efficacy remains an unanswered question for these new mechanisms. For example, the balance of tumor lysis and the cytokine storms plausibly due to hyperactive immune response is a critical element limiting the success of bispecific antibodies in treatment of cancers.

Mechanistic systems models that leverage the limited data from the available clinical trials and integrate it with known biological information from diverse sources can be very useful to create successful treatment regimens. Furthermore, combining the mechanistic models with patient specific attributes can

THE ROLE OF MECHANISTIC MODELS TO COMPLEMENT PHARMACOMETRICS IN MODEL INFORMED DRUG DEVELOPMENT.

potentially uncover deeper insights into the mechanism of action of the drug, paving the way to develop successful dosing strategies. On the other hand, pharmacometric modeling provides an efficient and robust platform to project population level predictions on treatment outcomes that can be directly used to evaluate trial success, but are limited as they rely on extensive data for their predictive capability and may not be able to infer mechanistic details.

This talk focuses on the complementary nature of these two approaches by leveraging learnings from various case studies wherein they were used to answer drug development questions. In the first example, we showcase the utility of a mechanistic model that elucidates the complex interplay of tumor growth, target shedding, and drug pharmacokinetics and can be useful to understand the effects of shed target on efficacy and support dose optimization. Next we demonstrate the application of our combined approach to quantify the interaction of pharmacokinetics, dynamics of target inhibition and target turnover and its implications for clinical development of covalent inhibitors.

ABOUT THE SPEAKERS

Dr. Karthick Vishwanathan

Executive Director, Head of CPQP Oncology, AstraZeneca Waltham Site Head
Waltham, MA, USA

Karthick Vishwanathan is currently the interim head of the Clinical pharmacology and pharmacometrics group at AstraZeneca. He joined AZ in 2010 and progressively took on increased responsibilities to currently manage the CPQP groups across therapy areas and modalities.

Prior to joining AZ, Dr. Vishwanathan received his B.Pharm. from Birla Institute of Technology and Sciences in India and his PhD in Pharmaceutical sciences from the University of Georgia (Athens, Georgia), USA in 2001. He has previously worked at Merck Research Labs and Wyeth Research prior to joining AZ. He has worked on multiple drugs across early discovery to regulatory approval across the world that has made significant impact on patients' lives. His interests include developing drugs across modalities in multiple TA and continuously develop novel approaches that increase discovery and development of drugs. Outside of work, he enjoys spending time with his family and loves to travel.

NOVEL MODELING APPROACHES TOWARDS DOSE OPTIMIZATION OF TCES

TCEs are developing into an important modality across multiple therapeutic areas and these agents need novel approaches for starting dose selection and optimization. These agents need to use step up dosing to slowly activate the immune system to achieve higher target doses. In this presentation, we will discuss on the challenges with dose selection for TCEs and some novel approaches (specifically QSP based MIDD approaches) that can be leveraged to select the starting dose, dose escalations that can be optimized to get to the RP2D quickly using one of the compound as a case study.

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THE ABSTRACTS MARKED WITH AN ASTERISK (*) WILL ALSO BE PRESENTED AS PODIUM PRESENTATIONS

ICC001

COMPARISON OF IV GENTAMICIN OD VS BD REGIMEN IN RESPIRATORY TRACT INFECTIONS: A POPPK STUDY IN SOUTH INDIAN PEDIATRIC PATIENTS

Mr.Bhaskar Phanindra Sharma, Mr.Deepan.B, Ms.Priya Tharsini.P, Ms.Ramya.S. Ms.Thusita.S, Dr.Keerthana.C, Dr.K.P.Arun
Department of Pharmacy Practice, JSS College of Pharmacy, JSS Academy of Higher Education and Research, Ooty

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Gentamicin is a narrow-therapeutic-index aminoglycoside that shows marked inter-individual pharmacokinetic variability in pediatric patients, making dose optimization especially important in South Indian children treated for respiratory tract infections. Once-daily (OD) gentamicin dosing has been proposed as a potentially better alternative to conventional twice-daily (BD) regimens due to improved pharmacokinetic and pharmacodynamic (PK–PD) characteristics and a lower risk of toxicity. The present study aimed to compare OD and BD intravenous gentamicin regimens by developing a population pharmacokinetic (popPK) model and performing simulations using clinical data obtained from a previously conducted PK–PD study in South Indian pediatric patients. Peak and trough gentamicin concentrations from nine children aged 2–11 years were used to develop a one-compartment model with first-order elimination, incorporating inter-individual variability in clearance and volume of distribution. Model performance was evaluated using goodness-of-fit plots and prediction-corrected visual predictive checks. Simulated pharmacokinetic profiles were compared with reported gentamicin PK parameters from the literature. Clinical response was assessed using the ReSVinet score, a validated scale for evaluating the severity of respiratory infections in children. The popPK analysis demonstrated substantial variability in clearance (86%) and moderate variability in volume of distribution (25%), reflecting the physiological heterogeneity of the pediatric population. Simulation results showed that the OD regimen produced higher peak concentrations and lower trough levels compared with BD dosing leading to improved PK–PD target attainment and a lower predicted risk of nephrotoxicity while maintaining adequate therapeutic exposure. Although clinical improvement was observed with both dosing regimens based on ReSVinet scores, OD dosing exhibited a more favorable PK–PD profile overall. In conclusion, population pharmacokinetic simulations support once-daily intravenous gentamicin as a safe and effective dosing strategy for South Indian pediatric patients with respiratory tract infections. Further prospective studies with larger sample sizes and richer sampling are warranted to confirm these findings and to better identify sources of pharmacokinetic variability.

ICC002

POPULATION PHARMACOKINETICS OF GEMCITABINE IN SOUTH INDIAN CANCER PATIENTS

Ms Akhila Jose, Dept of Pharmacy Practice, JSS College of Pharmacy, Ooty, Tamil Nadu

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Gemcitabine (dFdC) is an antimetabolite agent used to treat NSCLC and breast cancer. It is first phosphorylated to gemcitabine monophosphate(dFdC-MP), which is rapidly further phosphorylated to gemcitabine diphosphate(dFdC-DP) and gemcitabine triphosphate (dFdC-TP). dFdC-DP inhibits ribonucleotide reductase, which is necessary for DNA synthesis, and dFdC-TP can terminate DNA synthesis by incorporation into the DNA strand. It is then rapidly metabolised by cytidine deaminase into the metabolite 2`2`-difluorodeoxyuridine (dFdU). dFdU is excreted in urine. The metabolite dFdU has been assumed to be non-toxic at concentrations observed in patients; however, at high concentrations, toxic effects can be expected. This prospective open-label study aimed to establish population pharmacokinetic parameters of gemcitabine in South Indian cancer patients. The study was conducted at Bharat Hospital and Institute of Oncology, Mysuru, over one year, with 12 adult patients (6 male, 6 female; mean age 56.83 years, weight 61.39 kg) receiving oncologist-determined IV gemcitabine doses (1000–1600 mg). Blood samples (5 ml) were drawn 0.5 hours post-infusion, plasma separated/stored at −70°C, and concentrations quantified via validated reverse-phase HPLC. All collected data were analysed in NONMEM v7.1 using a two-compartment IV model (ADVAN3 TRANS3), with covariates tested via forward addition/backward deletion (ΔOF thresholds: 3.84/10.8). Twelve patients provided 15 samples; the mean 0.5-hour concentration was 37.541 µg/ml, with 11/15 samples in the assumed 30–45 µg/ml therapeutic window (2 sub-, 2 supratherapeutic), showing a linear dose-concentration relationship (R^2=0.999). NONMEM confirmed the two-compartment model with literature-comparable estimates (central clearance 113.41 L/h, volume 37.92 L, intercompartmental clearance 19.87L, steady-state volume 43.73L), but high interindividual variability (η>20–50%); gender initially affected clearance (ΔOF=4.23, p<0.05), though no covariates were significant in the final base model due to small and sparse sampling. Gemcitabine pharmacokinetics in this population fit a two-compartment model with marked variability similar to global data, advocating individualised over empirical dosing. Limited sampling precluded covariate confirmation; larger studies with rich profiles and cytidine deaminase pharmacogenetics are needed for dose optimisation.

ICC003

EXTERNAL EVALUATION OF POPULATION PHARMACOKINETIC MODELS FOR TACROLIMUS IN INDIAN KIDNEY TRANSPLANT RECIPIENTS: IMPLICATIONS FOR MODEL-INFORMED PRECISION DOSING

Arun Prasath Raju1, Ravindra Prabhu Attur2, Mahadev Rao1, Smita Pattanaik3, Surulivelrajan Mallayasamy1*
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Tacrolimus is a cornerstone immunosuppressant characterized by a narrow therapeutic index and high inter-individual pharmacokinetic (PK) variability, largely driven by CYP3A5 genetic polymorphisms. While Model-Informed Precision Dosing (MIPD) offers advantages over standard therapeutic drug monitoring, its efficacy depends heavily on the predictive performance of the underlying Population Pharmacokinetic (PopPK) model. Despite the distinct genetic landscape of the Indian population where CYP3A5 allele frequencies differ from Caucasian and East Asian cohorts, no PopPK models have been developed specifically for Indian kidney transplant recipients. This study systematically evaluated the predictive performance of published global PopPK models to identify a potential candidate for adaptation for Indian patients. An external validation was conducted using an independent dataset of 120 tacrolimus trough concentrations collected from 60 adult Indian kidney transplant recipients. Four published PopPK models were selected for evaluation: M1 (Woillard et al.), M2 (Andrews et al.), M3 (Benkali et al.), and M4 (Lu et al.). Predictive performance was assessed using Median Absolute Prediction Error (MdAPE) for precision and Median Prediction Error (MdPE) for bias in both a priori (population) and a posteriori (Bayesian) scenario. None of the evaluated models met the standard acceptance criteria for a priori prediction accuracy. M4 (Lu et al.) exhibited a substantial discrepancy between population predictions (MdAPE = 73.46%) and individual Bayesian estimates, suggesting significant model overfitting. Among the remaining candidates, M3 (Benkali et al.) demonstrated the most robust relative performance with the lowest prediction error (MdAPE = 35.46%), compared to M1 (MdAPE = 46.45%) and M2 (MdAPE = 45.02%). While M1 showed potential for Bayesian adaptation, structural diagnostics indicated misspecification when applied to the Indian dataset. Existing global PopPK models show limited generalizability when extrapolated to the Indian population, likely due to regional genetic and demographic heterogeneity. Although the Benkali model (M3) offered the best relative precision, the overall high prediction errors observed across all models highlight that direct clinical deployment is currently inadvisable. These findings emphasize the critical need to develop and validate a dedicated PopPK model for Indian kidney transplant recipients to enable effective precision dosing.

ICC004

EFFECT OF MDR1 GENETIC POLYMORPHISM ON THE PHARMACOKINETICS OF DIGOXIN IN SOUTH INDIAN PATIENTS

Ms Melda Jijo, Ms Maryann Jhon, Ms Aparna S Soman, Ms Manasi S Ahanya,
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Digoxin is a narrow-therapeutic-index cardiac glycoside and classic P-glycoprotein substrate, and interindividual and ethnic variability in MDR1 (ABCB1) expression and function may alter its oral absorption, systemic exposure and safety, potentially supporting a role for pharmacogenetic-guided dosing. This prospective, open-label study, therefore, aimed to evaluate the influence of the MDR1 C3435T polymorphism on steady-state digoxin pharmacokinetics in South Indian patients and explore whether genotyping could aid in dose individualisation. Thirty adults receiving 0.25 mg/day oral digoxin for more than 14 days were enrolled to ensure steady state, demographic and clinical characteristics were recorded, and 58 plasma samples were collected over 24 hours using a window-sampling scheme spanning absorption, peak, distribution and trough phases. Plasma digoxin concentrations were quantified, genomic DNA was isolated by phenol–chloroform extraction, quality-checked by spectrophotometry and agarose gel electrophoresis, and MDR1 C3435T genotyping was performed; pharmacokinetic indices and therapeutic-range status (0.9–2 ng/ml) were compared across genotypes. The cohort had a mean age of 56.78 years, weight 58.67 kg and BMI 23.03, with a mean of 7.11 concomitant medications; mean digoxin concentrations (ng/ml) were 0.67 in absorption, 2.44 at peak, 1.31 in distribution and 1.22 at trough, with greatest variability at peak, and males showed higher peak levels than females (1.79 vs 1.32 ng/ml, $p<0.05$) while trough concentrations were similar. At trough, 53% of patients were within the therapeutic window, 27% were subtherapeutic and 20% supratherapeutic, so 47% lay outside the desired range. Genotyping identified 16 CC (53%), 6 CT (20%) and 8 TT (27%) patients, with C and T allele frequencies of 63% and 37%, respectively; notably, 83% of TT and 17% of CT patients had digoxin levels above 2 ng/ml, whereas no CC patient exceeded this limit, indicating higher steady-state exposure in TT carriers. These findings suggest that the MDR1 C3435T polymorphism significantly contributes to variability in digoxin steady-state concentrations in South Indian patients, with the TT genotype associated with supratherapeutic levels, and that integrating MDR1 genotyping with clinical assessment may improve digoxin dose optimisation and minimise toxicity.

ICC005

ESTABLISHING BIOEQUIVALENCE OF GBL19, A RECOMBINANT ASPARAGINASE BIOSIMILAR, THROUGH POPPK MODELING AND VIRTUAL BIOEQUIVALENCE ANALYSIS

Jaya Shree Dilli Batcha[1], Rohan Gurjar[2], Varsha Bhatia[2], Nikita Ramwani[1], Vijay Ivaturi[1]
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[2]Gennova Biopharmaceuticals Limited, India.

Background: Acute lymphoblastic leukaemia (ALL) is a hematologic malignancy originating from lymphoid precursor cells, affecting both B- and T-cell subtypes. It is the most common childhood cancer, accounting for approximately 30% of pediatric malignancies and 80% of pediatric leukaemia cases. ALL cells rely on asparagine for growth and replication; reducing its blood levels leads to cell death. Asparaginase (ASNase), an enzyme that depletes L-asparagine by converting it to aspartic acid and ammonia, is a key component of multi-agent chemotherapy for pediatric ALL. Unlike cancer cells, normal cells can synthesize asparagine and are less affected by ASNase.
Spectrila® (medac, Germany) is the first recombinant E. coli-derived asparaginase approved by the European Medicines Agency (EMA) in 2016 for pediatric ALL. The standard dose for children aged 1–18 years is 5000 IU/m^2 every three days. However, Spectrila® is not readily available in certain regions, and its high cost limits clinical trial feasibility. To address these challenges, GBL19—a recombinant asparaginase biosimilar developed by Gennova Pharmaceuticals Limited—has been proposed as a cost-effective, locally marketable alternative. This study aimed to demonstrate the non-inferiority of GBL19 compared to Spectrila® using population pharmacokinetic (PopPK) and virtual bioequivalence analysis.

Methodology: A bioequivalence study was conducted in healthy adults with Spectrila® and GBL19. Data from this study was used to develop a PopPK model, which was scaled to pediatric patients for simulation. Demographic covariates (weight, body surface area, gender) were derived from CDC growth charts. Virtual bioequivalence was performed by simulating 40 pediatric subjects per treatment arm with 500 replicates using PopPK results. Non-inferiority was evaluated using nadir serum asparaginase activity (NSAA) ≥0.1 IU/mL at 72 hours post-dose, with error margins of 5% and 10%.

Results: A one-compartment model with zero-order absorption, incorporating weight and gender as covariates on clearance and volume, adequately described the clinical data. Simulated pediatric PK parameters (Cmax, Ctrough, Tmax) for GBL19 aligned with published Spectrila® data.

ICC005

ESTABLISHING BIOEQUIVALENCE OF GBL19, A RECOMBINANT ASPARAGINASE BIOSIMILAR, THROUGH POPPK MODELING AND VIRTUAL BIOEQUIVALENCE ANALYSIS

Jaya Shree Dilli Batcha[1], Rohan Gurjar[2], Varsha Bhatia[2], Nikita Ramwani[1], Vijay Ivaturi[1]
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Virtual bioequivalence analysis showed a 92% probability of GBL19 meeting bioequivalence criteria in pediatrics, while maintaining Type I error control at the observed T/R ratio. Non-inferiority analysis demonstrated ≥80% power even with small sample sizes.

Conclusion: Evidence from bioequivalence analysis, PopPK modelling, simulation, and non-inferiority analysis supports that GBL19 is bioequivalent to Spectrila® in paediatric patients.

ICC006

A REASSESSMENT OF TYPE I ERROR RATES IN STATISTICAL SUB-MODELS USING LR TEST IN PUMAS

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Introduction: Aligned with the objectives established in [1], this study aims to assess Type I error rates for the statistical sub-model via the log-likelihood ratio (LR) test. Here, we execute the framework using Pumas to determine the robustness of the original estimates and highlight any differences resulting from the advancement in computational algorithms.

Methods: Data were simulated from a one-compartment intravenous bolus pharmacokinetic model. Two models were fit to each dataset, the data generating model, and a model including an additional parameter. The difference in log likelihood between the two models was used to evaluate the type I error rate of the LR test. The additional parameter were tested on different variability terms as follows:

- Covariate effect on the interindividual variability of clearance (CL) or volume (V),
- Covariate effect on the residual error variability,
- False covariance term between CL and V,
- False variability in V.

Simulation conditions were systematically varied to explore their impact on type I error rates. Factors included number of individuals, number of samples per individual, magnitude of interindividual and residual variability, and the residual error distribution. Both the first-order (FO) and first-order conditional estimation (FOCE) methods in Pumas (v 2.7) were employed for model fitting.

Results: When using FOCE approximation method, the estimated type I error rates for inclusion of covariate effects on (i) interindividual variability and (ii) residual variability were consistent with expected nominal levels, provided that model approximations were valid. In contrast, the FO method generally resulted in higher type I error rates across most tested scenarios, regardless of residual distribution or data informativeness.

Conclusion: The study demonstrates that the choice of estimation method significantly affects type I error rates in likelihood ratio tests for pharmacometric models. FOCE maintained error rates close to nominal levels when model approximations were valid, whereas FO consistently produced inflated error rates across scenarios. These results align with previous findings using NONMEM and highlight the importance of selecting robust estimation methods to ensure reliable hypothesis testing in pharmacometric modeling. FO is rarely used in NLME modeling nowadays, but this work sets up the methodology to evaluate other algorithms in Pumas.

ICC007

MODEL INFORMED DOSAGE OPTIMIZATION OF CLOZAPINE - A RETROSPECTIVE PHARMACOMETRICS STUDY

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Treatment-resistant schizophrenia (TRS) refers to a condition where the patient experiences persistent positive symptoms despite ≥2 trials of antipsychotics, of which at least one of them must be an atypical antipsychotic given at adequate doses for an appropriate duration of time with adherence of 100%. Clozapine is an atypical antipsychotic drug which is approved for TRS. Despite the fact that it is the only drug that has been approved for TRS it is underutilized due to its dose dependent adverse drug reactions. This study aims to individualize the dosage of clozapine using PopPK analysis. The concentration v/s the dose plot (C/D ratio) was extracted from the literature using Delineate.pro. The dataset was constructed that includes variables such as patient's demographics, dose, gender and sampling time. First the base model was built and parameterized by apparent clearance (CL/F), apparent volume of distribution (Vd/F) of the central compartment and first-order absorption rate constant (ka). Further, covariates (i.e., gender and smoking status) were added to develop the final model. The PopPK analysis was done using PUMAS.ai. The study proved that the clearance of clozapine varies between individuals and it was found that gender and smoking have an influence on the clearance of clozapine that shows inter-individual variability. The clearance of base model was 0.776 and the clearance of final model was reduced to 0.314 which shows that smoking and gender has influence on the clearance of clozapine. This study has demonstrated that the serum clozapine concentration was influenced by smoking and gender. It has been found that the clearance of clozapine for smokers and male is higher when compared to non-smokers and female patients. The findings help in tailoring the dose based on patient-specific characteristics.

ICC008

A BAYESIAN POPULATION PHARMACOKINETIC ANALYSIS OF ORITAVANCIN IN PEDIATRIC SKIN INFECTION PATIENTS

Architha Aithal[1], Michael Tagen[1], Ting Chen[2], Stephen Duprez[2], Doug Girgenti[2], Clayton Litchmore[2], Michael Serenko[2], Joy Whitsett[2], Daniel Selig[2] [1]PumasAI, [2]CorMedix Therapeutics

Objectives: Oritavancin is a glycopeptide antibiotic approved in adults for the treatment of acute bacterial skin and skin structure infections (ABSSSI) with a dose of 1200 mg IV. Sparse pharmacokinetic (PK) data are available from two ongoing pediatric studies with age groups of 0 to <3 months, 3 months to <2 years, 2 to < 6 years, 6 to < 12 years, and 12 to < 18 years. Tested pediatric dosages included 15 and 20 mg/kg IV. The objective of this analysis was to characterize the pediatric PK of oritavancin with a population PK (popPK) model and perform stochastic simulations to support pediatric dose selection.

Methods: Sparse PK data from pediatric patients (N=85, including 3 neonatal patients aged < 3 months) were combined with sparse PK data from two pivotal Ph3 studies of adult ABSSSI patients (N=297). A three-compartment model with linear elimination was fit to the combined dataset using the Markov Chain Monte Carlo (MCMC) algorithm in Pumas software. Parameter estimates from a previous popPK model [1] were used as Bayesian priors. This model was developed with data from Ph1, Ph2 and earlier Ph3 studies (N=560 subjects) with mostly dense PK sampling. After fitting the base model, weight was assessed as a covariate on clearance and volume parameters. Stochastic simulations were performed using a virtual population (N=1000 per sex and year of age) created by sampling from CDC growth chart weight distributions. Probability of target attainment (PTA) was assessed against Staphylococcus aureus using previously established AUC(0-72)/minimum inhibitory concentration (MIC) ratio targets.

Results: The base model using Bayesian priors was successfully fit to the combined adult and pediatric dataset. All MCMC diagnostics showed adequate convergence of the chains. Mean post-hoc parameter estimates showed a strong trend with body weight and age. The allometric effect of body weight was estimated on clearance and volumes of distribution, with intercompartmental clearance exponents fixed to 0.75. The estimated allometric exponents were close to the typical exponents (0.75 for clearance and 1 for volumes of distribution). The final model showed no further trend of mean post-hoc estimates with body weight or age. It adequately described the PK of each age group as demonstrated by an age-stratified visual predictive check (VPC). Stochastic simulations of 15 mg/kg, the maximum tolerated dose in pediatrics, predicted that neonates have a geometric mean AUC(0-72) 0.65-fold of adults. Geometric mean Cmax and AUC(72-168), which may also be associated with efficacy, were 0.49-fold and 0.54-fold of adult values, respectively.

ICC008

A BAYESIAN POPULATION PHARMACOKINETIC ANALYSIS OF ORITAVANCIN IN PEDIATRIC SKIN INFECTION PATIENTS

Architha Aithal[1], Michael Tagen[1], Ting Chen[2], Stephen Duprez[2], Doug Girgenti[2], Clayton Litchmore[2], Michael Serenko[2], Joy Whitsett[2], Daniel Selig[2] [1]PumasAI, [2]CorMedix Therapeutics

PTA analysis of exposures in neonates following a 15 mg/kg dose showed a reduced probability of efficacy against Staphylococcus aureus at an MIC of 0.25 ug/mL.

Conclusions: The PK of oritavancin in pediatric and adult patients with ABSSSI was adequately described by a Bayesian three-compartment model. No trend of age with clearance was identified after controlling for the effect of body weight. Simulated exposures in neonates < 3 months of age were potentially sub-therapeutic at the maximum tolerated dose of 15 mg/kg.

ICC009

THE EFFECT OF CYP2C19 GENETIC POLYMORHISM ON THE METABOLISM OF AMITRIPTYLINE IN SOUTH INDIAN PATIENTS

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Amitriptyline has been the cornerstone of antidepressive therapy, especially in developing countries along with various other indications like migraine, neuropathic pain and post herpetic neuralgia. Amitriptyline is a narrow therapeutic index drug that produces considerable toxicity at increased concentrations. Genetic polymorphism of CYP2C19 and its effect on the metabolism of Amitriptyline was proven by researchers in populations like Japanese and Chinese. But the genetic polymorphism of CYP2C19 and its effect on the pharmacokinetics of Amitriptyline has not been studied in Indian population, especially in South Indian population. Therefore, this study aims to investigate the effect of CYP2C19 genetic polymorphism on the pharmacokinetics of Amitriptyline in South Indian population that has 31-35% of CYP2C19*2 mutation. A prospective open-label study was undertaken at the Government Head Quarters Hospital, Ooty, with 15 patients maintained on a fixed 25 mg nocturnal dose of amitriptyline for a minimum of two weeks to reach steady state. Blood samples collected 12 hours post-dose were subjected to simultaneous pharmacokinetic and pharmacogenetic analysis. Plasma drug estimation was performed using a developed and validated High-Performance Liquid Chromatography (HPLC) method, while genomic DNA was isolated from whole blood via the phenol-chloroform extraction technique. The CYP2C19*2 mutation was subsequently identified using PCR-RFLP analysis. The study revealed high inter-individual variability in drug handling, with a population mean plasma concentration of 39.86 ± 18.03 ng/ml. Genotyping identified one patient carrying the homozygous CYP2C19*2 defect. It is significant that this individual exhibited a plasma concentration of 73.6 ng/ml, the highest recorded in the cohort, compared to the wild-type range of 12.2 to 59.8 ng/ml, however the patient did not show any adverse drug reaction as the therapeutic dose of the drug is far higher (up to 150 mg/day) than prescribed to this patient. The findings emphasize that the significance of CYP2C19 polymorphism in assessing Amitriptyline clinical outcome should be further studied with large number of patients and dosage optimization should be done based on the genetic status of the patients.

ICC010

POPULATION PHARMACOKINETICS OF RIFAMPICIN IN TUBERCULOSIS PATIENTS WITH CKD

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Background and objectives: Tuberculosis remains a major global health concern. Rifampicin is a first line anti-tubercular agent, which shows considerable pharmacokinetic (PK) variability. The aim of this study was to develop a population pharmacokinetic (PopPK) model for rifampicin and recommend right doses to achieve right probability of target attainment (PTA).

Method: Data were obtained from the Department of Nephrology, Kasturba Hospital, Manipal, cleaned, and formatted for PopPK analysis, and subsequently analysed using nonlinear mixed-effects modelling in Pumas (version 2.6). Estimation was performed using the first-order conditional estimation(FOCE) method. A base model was developed and identified. The effect of covariates including creatinine clearance, diabetes mellitus, gender and body weight were evaluated on PK parameters. Model was chosen based on evaluation metrics. Model-based simulations were performed to assess AUC/MIC-based exposure targets and corresponding PTA across clinically significant covariates.

Results: In total, 385 observations from 170 subjects were included, of whom 61 had CKD. A one-compartment model with first-order absorption and an absorption lag time best described the data. The estimated PK parameters were 11.663 L/h, 7.847 L, 0.257 h^{-1} and their RSE% was found to be 11.45%, 25.29%, 4.28% for apparent clearance, apparent volume of distribution and absorption rate constant. Creatinine clearance on apparent clearance, diabetes mellitus and body weight on apparent volume of distribution were identified as significant covariates. Simulation-based dose optimisation to achieve a PTA ≥90% for AUC/MIC ≥271 decreased progressively with worsening renal function, while body weight exerted a modest secondary influence. Recommended doses ranged from 1000–1050 mg in patients with normal renal function, 900–950 mg in mild renal impairment, 800–850 mg in moderate impairment, 700 mg in severe impairment, and 550 mg in renal failure.

Conclusion: A Population pharmacokinetic model for rifampicin was developed and identified creatinine clearance on apparent clearance, diabetes mellitus and body weight on apparent volume of distribution as the significant covariates. Model-based simulations incorporating AUC/MIC-based targets and PTA enabled individualized rifampicin dose recommendations, supporting renal function–guided precision dosing to optimize therapeutic exposure.

ICC011

INFLUENCE OF CYP2C19 GENETIC POLYMORPHISM ON THE PHARMACOKINETICS OF IMIPRAMINE IN SOUTH INDIAN PATIENTS

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Imipramine, a well-established tricyclic antidepressant (TCA), remains a cornerstone in clinical practice, effectively managing conditions from major depression to chronic pain syndromes like post-herpetic neuralgia and migraine. Therapeutic use of the same is frequently complicated by significant inter-individual variability. Given Imipramine's narrow therapeutic window, this metabolic variability is a major concern: ultra-rapid metabolism increases the risk of sub-optimal response and treatment failure due to sub-therapeutic plasma concentrations. This risk is highly relevant in the Tamilian population where the prevalence is reported as 19.2%. This inconsistent metabolism is strongly tied to genetic polymorphisms in the Cytochrome P450 2C19 (CYP2C19) enzyme, a key factor in Imipramine's biotransformation. The same was proven by researchers in populations like Caucasian and East Asians. The objective of this investigation was to pharmacogenetically characterize this risk by assessing the prevalence of the CYP2C19*17 ultra-rapid metabolizer (UM) allele and its impact on Imipramine plasma concentration in a South Indian patient cohort, where such data was critically absent. A prospective, open-label clinical study was executed involving 20 patients stabilized on a consistent 25 mg daily dose of Imipramine. The research utilized two simultaneous analytical approaches: a validated RP-HPLC-UV method to quantify Imipramine in plasma at steady state, and the standard PCR-RFLP technique for CYP2C19*17 genotyping. Significant inter-individual variability was confirmed by drug analysis in metabolism across the cohort, with a mean plasma concentration: 227.74 131.9 ng/ml Crucially, the genotyping analysis yielded a complete absence of the CYP2C19*17 allele in the cohort, thereby precluding the intended genotype-to-phenotype correlation for this variant. This result contrasts with external reports indicating a significant CYP2C19*17 frequency in other regional populations, suggesting that limitations in our sample size or the specific ethnic composition of our cohort might have influenced the outcome. The findings strongly emphasize the critical need for personalized care, integrating CYP2C19 genotyping, allowing Imipramine regimens to be carefully calibrated to each individual's genetic profile. To fully realize this therapeutic goal, the clinical significance of CYP2C19 polymorphism must be further validated through larger-scale patient studies, enabling comprehensive dosage optimization guided by sophisticated simulation methods, such as PopPK modelling.

ICC012

POPULATION PHARMACOKINETICS OF PYRAZINAMIDE IN CHRONIC KIDNEY DISEASE AND NON-CHRONIC KIDNEY DISEASE PATIENTS.

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Background: Pyrazinamide is a key component of first-line tuberculosis therapy and demonstrates substantial interindividual pharmacokinetic variability, particularly in patients with renal failures. In the absence of well-defined dose adjustment recommendations, model-informed drug development approaches are essential to characterize variability and support rational dosing.

Objectives: To develop a population pharmacokinetic model for orally administered pyrazinamide in patients with and without chronic kidney disease.

Methodology : Pharmacokinetic data from 162 tuberculosis patients with normal renal function and chronic kidney disease were analysed using nonlinear mixed-effects modelling in Pumas (Julia), with data processing and exploratory analysis performed in R. Structural model development included evaluation of one-compartment and two compartment oral models with first-order absorption using FOCE method. Interindividual variability was described using exponential random-effects models, and residual unexplained variability using combined proportional and additive error models. Covariates effects of body weight, age, gender, creatinine and comorbidities such as chronic kidney disease, hypertension, and diabetes mellitus on pharmacokinetic parameters were systematically assessed.

Results: Both one-compartment and two-compartment structural models were evaluated as part of base model development. The one-compartment model demonstrated a superior fit to the observed data and was selected as the structural model. Covariate effects of age, body weight, gender, chronic kidney disease, hypertension, diabetes mellitus, and serum creatinine on pharmacokinetic parameters should be assessed. Further covariate refinement and development of the final population pharmacokinetic model will be completed, and the results will be presented at the conference.

Conclusion: This work establishes a robust PopPK model for pyrazinamide, forming the foundation for model-informed dose optimization in patients with renal impairment. The final model is expected to support safer and more effective use of pyrazinamide in clinical practice.

ICC013

QUANTITATIVE EVALUATION OF DOSE- RESPONSE RELATIONSHIPS IN ANTI-HYPERTENSIVE THERAPY

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Quantitative assessment of dose–response relationship is essential in antihypertensive therapy, where the goal is to achieve optimal blood pressure control while minimizing adverse events. Classical pharmacodynamic and clinical trial analyses have provided fundamental insights, yet variability in patient response—driven by comorbidities, demographics and concomitant medications, continues to challenge standardized dosing strategies. In this work, we explore and critically evaluate quantitative approaches used to characterize dose–response dynamics across major antihypertensive drug classes, including ACE inhibitors, calcium channel blockers, beta-blockers and diuretics. By integrating findings from published studies with principles of pharmacometric modeling, the discussion highlights how data-driven methods can improve prediction accuracy, capture inter-individual variability and inform rational dose selection. This dual perspective underscores the value of combining evidence synthesis with model-informed strategies to advance precision therapy by optimizing clinical outcomes and support regulatory decision-making in the management of hypertension.

ICC014

PREDICTIVE PERFORMANCE OF POPULATION PHARMACOKINETIC MODELS FOR SUNITINIB MALATE IN METASTATIC RENAL CELL CARCINOMA PATIENTS IN INDIAN POPULATION

Aims: Sunitinib malate is the standard first-line treatment for metastatic renal cell carcinoma (mRCC) in several low- and middle-income countries where immunotherapies are ill-afforded and continues to be the standard of care. High inter-individual variability in pharmacokinetics coupled with concentration-effect relationship make sunitinib an ideal candidate for therapeutic drug monitoring. The population pharmacokinetic modeling approach can aid in designing optimal dosage regimens for sunitinib in cancer patients. In this study, we attempt to identify the suitable population pharmacokinetic model for sunitinib from the published reports for the study population from an Indian setting.

Methods: Published population pharmacokinetic studies for sunitinib in adult and/ or paediatric population were identified. Data on structural models and typical pharmacokinetic parameters were extracted from the studies. For the clinical study, patients who met the inclusion criteria were enrolled at Tata Memorial Centre. Drug concentrations were estimated, and demographic and clinical data were collected. Several published population pharmacokinetic models are being replicated and will be identified. The population pharmacokinetic model, which would be able to predict the data well, will be considered a suitable model for the study population. Predicted concentrations will be compared against the observed concentrations. Furthermore, dosing regimens will be suggested for mRCC patients using the pharmacometrics simulation approach generated by the selected model.

Results: A total of 112 Ctrough plasma samples were collected from 112 patients. Fourteen population pharmacokinetic models were found for sunitinib in cancer patients. Model replication was performed for Chae et al (2016), Houk et al (2010) and Khosravan et al. (2016). Model replication for the other published models is in process. The population pharmacokinetic model which would be able to predict the data well, will be considered a suitable model for the study population.

Conclusions: So far, the population pharmacokinetic model reported by Chae et al. could be replicated well as compared to other evaluated models. Model replication is ongoing and eventually the model which would best predict the observed data will be selected. Finally, the goal is to develop nomogram for sunitinib in mRCC patients with the identified covariates in Indian population. A developed nomogram will assist the clinicians to design an optimal dosage regimen of sunitinib in mRCC patients.

ICC015

IDENTIFICATION AND EVALUATION OF GENERALIZABLE POPULATION PHARMACOKINETICS MODEL OF 5-FLUOROURACIL IN ONCOLOGY PATIENTS

Teshini[1], Surulivelrajan[2], Vijay Ivaturi[3], Renuka Munshi[4], Vikram Gota[5]

Background: 5-Fluorouracil (5-FU) is a traditional chemotherapeutic agent used in the treatment of multiple cancers. The high inter- and intra-patient variability reported necessitated the need of generalizable population pharmacokinetic (PopPK) for individualized dosing. The objective of this study is to develop a generalizable PopPK model for 5-FU in oncology patients.

Methodology: Seven studies of Population pharmacokinetics of 5-FU has been identified after systematic search. Three studies (Malothu et.al., Oltra et.al., Batey et.al.,) were replicated using Pumas 2.7.0. The cross validation will be carried wherein each model will be considered as a reference model. Pharmacokinetic simulations will be performed using one reference model and the typical patient and dose from the other reported studies. The simulated trough concentration will be compared against the reported trough concentrations of each study using RMPE% and rRMSE.

Results: Replication of three studies were completed. Two studies (Malothu et.al., and Batey et.al.,) has reported one compartment with first order elimination with age as a significant covariate (Batey et.al.,) and one study has reported two compartment with first order elimination with covariate free final model. Cross-validation is yet to be performed to find out the generalizable model using the prediction metrics for assessing the bias and precision of PopPK models.

Conclusion: The PopPK models are replicated and will be cross validated for the identification of Generalizable PopPK model.

ICC016

A RE-ASSESSMENT OF ACTUAL SIGNIFICANCE LEVELS FOR COVARIATE EFFECTS USING PUMAS

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Background: We aim to evaluate the actual significance levels associated with the likelihood ratio test for covariate effects, replicating the core scientific inquiry reported by Wahlby et.al.,(1) . By conducting this assessment in Pumas, we seek to determine if the originally reported discrepancies between nominal and actual levels are reproducible within this modern computational environment.

Methods: Three structural models were simulated: one compartment intravenous bolus, one compartment first order input, and linear regression. Model estimation was performed using three likelihood-based methods: First order (FO), First-Order Conditional Estimation (FOCE), and Laplace with Interaction (Laplace-I). A default model with one-compartment iv bolus model, simulated with 1000 and 10,000 independent datasets and estimated with FO were generated under the null hypothesis (no true covariate effect). The impact of covariate distribution (categorical, continuous), on the default model was studied on LRT and their corresponding significance levels. The residual error magnitude was studied on multiple subjects (10, 25, 50, 250, 1000) with different sampling frequency (2, 4, 19 observations) using FO, FOCE estimation methods. Likelihood ratio tests were applied to compare models with and without a covariate effect, and the empirical type I error rate (actual significance level) was calculated by the proportion of false-positive rejections at the nominal 5% and 1% level.

Results: Across all three models and both dataset sizes (1,000 and 10,000 simulations), the actual significance level closely matched the nominal level of 0.01. However, deviations were observed at the 5% nominal level. Laplace-I consistently yielded more accurate likelihood approximations, resulting in actual significance levels that remained closer to nominal values. In contrast, the FO method exhibited inflated type I error rates across all tested scenarios, regardless of model type. No major difference is seen between covariate distributions, regardless of whether continuous (normally or uniformly distributed) or categorical (dichotomous or trichotomous) covariates were used in the model. From 50 up to 1000 individuals, the significance levels are rather constant within each sampling strategy. The FOCE method performs consistently better than the FO method. It was observed that the frequency of samples largely affects the actual significance levels when estimated with FO creating inflated significance levels.

ICC016

A RE-ASSESSMENT OF ACTUAL SIGNIFICANCE LEVELS FOR COVARIATE EFFECTS USING PUMAS

Teshini Suthahar[1], Tejashree Pasumarthi[1], Jayashree D[2], Surulivelrajan[3], Vijay Ivaturi[*]

Conclusion: For a stepwise model building, the present results point to the use of the likelihood ratio test with nominal significance levels as the sole selection criterion for inclusion of covariate relationships is associated with a high risk of false covariate relationships when the FO method is used. These results obtained using Pumas closely matched to the reported NONMEM results.

ICC017

PREDICTIVE PERFORMANCE OF POPULATION PHARMACOKINETIC MODELS OF ISONIAZID IN TUBERCULOSIS POPULATION.

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Background: Isoniazid (INH) remains a cornerstone of tuberculosis treatment, yet its pharmacokinetics exhibit substantial interindividual variability driven by demographic, physiological, and metabolic factors. Robust evaluation of predictive performance is essential to ensure the reliability of population pharmacokinetic (PopPK) models for dose optimization and clinical decision-making. The objective of this study was to evaluate the predictive performance of population pharmacokinetic models for isoniazid in tuberculosis patients.

Methods: Previously developed PopPK models for INH in tuberculosis patients were collected from the literature. Demographic details, final parameter estimates and covariate information was extracted. The models were replicated and evaluated using an external dataset in Pumas Software (version 2.7.0). Various prediction-based metrics like Relative mean prediction error percentage [rMPE (%)], relative median absolute prediction error percentage [rMAPE (%)] and relative root mean squared error (rRMSE) were used for assessing the bias and precision of PopPK models using individual predictions.

Results: Three PopPK models were replicated, where NAT2 genotype had significant effect on clearance. All the three models couldn't perform well, as we removed the effect of NAT2 genotype in the models. Among the 3 PopPK models, the one reported by Gracia et. al, had better performance.

Conclusion: Since there was insufficient data available on NAT2 genotype in the external dataset, none of the models could perform better. We could propose to develop a model with this external dataset with relevant covariate information for predicting the parameter values.

ICC018

GENERALIZABLE POPULATION PHARMACOKINETIC MODEL FOR VANCOMYCIN IN CRITICALLY ILL PATIENTS

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Background: Vancomycin is a critical therapeutic agent for managing severe Gram-positive infections in critically ill patients; however, substantial pharmacokinetic variability continues to challenge optimal dosing. A population pharmacokinetic (PopPK) model that is generalizable across diverse patient groups is essential to support individualized therapy and improve clinical outcomes. The aim of this study was to identify a generalizable PopPK model for vancomycin in critically ill patients.

Methodology: A systematic literature review was conducted using PubMed and Web of Science to identify recently published vancomycin PopPK models. Models that met predefined inclusion criteria as broad population range and aligned with the 2020 IDSA (Infectious Diseases Society of America) recommendations prioritizing CrCl (Creatinine clearance) and body weight–based dosing, focusing on achieving a target vancomycin exposure based on AUC (Area Under Curve)-guided dosing rather than trough concentration-based dosing were replicated. The models are Alqahtani et al, Bae et al,Goti et al, Robert et al are taken and replicated using the PUMAS 2.7 package in Julia 1.11.5. For each study, a typical subject was created using mean or median demographics and corresponding dosing regimens. Simulated trough concentrations or AUC values were compared with reported values to assess replication accuracy. A cross-validation framework was then implemented, where each model served sequentially as a reference and was evaluated against the typical patient and dosing characteristics of the remaining studies. The model demonstrating the closest predictive agreement (RMSE < 20%) across most studies was identified as the candidate generalizable model. The selected model will undergo external evaluation using prospective clinical data. Model predictions will be compared with observed concentrations and integrated into a clinical decision support system for vancomycin dosing.

Results: Models were replicated and cross-validation is being carried out. Algatani et al's model is being taken for cross validation step. Other models will be taken for this step.

Conclusion: Full cross-validation will identify the most generalizable model, which will then be externally evaluated and taken for clinical implementation.

ICC019

POPULATION PHARMACOKINETIC ANALYSIS OF RIFAMPICIN IN SOUTH INDIAN PULMONARY TUBERCULOSIS PATIENTS

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Rifampicin, the primary medication for tuberculosis treatment, exhibits notable variations in pharmacokinetic profiles across diverse populations. Physicians typically determine dosing schedules empirically based on their clinical experience, adjusting them according to individual patient response. Utilizing population pharmacokinetic analysis offers a distinct method for crafting drug dosage regimens specific to particular ethnic groups and customizing treatment plans for individual patients. The purpose of the study is to investigate the population pharmacokinetics of Rifampicin in pulmonary tuberculosis patients in South India. The objective of the study is to assess the population pharmacokinetics to identify potential variables influencing the variation of rifampicin, a major antitubercular medication, at steady-state. A prospective open-label study was carried out at various DOTS centres in Nilgiris District. Thirty-five patients were enrolled, and blood samples were collected from different window time-blocks. High-performance liquid chromatography (HPLC) was utilized to analyse the plasma drug concentrations, and population pharmacokinetics study was performed. The findings indicate that Rifampicin clearance in these study patients was notably lower compared to values reported in the literature. In this population, patient's body weight should be considered a covariate for calculating individual clearance. Additionally, the volume of distribution was observed to be lower than in various other populations, with no covariate influencing Rifampicin's volume of distribution in these study patients. Although, the data was collected from a limited number of patients, it clearly demonstrated a trend in Rifampicin's pharmacokinetic behaviour in this population. The research study should be expanded to include a significant number of people from the same ethnic and/or cultural group to generate dosage guidelines for Rifampicin tailored specifically to this population.

ICC020

SWITCHING PATIENTS WITH SCHIZOPHRENIA FROM RBP-7000, A SUBCUTANEOUS ONCE MONTHLY RISPERIDONE, TO TV-46000, A LONG-ACTING SUBCUTANEOUS ANTIPSYCHOTIC: POPULATION PHARMACOKINETIC-BASED STRATEGIES

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Background: Differences in pharmacokinetic properties between various risperidone long-acting injectable antipsychotics (LAIs), combined with a lack of clinical studies on transitioning patients between them, contribute to uncertainty during switching. RBP-7000 is a subcutaneous (sc) LAI formulation of risperidone administered in the abdomen once monthly (q1m; Perseris®). TV-46000 is a sc LAI formulation of risperidone administered in the upper arm or abdomen q1m or once every 2 months (q2m). There is a lack of data on how switching strategies impact total active moiety (TAM) plasma levels. Therefore, the objective of this study was to use population pharmacokinetics (PopPK)–based models to characterize dosing conversions and switching strategies from RBP-7000 to TV-46000.

Methods: TAM (risperidone + 9-OH risperidone) concentration-time profiles were simulated based on published PopPK models for RBP-7000 [1] and TV-46000 [2] with virtual populations of 5000 patients. Covariates included in the models were randomly sampled from within the demographic ranges of the RBP-7000 phase 1 and TV-46000 phase 1 and phase 3 clinical trials. Simulations were performed to predict PK exposures for TAM when switching to TV-46000 q1m and q2m 4, 5, and 6 weeks after the last injection of RBP-7000 at steady state. PK exposure measures (maximal [C_{max}], minimal [C_{min}], and average [C_{avg}] plasma concentrations) were compared between TV-46000 and RBP-7000 at first dose and steady-state. PK parameters were computed using noncompartmental methods and Pumas (v2.4.1) was used to conduct simulations on switching strategies.

Results: The most comparable doses of oral risperidone, TV-46000, and RBP-7000 were identified (Table 1). Switching to TV-46000 4 weeks after the last RBP-7000 injection was estimated to provide the most comparable values of C_{max}, C_{min} and C_{avg} over other evaluated time points. Initiating TV-46000 q1m 4 weeks after the last dose of RBP-7000 resulted in slightly higher, but generally comparable C_{max}, C_{min} and C_{avg} plasma concentration values at first dose and steady-state for TV-46000 compared to RBP-7000.

ICC020

SWITCHING PATIENTS WITH SCHIZOPHRENIA FROM RBP-7000, A SUBCUTANEOUS ONCE MONTHLY RISPERIDONE, TO TV-46000, A LONG-ACTING SUBCUTANEOUS ANTIPSYCHOTIC: POPULATION PHARMACOKINETIC-BASED STRATEGIES

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For TV-46000 q2m C_{max} was higher than RBP-7000 4 weeks after last dose of RBP-7000; however, C_{avg} and C_{min} were generally comparable to RBP-7000, oral risperidone and TV-46000 q1m. Similar trends in plasma concentrations were observed for both upper arm and abdominal administration following TV-46000 injections.

Conclusions: PopPK simulations revealed switching to TV-46000 4 weeks after the last dose of RBP-7000 provided generally comparable PK exposures at first dose and at steady-state of TV-46000. If clinicians seek to avoid higher C_{max} peaks associated with switching to TV-46000 q2m, then q1m can be administered. Clinician discretion will determine whether to initiate q1m or q2m TV-46000 4 weeks after the last dose of RBP-7000 based on a variety of factors, such as patient preference, scheduling convenience, and concerns about tolerability or symptom breakthrough.

ICC021

PHARMACOMETRIC LANDSCAPE IN INDIA

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Research on pharmacometrics started around 2000s in India. First research in the population pharmacokinetics appeared around 2008 from a pharmacology lab at the Kakatiya university, Andhra Pradesh. That lab continued to work and train researchers in this domain. Different institutions started working in this domain. In the same year (2008) another group named Population approach group in India (PAGIN) started training researchers in the population pharmacokinetics analysis with experts coming from different countries. This group was instrumental in training many pharmacometricians till now. Between 2010 and 2020 different groups started publishing population pharmacokinetic studies. Research groups focusing on cancer from Mumbai and infectious disease along with a group in Manipal collaborated on the quantitative sciences through a consortium known as Consortium of Dose optimization (CODE). Apart from these groups, few other groups also are working independently on the science of applying pharmacometrics to the clinical decision-making process.

Post 2020, PAGIN group evolved into a full-fledged Society of Pharmacometrics and Health Analytics (SOPHAS). This group initiated long term courses for training in pharmacometrics and another course on applications of AI in drug development with collaboration with industry stakeholders. In the last two decades, research on population pharmacokinetics spanned areas including anti-epileptics, anti-infectives, anti-cancer and Immunosuppressant drugs. In the same period, Indian pharmaceutical industries were also implementing model informed drug development approach in their generic drug development efforts. With the initiation of the international conference focused on pharmacometrics in collaboration with international society of Pharmacometrics (ISOP) in India, more interactions and collaboration is expected to happen among all the stakeholders. In the next two decades, pharmacometrics discipline in India is expected to have adequate pharmacometricians to take forward this science for the benefit of all the stakeholders. Center for pharmacometrics at Manipal taken the lead to conduct a leadership summit to work with all stakeholders and bring about necessary regulatory eco-system for the growth of quantitative sciences and MIDD.

ICC022

PHYSIOLOGICALLY BASED PHARMACOKINETIC (PBPK) MODELING TO PREDICT DULOXETINE EXPOSURE IN PATIENTS WITH HEPATIC IMPAIRMENT

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Background: Hepatic impairment (HI) affects enzyme abundance, protein binding, and blood flow, leading to altered drug exposure, necessitating clinical studies and dose adjustments. However, such studies are resource-intensive and logistically challenging like patient enrollment. Physiologically based pharmacokinetic (PBPK) modeling and simulation can be used to predict drug PK and is recognized by regulatory authorities as potential approach to design clinical studies or reduce the need of clinical studies.

Objective: PBPK model was developed for duloxetine, a potent serotonin and norepinephrine reuptake inhibitor for depressive and generalized anxiety disorders. It is eliminated via hepatic metabolism by CYP1A2 and CYP2D6 enzymes. The goal was to predict duloxetine PK in HI, defined by the Child-Pugh (CP-A, B, and C) classification.

Methods: The duloxetine PBPK model was built in open-source PK-Sim (v12). Default physiological parameters were used for healthy volunteers (HV) and HI population, and drug physicochemical properties were obtained from literature. To recover the observed PK in HV, tissue permeability and partition coefficients were optimized. In-house meta-analysis based altered relative protein abundances of CYP1A2 and CYP2D6 in HI were integrated in the PK-Sim physiology. The model was first developed in HV and validated against published PK data after single oral dose ranges (15-90 mg) and multiple doses (30 mg QD and BID as well as 60 mg QD). The model was then extrapolated to predict PK in HI and compared against observed PK data in CP-B class, 5-8 and prospectively predict PK in CP-A and C classes.

Results: The model was able to reasonably capture the observed PK-profiles in HV. The predicted PK endpoints, including AUC, Cmax, Tmax and t-half were within 2-fold of the observed clinical data. In CP-B, predicted duloxetine exposure was 2.5-fold higher than in HV, and the predicted to observed HI/HV ratio was within 1.25-fold.

Conclusion: A duloxetine PBPK model was successfully developed and validated across several single and multiple oral doses, and was applied to predict impact of HI. The validated model can be used to predict PK in untested scenarios and inform study design (sample size and sampling window) and dose selection.

ICC023

APPLICATION OF PHYSIOLOGICALLY BASED PHARMACOKINETIC (PBPK) MODELING TO SUPPORT SUPAC LEVEL III FORMULATION CHANGES INVOLVING NITROSAMINE REMEDIATION

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Objective: Development of PBPK models to assess the impact of excipients on in-vivo performance of two BCS class II molecules to support SUPAC Level III formulation changes involving remediation of nitrosamine drug substance related impurities.

Methodology: Two independent PBPK models were developed using GastroPlus®, v9.9. Further, the models were validated and applied for demonstrating the virtual bioequivalence (VBE) of reformulated products against RLD.
Case 1: PBPK model to predict the bioequivalence of reformulated SPIL-C ER capsules, 40 mg (SC-TR), containing a nitrosamine quencher. In-vitro dissolution data of SC-TR was integrated, and VBE was conducted against the RLD.
Case 2: PBPK model to demonstrate bioequivalence of reformulated SPIL-D DR capsules, 60 mg (SD-TR), containing nitrosamine quencher against RLD. The model was also used for risk assessment of increased permeability caused by the used nitrosamine quencher.

Results: Prediction errors (PE) for both the models were well within 10% and they were successfully applied to achieve the stated objectives.

Case 1: The PBPK model showed a PE of 4.22% for C_{max} and 0.69% for AUC_{0-t}. VBE simulations predicted that addition of nitrosamine quencher did not impact the in-vivo performance. An actual bio-study with SC-TR confirmed the prediction, with the BE results showing a %deviation of <2.12 . These results provide evidence of the utility of robust PBPK model in securing biowaivers for SUPAC Level III changes.

Case 2: The PBPK model for SPIL-D DR capsules, 60 mg, showed a PE of (–)3.96% for C_{max} and 3.90% for AUC_{0-t}. VBE simulations between SD-TR and the RLD confirmed bioequivalence within the USFDA 80–125% range (Table 2). Moreover, bioequivalence was maintained even with a 10% increase in P_{eff} (Table 2). The model and findings provided in silico justification for high impact regulatory submission involving clinical study biowaiver.

ICC023

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Conclusion: The development of two independent PBPK models demonstrated their effectiveness in supporting formulation changes under SUPAC Level III. The outcomes from both the cases highlight utility of PBPK modeling as a strategic tool for regulatory support and risk assessment in formulation development.

ICC024

RE-OPTIMIZATION OF A PK-SIM LIBRARY PBPK MODEL INCORPORATING NONLINEARITY AND REALISTIC SOLUBILITY TO ENABLE PEDIATRIC DOSE SCALING

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Background: A previously reported PBPK model available in the PK-Sim® library did not adequately capture nonlinear pharmacokinetics and relied on solubility assumptions that were inconsistent with experimental in vitro data. These limitations reduced its reliability for clinical translation, particularly for pediatric dose-scaling and nonlinear drug–drug interaction assessment.

Objective: The objective of this work was to re-optimize the published PBPK model by incorporating physiologically plausible solubility parameters and mechanistic saturation processes to improve prediction of adult pharmacokinetics and to enable informed pediatric extrapolation.

Methods: A mechanistic PBPK model was developed in PK-Sim® using saturable CYP3A4-mediated metabolism at both intestinal enterocytes and systemic tissues, P-glycoprotein saturation affecting intestinal efflux, CYP3A4 auto-inhibition, and UGT1A2 inhibition as relevant pathways contributing to nonlinear pharmacokinetics. Experimentally derived solubility values replaced the prior unrealistic inputs. The model was calibrated and evaluated using adult clinical pharmacokinetic data from single oral doses of 100–1200 mg, with performance assessed through comparison of simulated versus observed Cmax and AUC values. Following successful verification, pediatric simulations were conducted for children under 13 years of age using age-dependent physiological parameters to explore exposure trends.

Results and Conclusion: The re-optimized PBPK model successfully reproduced the nonlinear increase in systemic exposure observed in adults, with predicted Cmax and AUC values consistently within a two-fold error margin across the full 100–1200 mg dose range. Integration of saturable metabolism, transporter saturation, and auto-inhibition mechanisms corrected the underprediction and inaccurate exposure curvature seen in the original library model. Revision of solubility assumptions eliminated physiologically

ICC024

RE-OPTIMIZATION OF A PK-SIM LIBRARY PBPK MODEL INCORPORATING NONLINEARITY AND REALISTIC SOLUBILITY TO ENABLE PEDIATRIC DOSE SCALING

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implausible supersaturation behavior and improved absorption predictions. Pediatric simulations yielded physiologically plausible exposure ranges informed by maturation and fed-state conditions. Overall, the refined PBPK model incorporating mechanistic nonlinear processes and realistic solubility provides substantially improved predictive performance and offers a physiologically credible framework to support future pediatric dose-scaling considerations and nonlinear DDI evaluations.

ICC025

DEVELOPMENT AND EVALUATION OF PHYSIOLOGICALLY BASED PHARMACOKINETIC DRUG-DISEASE MODEL FOR PREDICTING RIFAMPICIN PHARMACOKINETICS ASSOCIATED WITH BILE SALT VARIATIONS IN HEPATOBILIARY DISORDERS

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Hypothesis: Disease-driven variations in intestinal bile salt concentrations regulate rifampicin solubilization as well as absorption[1,2], and such effects can be mechanistically captured using a physiologically based pharmacokinetic (PBPK) drug–disease model[3].

Objective: To construct and evaluate a whole body PBPK drug–disease model of rifampicin by incorporating in vitro dissolution data generated in biorelevant media representing healthy, Crohn's disease, and cholestasis conditions, and to predict rifampicin pharmacokinetics under altered bile salt physiology.

Methods: In vitro dissolution studies were performed in FaSSIF media containing bile salt concentrations mimicking healthy adults (3–5 mM), Crohn's disease (<2 mM), and cholestasis (>10 mM). Rifampicin release profiles were fitted and integrated into a whole-body PBPK model constructed using PK-Sim®. Baseline healthy models were first validated against published plasma concentration–time profiles following intravenous and oral dosing[3]. Disease-specific models were then generated by incorporating dissolution-dependent absorption parameters along with physiological changes relevant to Crohn's disease and cholestasis.

Results: Biorelevant dissolution demonstrated markedly reduced rifampicin release in FaSSIF-CD, while FaSSIF-cholestasis showed enhanced solubilization relative to healthy media. The PBPK model incorporating these profiles predicted lower C_{max} and AUC in Crohn's disease (C_{max} ~4.7 mM/L) and higher exposure in cholestasis (C_{max} ~10.7 mM/L) compared with healthy individuals (C_{max} ~6.9 mM/L). All predictions were within accepted two-fold error of expected pharmacokinetic behaviour.

Conclusion: The PBPK drug–disease model demonstrates that Crohn's disease can substantially reduce rifampicin exposure, whereas cholestasis has minimal impact. This integrated in vitro–in silico framework supports dose optimization and therapeutic drug monitoring in patients with impaired bile salt physiology.

ICC026

A SIMULATION-DRIVEN WORKFLOW FOR CONDUCTING MODEL-BASED BIOEQUIVALENCE (MBBE) USING PUMAS

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Background: Model-Based Bioequivalence (MBBE) integrates population pharmacokinetic (PopPK) modeling with repeated virtual clinical trial simulations to assess bioequivalence (BE) between test and reference formulations. This approach enables comprehensive evaluation of variability, uncertainty, and study design performance beyond what is feasible in traditional BE trials.

Objective: To demonstrate a complete, reproducible workflow for implementing MBBE using Pumas, including model development, design generation, simulation execution, MBBE analysis, and power determination.

Methods: A one-compartment PopPK model with oral absorption was developed, incorporating covariates for sequence, period, and formulation to estimate relative bioavailability. Parallel study designs were generated for sample sizes ranging from 40 to 200 subjects per arm. For each design and a range of test-to-reference (T/R) ratios, 1000 replicated virtual trials were simulated. Resulting datasets were analyzed using Pumas MBBE tools to estimate geometric mean ratios (GMRs) for Cmax and AUC and corresponding confidence bounds. Power was calculated as the proportion of simulations meeting BE acceptance limits (80–125%).

Results: Simulated pharmacokinetic parameters (CL and Vd) showed overlapping distributions between formulations, validating model assumptions. GMRs increased linearly with T/R ratios, confirming internal consistency. Power analyses highlighted how required sample size increases as T/R ratios deviate from unity, providing clear thresholds for achieving ≥80% power.

Conclusion: This workflow demonstrates how Pumas enables efficient and transparent implementation of MBBE through PopPK modeling, flexible design generation, and large-scale simulation. MBBE offers a robust alternative or complement to empirical BE studies, supporting formulation development and regulatory decision-making.

ICC027

SWITCHING PATIENTS WITH SCHIZOPHRENIA TO TV-46000, A LONG-ACTING SUBCUTANEOUS ANTIPSYCHOTIC, FROM ARIPIPRAZOLE ONCE MONTHLY: PHARMACOKINETIC-PHARMACODYNAMIC MODELING AND SIMULATION

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Background: TV-46000 is a long-acting injectable (LAI) subcutaneous risperidone antipsychotic administered once monthly (q1m) or every 2 months (q2m) for schizophrenia. Transitioning from aripiprazole once monthly (AOM), a partial dopamine D2-receptor (D2R) agonist (allows 25% D2R activity), to TV-46000, a D2R antagonist (blocks receptor activity), requires consideration of pharmacodynamic differences. Aripiprazole has higher D2-binding affinity and requires high receptor occupancy (D2RO) for antagonism, while risperidone exerts antagonism at any D2RO. This study used population pharmacokinetic-pharmacodynamic modeling to simulate AOM to TV-46000 switching and assess D2RO and antagonism.

Methods: Population pharmacokinetic models were used to simulate plasma concentrations, D2RO, and antagonism during a switch from AOM 400 mg to TV-46000 125 mg q1m or 250 mg q2m, 28 days after the last AOM dose among 500 virtual participants. Competitive binding models evaluated D2RO and antagonism over time.

Results: AOM pre-switch D2RO was 91%, with 68% antagonism. After first TV-46000 q1m dose, D2RO was 71% for AOM/19% for TV-46000 (total=90%); antagonism was 53%/19%, respectively (total=73%). After first TV-46000 q2m dose, D2RO was 62% for AOM/27% for TV-46000 (total=89%); antagonism was 47%/27%, respectively (total=74%). As TV-46000

ICC027

SWITCHING PATIENTS WITH SCHIZOPHRENIA TO TV-46000, A LONG-ACTING SUBCUTANEOUS ANTIPSYCHOTIC, FROM ARIPIPRAZOLE ONCE MONTHLY: PHARMACOKINETIC-PHARMACODYNAMIC MODELING AND SIMULATION

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approached steady-state (after 3 doses), antagonism was 14%–29% (AOM) and 49%–64% (TV-46000). AOM's contribution to total antagonism was <5% after 5 (q2m) or 9 (q1m) TV-46000 doses.

Conclusions: Simulations demonstrated that switching from AOM 400 mg to TV-46000 125 mg q1m or 250 mg q2m maintained total antagonism despite slightly lower D2RO. Clinicians should consider patient preference and tolerability when switching LAIs.

Short Description: This study used pharmacokinetic-pharmacodynamic modeling to simulate switching from aripiprazole once monthly 400 mg to TV-46000, a long-acting risperidone formulation for schizophrenia, 125 mg once monthly or 250 mg once every 2 months. Simulations showed that TV- 46000 maintained comparable dopamine D2-receptor occupancy and antagonism despite pharmacologic differences. Results support that switching between the 2 formulations preserved D2-receptor antagonism, however clinical decisions should be guided by patient preference, convenience, and tolerability.

ICC028

OPTIMIZING FIRST-IN-HUMAN PHARMACOKINETIC PREDICTIONS THROUGH INFORMED USE OF MECHANISTIC AND ALLOMETRIC SCALING

Predicting the first-in-human (FIH) dose remains a key translational challenge due to interspecies variability in pharmacokinetics (PK). Conventional allometric scaling, which extrapolates PK parameters from animals to humans based on body weight, can reasonably estimate the volume of distribution (Vd), yet often performs poorly for clearance (CL) because it does not account for interspecies differences in enzyme expression, metabolic pathways, and plasma protein binding. In this work, we investigated whether integrating mechanistic correction factors for CL with traditional allometric scaling for Vd could improve the accuracy of human PK predictions. Intrinsic clearance (CLint) data from in vitro hepatocyte assays across preclinical species were compared, and species-specific scaling factors (SF) were calculated as the ratio of in-vivo to in-vitro clearance (SF = CLin-vivo / CLin-vitro). Because in-vitro assays frequently underpredict true clearance due to reduced metabolic activity or loss of essential cofactors, these factors were applied to correct human in-vitro clearance estimates. Importantly, such correction factors should only be applied when the enzymology of the preclinical species used to derive the scaling factor closely resembles that of humans, ensuring comparable metabolic pathways and catalytic efficiency. Given the strong enzymatic similarity between monkeys and humans, a monkey-derived scaling factor (SFmonkey) was used to adjust human hepatocyte data (CLint,human,predicted = CLint,human,in vitro × SFmonkey). In parallel, Vd was estimated using body-weight–based allometric equations (Vd = a × BWb) to reflect physiological scaling. This combined framework reduced prediction error for human PK parameters by applying mechanistic rigor to elimination processes while maintaining empirical scaling for distribution. Overall, this hybrid extrapolation strategy enhances confidence in FIH dose selection and strengthens the translational reliability of preclinical data for early clinical development.

ICC029

EVALUATE ROBUSTNESS AND PRECISION IN DISCOVERING THE DYNAMICS OF INDIRECT RESPONSE MODELS USING DEEPNLME

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Background: Indirect response (IDR) models describe systems in which endogenous mediators are governed by production (k_"in") and loss (k_"out") processes, often influenced by nonlinear stimulation or inhibition effects. Traditionally, the structure of these dynamics is specified in advance based on mechanistic assumptions or empirical experience. This can be limiting when the true system behavior is unknown or more complex than expected. Deep-NLME combines neural networks with nonlinear mixed-effects modeling to enable data-driven learning of system dynamics directly from longitudinal data. This approach reduces reliance on predefined model structures while still accounting for population-level behavior and inter-individual variability.

Objectives:

- To assess whether Deep-NLME can identify the underlying dynamics of the four IDR models directly from data, including unknown nonlinear effects on k_"in" and k_"out", without assuming a specific mechanistic form.
- To examine how different train–test split ratios, across varying cohort sizes, influence the robustness, precision, and predictive performance of Deep-NLME models.

Methodology: A mechanistic IDR stimulation model was used as the data-generating process. Synthetic populations were simulated for three cohort sizes (N = 20, 40, 80). For each scenario, 100 replicate datasets were generated. Three train–test split ratios were evaluated, with 25%, 50%, or 75% of subjects used for training and the remainder reserved for prediction. Deep-NLME models were estimated using MAP (FOCE). Model performance was evaluated on held-out subjects using root mean squared error (RMSE) of pharmacodynamic predictions. Additional metrics, including MAE, bias, and prediction variance, were used to assess accuracy, precision, and robustness.

Results: Results are currently being generated across all simulation scenarios. Preliminary analyses indicate that Deep-NLME is able to recover the underlying indirect response dynamics directly from the longitudinal data, closely matching the true data-generating dynamics. With respect to predictive performance, the 75% training split achieved the highest accuracy, as reflected by the lowest RMSE and MAE on held-out subjects. The 50% split, although slightly less accurate, yielded more precise predictions, demonstrated by lower prediction variance across replicates.

ICC030

A COPULA FRAMEWORK FOR CAPTURING MULTIVARIATE VARIABILITY IN IN SILICO CLINICAL TRIALS

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Accurately representing inter-individual variability and parameter dependence is central to building credible in-silico clinical trials (ISCTs). While nonlinear mixed-effects (NLME) modeling provides estimates of population distributions and correlation structures, efficiently translating these into large virtual populations remains a methodological challenge, particularly when parameters follow heterogeneous marginal distributions. Here, we present a generalizable workflow implemented in Julia/Pumas that uses copula-based sampling to generate coherent sets of correlated parameters for ISCT applications. The workflow separates marginal specification from dependence modeling, enabling flexible incorporation of empirical or literature-informed parameter distributions while preserving rank-based correlations typically estimated in NLME fits. We detail computational steps for constructing Gaussian and alternative copulas, transforming samples via inverse-CDF methods, validating correlation preservation, and integrating sampled parameters into forward simulation pipelines in Pumas.

Our workflow serves as a reusable template for pharmacometricians seeking robust, transparent, and extensible methods for parameter sampling within Pumas-based modeling ecosystems.

ICC031

LEVERAGING MODEL-INFORMED BIOEQUIVALENCE AND NON-INFERIORITY ANALYSIS TO WAIVE THE NEED FOR A PHASE-III EFFICACY STUDY OF HAMSYL® IN PAEDIATRIC ACUTE LYMPHOBLASTIC LEUKAEMIA

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Background: Acute lymphoblastic leukaemia (ALL) is the most common paediatric cancer and depends on extracellular asparagine for tumour growth. L-asparaginase is a key component of ALL therapy, but native formulations are limited by immunogenicity. Pegylated L-asparaginase (pegaspargase) improves tolerability and prolongs half-life. Oncaspar® is an approved pegaspargase, while Hamsyl® is a biosimilar developed to improve access in low- and middle-income countries. A pharmacokinetic bioequivalence study in paediatric patients with relapsed ALL compared a single intramuscular dose of Hamsyl® and Oncaspar®. Bioequivalence was demonstrated based on AUC_0–t, with comparable pharmacodynamic, immunogenicity, and safety profiles.

Objective: This analysis was aimed to use modelling and simulations to strengthen the available evidence and confirm the non-inferiority of Hamsyl® versus the reference Oncaspar® in paediatric patients with ALL.

Methodology: First, data from the BE study was used to develop a population pharmacokinetic (PopPK) model. A one-compartment model with first-order absorption and linear elimination, incorporating body surface area on clearance and volume best described the PK data. Relative bioavailability of Hamsyl® compared to Oncaspar® was estimated at 0.974, consistent with observed BE results. Then, the popPK model was utilized to perform model-informed bioequivalence (MIBE) and non-inferiority (MINI) analyses for different sample sizes and BE acceptance ranges to strengthen the evidence for BE. The non-inferiority (NI) criterion was the percentage of subjects achieving target nadir serum asparaginase activity ≥ 100 IU/L at the end of Day 14.

Results: MIBE simulations indicated that a minimum sample size of approximately 80 subjects would be needed to demonstrate BE, considering the standard acceptance range of 80%-125%. MINI simulations showed that NI error margins (−5% to −10%) could achieve ≥80% power with fewer than 50 subjects.

Conclusion: These integrated analyses demonstrate that Hamsyl® is bioequivalent and non-inferior to Oncaspar® in paediatric ALL, obviating the need for a traditional Phase III efficacy study. Hamsyl® offers a cost-effective and accessible alternative for resource-limited settings. A post-marketing study is underway to further validate these findings in real-world clinical practice.

ICC032

INFLUENCE OF SHRINKAGE ON THE RELIABILITY OF EBE-BASED DIAGNOSTICS: AN EVALUATION USING PUMAS

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Background: The primary aim of this study is to evaluate the usefulness of Empirical Bayes Estimates (EBEs) of and their associated diagnostics (such as Individual Predictions (IPRED) and Individual Weighted Residual Errors (IWRES)) under shrinkage conditions, as originally proposed by Savic et al. In this work, we conduct this assessment using Pumas. This approach allows us to validate the diagnostics within the Pumas ecosystem and establish a foundational methodology that can subsequently be extended to non-Gaussian variability models.

Methodology: Eight pharmacokinetic or pharmacodynamic models explicitly mentioned in the original paper were simulated by altering the sampling frequencies and sampling time. EBEs were then estimated by fitting the data to either the true model or intentionally misspecified model to assess the influence of shrinkage on various diagnostics. Several commonly used EBE-diagnostics were explored: EBE distribution to assess the normality of EBE, ETABAR outcome to determine the effect of the early sampling on absorption rate constant and last sample on clearance, EBE-EBE correlation to assess whether shrinkage masks the true correlation or falsely induce correlation, EBE-Covariate correlation, Dependent variable (DV) versus IPRED plot to detect the structural model misspecification, |IWRES| versus IPRED plot to assess how increasing shrinkage reduces its power to detect the residual error model misspecification, and relationship between η- and ε-shrinkage was examined.

Results: When the individual-level data were rich and informative, the individual parameter prediction depends highly on the observed data and shrinkage was minimal. Conversely, with sparse or uninformative individual-level data, shrinkage occurs, resulting in less deviation of EBEs from the population parameter. Under high shrinkage (>20-30%), EBE-based diagnostics lost its informativeness and led to misleading conclusions such as non-normal or asymmetric EBE distributions, hidden or falsely induced correlations, distorted parameter-covariate relationships and also masking the model misspecification. Thus, as the shrinkage increases, the EBE-based graphical diagnostics lose their usefulness, and often misleading during model development.

Conclusion: Significant Shrinkage does not indicate any problem with the dataset or model but reduces the reliability of EBE-based diagnosis in model building process. These results align and match up with the work previously reported by Savic et al.

ICC033

A WORKFLOW FOR STRUCTURAL IDENTIFIABILITY ANALYSIS IN PUMAS

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Structural identifiability analysis is essential to determine whether model parameters can be uniquely estimated from given data, thereby ensuring robustness in modelling. It is essential to include identifiability analysis into model-informed drug development workflows.

Objective: The objective was to develop and demonstrate a structured workflow for assessing structural identifiability within a Julia-based modelling environment, with Pumas' framework for nonlinear mixed-effects models.

Methods: Workflow was implemented using Julia packages Pumas, ModelingToolkit.jl, and StructuralIdentifiability.jl. The process begins by specifying three key components: (i) the dynamical system represented as a system of ordinary differential equations, (ii) the inputs (such as dosing events) and their action on the system, and (iii) the observed quantities and their relationship to system states. Using ModelingToolkit.jl, symbolic representation of Pumas models is extracted, expanded with dosing inputs and observation equations, and apply differential algebra techniques via StructuralIdentifiability.jl to assess identifiability. We tested the workflow on a semi-mechanistic pharmacometric model.

Results: The workflow identified structurally identifiable and non-identifiable parameters, highlighting the influence of model structure for given data.

Conclusion: This workflow provides a systematic approach to integrate structural identifiability analysis into Pumas-based modelling. By ensuring identifiability early in the modelling process, this approach enhances predictive performance and confidence in model- based inference.

ICC034

COST-SAVING MODELING AND SIMULATION STRATEGY FOR MULTIPLE DOSE PHARMACOKINETIC ENDPOINT STUDY WAIVER.

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Objective: To demonstrate a cost-saving strategy using modeling and simulation to waive the requirement for a multiple-dose pharmacokinetic (PK) endpoint study for ABC prolonged-release capsules.

Introduction: ABC prolonged-release capsules are indicated for the treatment of anxiety and depression disorders. The test product was shown to be bioequivalent to the reference product under single-dose conditions using standard bioequivalence (BE) criteria. However, the regulatory agency requested additional data from a multiple-dose PK study. To address this, a model-informed approach was adopted to simulate the multiple-dose PK profile.

Method: In-house PK data from a single dose BE study were used to develop a population pharmacokinetic (PopPK) model. Model performance was evaluated using visual predictive checks (VPC) and goodness-of-fit (GOF) diagnostics. The final model parameters and empirical Bayes estimates were used to simulate a multiple-dose crossover BE study. Non-compartmental analysis (NCA) was performed on the simulated data to compute BE metrics.

Results: Published regulatory data confirmed the linear PK behaviour of ABC across dosing regimens. Comparison of simulated multiple-dose BE metrics with observed single-dose data revealed no significant differences in steady state PK endpoints for test and reference, supporting the validity of the simulation approach.

Conclusion: Integrating PK knowledge with PopPK modeling enabled reliable prediction of multiple-dose PK behaviour. The approach highlights the potential of model-informed drug development (MIDD) to reduce clinical study burden, accelerate timelines, and optimize resource utilization in generic drug development.

ICC035

BEYOND MICHAELIS-MENTEN: HYBRID DEEPNLME APPROACHES TO TARGET-MEDIATED DRUG DISPOSITION

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Background: Target-Mediated Drug Disposition (TMDD) models are essential for characterizing biologics but are often simplified to enable estimation. A common approach reduces drug–target interactions to a static nonlinear elimination term, classically represented by Michaelis–Menten (MM) kinetics. While practical, this simplification collapses unobserved target dynamics into an instantaneous function of drug concentration, implicitly assuming quasi-equilibrium (QE) behavior and precluding hysteresis, delay, or memory effects.

Methods: We investigate a hierarchy of hybrid nonlinear mixed-effects (NLME) models implemented in DeepPumas. First, we consider static nonlinear clearance models, including classical MM and a more flexible learned rate law, NN(C, η), where population variability is modeled through random effects. This formulation generalizes MM while retaining the same structural assumption of instantaneous concentration-dependent elimination. Next, we extend this framework by introducing an explicit secondary state representing target engagement or an effect compartment. The nonlinear elimination process is parameterized by a neural network acting on model states rather than absolute time, yielding a low-dimensional, state-dependent dynamical system capable of representing delay and hysteresis.
We also assess models of the form NN(t, C, η), which can provide excellent fits in single-dose settings but rely on explicit time dependence.

Results: Static nonlinear clearance models, including NN(C, η), successfully capture a wide range of saturable QE-like behaviors and provide substantially greater flexibility than classical MM. However, as memoryless reductions, they cannot reproduce hysteresis or path-dependent kinetics arising from non-equilibrium target dynamics.
Models using NN(t, C, η) can fit delayed behavior in single-dose scenarios but incorrectly attribute dynamical effects to absolute time, resulting in poor generalization to altered dosing regimens. In contrast, introducing a single explicit state enables the model to represent hysteresis and kinetic delays while remaining compact and regimen-invariant.

ICC035

BEYOND MICHAELIS-MENTEN: HYBRID DEEPNLME APPROACHES TO TARGET-MEDIATED DRUG DISPOSITION

Harissh Chandrasekaran[1], Niklas Korsbo[2], Vijay Ivaturi[1, 2]
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Conclusion: This work frames TMDD modeling as a hierarchy of simplifying assumptions, from static nonlinear clearance to state-dependent hybrid dynamics. Learned rate laws within DeepNLME provide a flexible generalization of classical MM under QE-like conditions, while minimal state augmentation is sufficient to capture non-equilibrium TMDD behavior. This approach offers a principled and extensible pathway for modeling complex biologics when full mechanistic detail is unavailable.

ICC036

PUMAS ESTIMATION METHODS AND THEIR PRECISION, BIAS, AND ROBUSTNESS

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Background: Estimation methods are a critical component of population pharmacokinetic–pharmacodynamic (PK–PD) modelling, as the choice of algorithm directly influences the reliability of parameter estimates and the validity of model-based inferences. Performance is typically evaluated using metrics such as bias (systematic deviation from the true value), precision (variability of estimates across replicates), robustness (stability of convergence under varying initial conditions), and computational efficiency (runtime performance).

Methodology: Multiple estimation algorithms were evaluated using a set of representative pharmacodynamic (PD) models to characterize their strengths and limitations. Four PD response models were developed to reflect commonly encountered clinical endpoint types: continuous, binary, ordinal, and count outcomes. Each model was fitted using established estimation procedures First-Order (FO) Estimation, First-Order Conditional Estimation (FOCE) and the Laplace Approximation (LAPLACE) method.
A stochastic simulation study was conducted for each PD model, in which 500 datasets were generated from known parameter values and subsequently re-estimated using all three algorithms. Bias was quantified using the normalized estimation error (NEE), and precision using the relative root mean squared error (rRMSE). Robustness was assessed by performing repeated estimations from randomly sampled initial values and calculating the proportion of resulting estimates that fall within the confidence intervals derived from the true-parameter fits. Computational efficiency was evaluated by recording runtime under true-value initialization.

Results and Conclusion: The findings of this simulation study were consistent with previous evaluations of traditional estimation methods. FOCE demonstrated stable and reliable performance across all metrics for continuous outcomes, whereas LAPLACE exhibited consistently strong performance for discrete response types.

ICC037

DEEP NLME FOR VIRAL DYNAMICS

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Background: Accurately modeling viral dynamics remains a major challenge due to biological complexity and limited clinical measurements, which typically capture only viral RNA over time. Classical frameworks often require strong assumptions on target cell types, production rates, and viral compartment approximations. Such assumptions can limit model flexibility and hinder predictive accuracy in real-world scenarios.

Objective: We hypothesized that neural network-based viral dynamic models can provide accurate and parsimonious descriptions of HIV infection kinetics, rival traditional mechanistic frameworks while improving flexibility and generalizability.

Methods: Two DeepPumas neural models were evaluated: (i) a minimal model expressed as, where the neural network uses HIV drug concentration as input to predict viral dynamics (V); and (ii) an expanded model that describes target cells and the infection term; incorporating drug effect as an Imax function along with current viral RNA within the neural network () to define the infection term, from which viral RNA was derived. Training data was generated from a mechanistic model incorporating compartments for target cells, actively infected cells, latently infected cells, and long-lived cells. All simulations and neural model development were implemented in DeepPumas to ensure reproducibility and computational efficiency. Neural models were validated externally on an independent (synthetic) dataset, featuring multiple dosing regimens, altered dose levels, and extended follow-up.

Results: Both neural models provided reasonable fits to viral load trajectories compared to the mechanistic reference. The minimal neural model delivered accurate individual predictions despite its simplicity, capturing nonlinear dynamics without explicit mechanistic constraints. As expected, the data-generating mechanistic model achieved the best fit (log-likelihood -244.89 vs. -292.3 and -351.36 for neural (i) and (ii)), the neural approaches represent viable alternatives with potential for further optimization. External validation confirmed robustness: predictive accuracy on synthetic data was maintained under varied dosing schedules and extended follow-up.

Conclusion: Neural viral dynamic models offer a promising alternative to traditional compartmental approaches, combining parsimony with predictive performance. Their ability to adapt to varying regimens and extended follow-up suggests broad utility for HIV

ICC037

DEEP NLME FOR VIRAL DYNAMICS

Sreenath Krishnan (1), Vijay Ivaturi (1, 2#), Niklas Korsbo (1).
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and potentially other infectious diseases. These findings pave the way for integrating neural approaches into model-informed drug development, optimizing antiretroviral therapy, and enabling personalized treatment strategies.

ICC038

EXTENDING A QUANTITATIVE SYSTEMS PHARMACOLOGY MODEL OF ULCERATIVE COLITIS TO A SINGLE ALL-COMERS VIRTUAL POPULATION FOR OPTIMIZING THERAPEUTIC COMBINATIONS IN PHASE 3 TRIALS.

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Objectives : In this poster, we have used a calibrated and validated QSP model of UC with a single all-comers Virtual Population calibrated to multiple approved therapies to predict the efficacy of novel therapeutic combinations of anti-TL1A in Phase 3 clinical trials of UC patients.

Background and Motivation : UC is an autoimmune disease of the bowel (categorized as an Inflammatory Bowel Disease, or IBD) with an annual incidence rate of 10.5 to 46.14 per 100,000 in Europe. IBD presents an unmet treatment need, with patients losing response to treatment (biologics) over time; one study reported that over half of UC patients were not in remission at 12 months, while a third showed inadequate response. Hence, it is imperative to find novel therapies and combinations that can provide alternatives to existing therapies. QSP modeling can facilitate this process by predicting the impact of novel therapies and combinations using Virtual Populations to simulate clinical outcomes.

Method : We modified and expanded a published model of Ulcerative Colitis to include a representation of epithelial barrier and the primary clinical measure of the disease (Mayo Score). In line with prior modelling approaches for Autoimmune diseases, the Mayo Score is linked semi-mechanistically to key inflammatory cells. A single virtual population was calibrated to match outcomes from multiple clinical trials simultaneously.

Result : 1) We created and calibrated an allcomers virtual population matched to mean baseline characteristics, and post-therapy outcomes as reported in Phase 3 induction trials for Golimumab, Guselkumab, Ustekinumab, Vedolizumab and Phase 2 trials for Afimkibart, and Goli+Gusel combination. 2) We identified the drivers of efficacy for Adalimumab and Afimkibart in the model by analysing the relative impact of different pathways towards the overall efficacy. 3) We predict the efficacy of two different combinations of anti-TL1A which are of potential clinical interest in this Virtual Population, i.e., Afimkibart + Adalimumab, Afimkibart + Vedolizumab.

ICC038

EXTENDING A QUANTITATIVE SYSTEMS PHARMACOLOGY MODEL OF ULCERATIVE COLITIS TO A SINGLE ALL-COMERS VIRTUAL POPULATION FOR OPTIMIZING THERAPEUTIC COMBINATIONS IN PHASE 3 TRIALS.

Netravat Pendsey[1], Subashini Chandramohan[1], Animesh Shukla[1], Tanvi Joshi[1], Maithreye Rengaswamy[1]
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Conclusion : We demonstrate the utility of a calibrated QSP model of IBD in predicting the Phase 3 efficacy of novel combinations of therapies of interest. We propose to continue model development by calibrating to other approved and failed therapies (e.g., Tofacitinib, Secukinumab) to refine the representation of disease and enable efficacy prediction of novel therapies and combinations.

ICC039

A MODULAR QSP FRAMEWORK ENABLING CLINICAL TRANSLATION OF AAV GENE THERAPIES

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The increase in recent regulatory approvals demonstrates the growing contribution of gene therapies, yet the role of model-informed drug discovery and development (MID3) in this area is lagging behind. Most gene therapies use a therapeutic gene packaged into a virus vector, a complex modality with several sequential steps between dosing and effect, including PK/biodistribution of the vector, viral transduction leading to intracellular processes from uncoating to stable DNA transfection, transgene expression, and subsequent secretion and biodistribution of the gene product. Because of this complexity and the durable effect after a single dose, modelling approaches different from traditional PK/PD are required, and standard allometric scaling often does not translate for this modality. Therefore, mechanistic modelling approaches have been proposed to support translation of AAV gene therapy dose-response, and we developed a framework for mechanistic modelling of AAV gene therapeutics to capture their non-trivial PK/PD behaviour and support translation across species. The framework consists of three modules: (1) AAV PK/biodistribution, (2) viral transduction model, and (3) transgene product biodistribution model; an optional disease-pathway module may be added. The model is based on ODEs and parameterized using physiological parameters and mechanistic knowledge of the viral transduction pathway. Vector and transgene-specific parameters may be tuned using preclinical data, and literature data on AAV and protein PK can be used for parameterizing individual modules. Interspecies scaling approaches are applied to each module separately to obtain the final scaled model. Application was demonstrated using a case study based on pooled data from multiple AAV gene therapy programs. The modular framework enables tailoring to specific AAV programs, calibration using preclinical biodistribution/transduction and protein expression data, and identification of processes where traditional scaling does not apply. In our multispecies example (mouse, rat, NHP, human), AAV PK scaled using allometry, protein biodistribution scaled using mechanistic/physiology-based approaches, and the link between viral transduction and protein expression required a power-law approach (exponent ~2). The combined scaled model predicted human dose-response from preclinical data. This modular, transgene-agnostic framework supports development of AAV gene therapies by describing complex PK/PD relationships, reducing translational uncertainty, and improving prediction of efficacious human doses.

ICC040

INTEGRATING QUANTITATIVE SYSTEMS PHARMACOLOGY AND MACHINE LEARNING FOR PERSONALIZED AMINOGLYCOSIDE DOSING IN INDIAN INTENSIVE CARE UNIT PATIENTS: A COMPUTATIONAL FRAMEWORK

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Optimizing aminoglycoside dosing in Indian intensive care unit (ICU) patients is complicated by pharmacokinetic variability (Duong et al., 2021) and the narrow therapeutic index of the drug (Mingeot-Leclercq & Tulkens, 1999). Current dosing methods often fail to balance efficacy and nephrotoxicity, especially given the lack of pharmacokinetic data specific to the Indian population. We developed and evaluated a computational framework integrating quantitative systems pharmacology (QSP) and machine learning (ML) to personalize aminoglycoside dosing for Indian ICU patients (Folguera et al., 2024). The framework involved (1) data preprocessing, (2) Bayesian two-compartment pharmacokinetic modelling (Pai et al., 2011), (3) target attainment analysis, (4) ML-based outcome prediction, (5) Bayesian dose optimization, and (6) comprehensive validation. The ML component used a staged approach, starting with baseline features, then expanding via feature engineering (including domain-specific interactions and risk scores), comparing XGBoost, LightGBM, and CatBoost models (Prokhorenkova et al., 2018), and finally applying SHAP (SHapley Additive exPlanations) analysis for interpretability (Ponce-Bobadilla et al., 2024). Synthetic data representing 1,500 Indian ICU patients were used to predict post-dose nephrotoxicity and clinical cure (Azizi et al., 2021). Pharmacokinetic modelling identified creatinine clearance and weight as important covariates (Pai et al., 2011). Only 44.6% of patients met both efficacy (Cmax/MIC ≥ 8) (Moore et al., 1987) and safety (trough < 2 mg/L) (Mingeot-Leclercq & Tulkens, 1999) targets with the current dosing. The ML model performance improved through the four phases, with XGBoost showing an optimal test AUC (0.89). SHAP analysis identified trough concentration, AUC24, and baseline creatinine as the top nephrotoxicity predictors (Ponce-Bobadilla et al., 2024). Risk stratification showed a high nephrotoxicity rate (83%) in the high-risk group compared to 8.8% in the low-risk group. The framework generated personalized dose recommendations that balanced efficacy and safety. Our QSP-ML framework demonstrates the feasibility of integrating mechanistic models and transparent ML for personalized aminoglycoside dosing in Indian ICU settings (Folguera et al., 2024). Further prospective validation is needed before clinical implementation; however, this approach offers a methodological template for interpretable decision support in pharmacotherapy (Ponce-Bobadilla et al., 2024).

ICC041

ACUTE ECT-INDUCED CLOZAPINE CONCENTRATION ELEVATION MEDIATED BY INFLAMMATORY BIOMARKERS: QUANTITATIVE SYSTEMS PHARMACOLOGY APPROACH

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Background: Electroconvulsive therapy (ECT), an established augmentation strategy for treatment-resistant schizophrenia, has been associated with unpredictable and clinically significant elevations in serum clozapine concentrations, increasing the risk of toxicity. This study aimed to develop a quantitative systems pharmacology (QSP) model to mechanistically explain this interaction and its clinical consequences.

Methods: A QSP framework was developed by integrating a two-compartment pharmacokinetic model for clozapine with dynamic models of key inflammatory mediators - interleukin-6 (IL-6), C-reactive protein (CRP), and tumor necrosis factor-alpha (TNF-α). These biomarkers were linked mechanistically to CYP1A2 suppression, representing their modulatory effect on clozapine metabolism. Model parameters were drawn from literature data and validated using observed clinical pharmacokinetic profiles from patients undergoing ECT augmentation.

Results: The model recapitulated the progressive, multi-fold rise in serum clozapine concentrations across six ECT sessions. Each ECT pulse triggered a transient, pulsatile inflammatory response, resulting in a cumulative, stepwise decline in CYP1A2 activity to roughly 30% of baseline by the final session. Simulated outcomes indicated that dopamine D2 receptor occupancy exceeded the 80% threshold associated with extrapyramidal symptoms (EPS) following the fourth ECT session.

Conclusion: This mechanistic QSP model provides a biologically grounded explanation for the ECT-induced elevation in clozapine levels, implicating inflammation-driven CYP1A2 inhibition as the key pathway. The framework offers a predictive platform for assessing patient-specific risk and supports the development of model-informed dosing strategies to optimize safety during ECT-clozapine co-administration.

ICC042

A SCALABLE WORKFLOW FOR GLOBAL SENSITIVITY ANALYSIS (GSA) IN PUMAS

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As Quantitative Systems Pharmacology (QSP) and Physiologically Based Pharmacokinetic (PBPK) models expand to capture detailed biological mechanisms, the dimensionality of the parameter space increases significantly. Rigorous assessment of parameter influence is essential for model validation and experimental design. While local sensitivity analysis is limited to small perturbations, Global Sensitivity Analysis (GSA) using variance decomposition methods (e.g., Sobol indices) is required to robustly quantify the impact of parameters on system dynamics, accounting for non-linearities and parameter interactions across broad ranges. However, these methods are computationally intensive, requiring an exponential increase in simulations for convergence. This work presents a high-performance GSA workflow within the Pumas ecosystem (Julia) designed to overcome these computational bottlenecks. We demonstrate this workflow using a PBPK model of oral Voriconazole to assess parameter sensitivity regarding Cmax and area under the curve (AUC). Total order Sobol indices identified effective gastrointestinal permeability and metabolism/efflux mechanisms (MPPGI) as the primary drivers of pharmacokinetic variability, while solubility and intestinal transit time were determined not to be rate-limiting. This established workflow facilitates efficient, multivariate sensitivity analysis, enabling robust model verification and determining parameter identifiability critical for Model-Informed Drug Development (MIDD).

ICC042A

INTEGRATING IN SILICO MODELLING WITH ORGAN-ON-CHIP PLATFORMS TO ENABLE EXPERIMENTAL DESIGN, INTERPRETATION, AND HUMAN TRANSLATION

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Next generation non-animal methodologies (NAMs) such as organ-on-a-chip (OOC) systems and 3D human organoids are gaining rapid industry and regulatory adoption as drug discovery and safety assessment tools. The FDA Modernization Act 3.0 removes the statutory requirement for animal testing where non-animal NAMs, including in-vitro and in-silico models, are scientifically justified for regulatory submissions. The human relevance enabled by induced pluripotent stem cell (iPSC) technology allows these platforms to capture dynamic biological responses and tissue-tissue interactions supporting the assessment of toxicity, efficacy, and mechanism of action (MOA). The richness, complexity, and lab to lab variability of OOC datasets create a need for an integrated framework for experimental design, data analysis/interpretation, and translation to human outcomes, lest OOCs remain descriptive rather than decision-enabling. This poster highlights the role of mechanistic and statistical in-silico modelling as a translational layer across the OOC lifecycle, drawing on established case studies and modelling workflows. Three case studies illustrate how computational modelling can inform study design, disentangle active and passive processes (e.g., metabolism versus permeability), and enable in-vitro - in-vivo extrapolation (IVIVE) for clinical decision making. A published heart-liver OOC for terfenadine induced cardiotoxicity (QT elongation), a malaria-on-a-chip model for PK/PD driven in vivo efficacy estimation[2], and DigiLoC's digital twin framework for hepatic clearance[3] are presented demonstrating how in-silico approaches support mechanistic interpretation and translation to predicted clinical outcomes. Integration of in-silico driven OOC data with physiologically based pharmacokinetic (PBPK) models further supports prediction of human pharmacokinetics and inter-individual variability. These examples highlight the need for integrated computational frameworks capable of unifying PK/PD, IVIVE, PBPK, and systems-level analyses to support scalable, reproducible, and decision-ready interpretation of OOCs.

ICC043

PREVALENCE OF HYPERTENSION AMONG TYPE 2 DIABETES MELLITUS PATIENTS IN INDIA: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Hypertension (HTN) frequently coexists with Type 2 Diabetes Mellitus (T2DM) and significantly elevates cardiovascular risk. This systematic review and meta-analysis aimed to quantify the prevalence of hypertension among T2DM patients in India, considering regional, gender, and urban-rural disparities. Adhering to PRISMA protocols, a thorough search of various databases up to December 2024 identified observational studies reporting hypertension prevalence in adult T2DM patients across India. Data extraction and quality evaluation were conducted independently by two reviewers, employing the random-effects DerSimonian-Laird model for meta-analysis and subgroup analyses based on gender and residence type. Ten studies across diverse Indian regions, including Tamil Nadu and Gujarat, were included, revealing a pooled hypertension prevalence of 43.6% (95% CI: 38.0–49.0) with notable heterogeneity (I^2=87%, p<0.001). Male patients exhibited a higher prevalence (51.8%) compared to females (45.3%), and urban residents had a significantly higher prevalence (59.2%) than their rural counterparts (47.1%). The findings indicate a substantial prevalence of hypertension among Indian T2DM patients, particularly in males and urban areas, underscoring the need for targeted screening and preventive measures tailored to demographic and regional factors to mitigate cardiovascular risks in this population.

Keywords: Hypertension, Type 2 Diabetes Mellitus, Prevalence, India, Meta-analysis

ICC044

QSP MODEL-INFORMED OPTIMIZATION OF STEP-UP DOSING STRATEGIES FOR CD3 BISPECIFIC T CELL ENGAGERS

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Introduction: CD3 bispecific T cell engagers (TCEs) are powerful immunotherapies that direct T cells toward tumor-associated antigens but frequently induce cytokine release syndrome (CRS), particularly during initial dosing. Step-up (priming) dosing is employed to reduce CRS risk, although these regimens are often established empirically through dose-escalation studies. Epcoritamab, a subcutaneous CD3 × CD20 bispecific antibody, has demonstrated promising activity in B-cell non-Hodgkin lymphoma, with CRS emerging as a primary early toxicity that informed the implementation of step-up strategies.

Objective: To assess whether early-phase clinical data from Epcoritamab can be incorporated into a mechanistic QSP modeling framework to define efficient step-up dosing strategies and appropriate target doses, with the goal of informing rational priming approaches and therapeutic dose selection across diverse patient populations.

Methods: A mechanistic QSP model was developed to capture subcutaneous pharmacokinetics, CD3/CD20 trimerization, T cell activation, cytokine release, and tumor growth inhibition (TGI). The model was informed by early clinical cohort data from the EPCORE NHL-1 study and applied to evaluate a range of dosing strategies. To account for interpatient variability in immune response and tumor burden, a virtual population (Vpop) was constructed, within which step-up regimens consisting of 2-4 escalation steps were assessed for their impact on predicted CRS, target engagement, and tumor cell killing.

Results: Across dose levels, the simulations reproduced observed patterns of CRS occurrence and tumor growth inhibition. Shorter step-up dosing schedules showed similar safety and antitumor effects compared with more gradual escalation approaches. Evaluation across the Vpop further indicated that well-designed step-up strategies can lessen CRS risk while maintaining effective T cell activation and tumor control.

Conclusions: This case study demonstrates how incorporating early clinical data into a mechanistic QSP framework can support the rational design of step-up dosing strategies for CD3 bispecifics. For T cell engagers, a model-informed approach to priming may limit reliance on prolonged cohort-based dose escalation, enable faster progression to therapeutic dose levels, and guide adaptive dosing strategies in future clinical development.

ICC045

ESSENTIAL IN VITRO ADME DATA PACKAGE FOR PREDICTIVE MODELING AND SIMULATION IN DRUG DEVELOPMENT

In-vitro data serve as a cornerstone for early-stage pharmacokinetic (PK) modeling and simulation, enabling accurate prediction of drug disposition and systemic exposure. These data provide critical insights into absorption, distribution, metabolism, and excretion (ADME) properties, which are essential for building robust mechanistic models. Key parameters such as solubility and Log D inform on drug lipophilicity and dissolution potential, influencing oral absorption and formulation strategies. Permeability assessments, typically via Caco-2 or MDCK assays, predict intestinal transport and bioavailability, while fraction unbound in plasma (fu) determines the free drug concentration available for pharmacological activity and clearance.

Additionally, intravenous PK parameters derived from preclinical studies, including clearance (CL), volume of distribution (Vd), and half-life (t½), are indispensable for scaling and validating in silico models. These parameters, combined with in vitro metabolic stability and enzyme kinetics, allow for extrapolation to human PK using physiologically based pharmacokinetic (PBPK) frameworks. The integration of solubility, Log D, permeability, and fu data with IV PK metrics ensures a comprehensive understanding of drug behavior across biological compartments, supporting dose selection and risk assessment.

ARV-110 (Bavdegalutamide), a protac molecule is evaluated in essential in-vitro ADME and primary PK data to understand the kinetics, in-vitro - in-vivo correlation and further build the predictive models/allometric scaling for dose predictions.

The outcome of this approach is a predictive model that informs decision-making in lead optimization and clinical trial design. However, while in-vitro data provide a strong foundation, further refinement through PBPK modeling is essential to confirm predictions under physiological conditions. PBPK simulations incorporate system-specific variables such as organ blood flow, tissue composition, and enzyme expression, thereby enhancing translational accuracy and reducing uncertainty in human PK projections.

In summary, ARV-110 showed reasonable correlation. In-vitro ADME and IV PK data enable early prediction of drug disposition, but confirmation through PBPK modeling is critical for reliable human pharmacokinetic outcomes.

ICC047

IDENTIFICATION OF GENERALIZABLE POPULATION PHARMACOKINETIC MODELS FOR COLISTIN IN PATIENTS WITH SEPSIS OR SEPTIC SHOCK

Tania Sidana[1], Nusrat Shafiq[1], Ritika Kondel Bhandari[1], Nipun Verma[2], Surulivelrajan Mallayasamy[3], Vijay Ivaturi[3] , Nikhil Aravind[1]
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Background: Colistin is one of the last-resort antimicrobials used for the treatment of multidrug-resistant Gram-negative infections, particularly in patients with sepsis or septic shock. In this population, profound pathophysiological alterations such as organ dysfunction, hemodynamic instability, augmented or impaired renal clearance, and aggressive supportive therapies contribute to marked pharmacokinetic variability. Given the narrow therapeutic window of colistin and the associated risk of nephrotoxicity, a population pharmacokinetic (PopPK) model that is generalizable to patients with sepsis or septic shock is essential to support model-informed precision dosing. The objective of this study was to identify a generalizable PopPK model for colistin in patients with sepsis or septic shock

Methodology: A structured literature review was conducted using PubMed, Embase, and Scopus to identify published population pharmacokinetic models of colistin developed in critically ill patients with sepsis or septic shock. Models were screened using predefined inclusion criteria focusing on relevance to sepsis or septic shock populations, intravenous administration of colistimethate sodium, availability of model equations and parameter estimates. Selected models will be implemented and replicated using the PUMAS 2.6 package in Julia 1.10.6. For each study, a typical septic patient profile will be constructed using reported mean or median demographic characteristics and corresponding dosing regimens. Model-predicted colistin exposures will be compared with published values to assess replication accuracy. A cross-validation framework will also be applied. Predictive performance will be assessed using quantitative metrics, including root mean square error.

Results: Five population pharmacokinetic models met the inclusion criteria, and model implementation is currently ongoing. Upon successful model replication, cross-validation will be performed for the selected models to assess their predictive performance across different study populations.

ICC047

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Conclusion: Systematic replication and cross-validation of published population pharmacokinetic models will enable the identification of a generalizable model for colistin in patients with sepsis or septic shock. The selected model will subsequently undergo external evaluation using prospective clinical data and may support model-informed precision dosing to improve therapeutic outcomes in this population.

ICC048

TO DEVELOP A FRAMEWORK FOR INDIVIDUALIZED PATIENT DOSING FOR MEROPENEM IN PATIENTS WITH CIRRHOSIS AND SEPSIS OR SEPTIC SHOCK THROUGH EVALUATION OF CLINICAL AND MICROBIOLOGICAL COVARIATES OF SIGNIFICANCE: A PRELIMINARY PILOT STUDY

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Objective: Standard antimicrobial regimens often fail in critically ill patients because sepsis-induced physiological alterations especially inflammatory capillary leak and third-spacing which expand the volume of distribution and reduce drug concentrations, compromising exposure. Meropenem, a broad-spectrum carbapenem used as empirical therapy in sepsis and septic shock, is particularly affected by these alterations. In cirrhosis, liver failure further perturbs antibiotic pharmacokinetics by altering drug distribution and clearance. Small cohorts of patients with acute-on-chronic liver failure have already demonstrated a markedly increased volume of distribution of meropenem. However, robust data on meropenem pharmacokinetics specifically in patients with cirrhosis sepsis or septic shock remain limited. This pilot study aims to characterize meropenem pharmacokinetics in this population and explore the influence of key clinical, disease severity, and microbiological covariates on drug exposure.

Methodology: This ongoing single-centre prospective pilot study includes a small cohort of adult patients with cirrhosis receiving meropenem as part of standard clinical care for sepsis or septic shock. Serial plasma samples are collected using a sparse sampling strategy, and meropenem concentrations are quantified using a validated liquid chromatography-tandem mass spectrometry (LC–MS/MS) method. Pharmacokinetic analysis is performed to estimate meropenem exposure parameters. An exploratory assessment of clinically relevant covariates is undertaken, including demographic characteristics, renal function indices (serum creatinine and creatinine clearance) and liver disease severity measures like Model for End-Stage Liver Disease–Sodium (MELD-Na) score, Sequential Organ Failure Assessment (SOFA) score, and Chronic Liver Failure–Consortium Organ Failure (CLIF-C OF) score. Additional clinical variables include the number and type of organ failures. Microbiological variables such as the site of infection, infecting organism, and antimicrobial susceptibility patterns are evaluated descriptively to contextualize pharmacokinetic exposure.

ICC048

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Results: Pharmacokinetic analysis of meropenem in the enrolled pilot cohort is currently ongoing. Summary pharmacokinetic parameters and exposure profiles will be presented. Exploratory analyses will describe inter-individual variability and examine trends between meropenem exposure, disease severity, organ dysfunction, and microbiological characteristics.

ICC049

IDENTIFICATION AND EVALUATION OF GENERALIZABLE POPULATION PHARMACOKINETIC MODEL OF VORICONAZOLE IN FUNGAL INFECTIONS.

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Background: Voriconazole (VRC) is used as a first-line antifungal agent for invasive fungal infections. However, its variable pharmacokinetics often result in subtherapeutic or toxic concentrations. The objective of the study was to identify a Generalized population pharmacokinetics model (PopPk) of voriconazole in critically ill adults for individualized dosing.

Methodology: A systematic literature review was conducted using PubMed and Web of Science to identify published Voriconazole (PopPK) models. Models were selected based on inclusion criteria, such as the adult population, covariates (albumin, body weight, and GGT), and exclusion of genetic polymorphism. The selected models were (Chen et al., 2015: CL = 3.9 L/h ; Chantharit et al., 2020: CL = 2.1 L/h; Khan-Asa et al., 2020:CL = 3.43 L/h; Wang et al., 2023:CL = 3.22 L/h) replicated using the Pumas v2.7 software in Julia 1.15, by extracting demographic data, parameter estimates (e.g., CL 1.45-4.34 L/h, V 97-132 L), and covariates to ensure an accurate replication of the model. The replicated model was compared with the literature model to assess the accuracy of replication. A cross-validation framework was implemented, where each model served as a reference and was evaluated against the typical populations and the dosing characteristics of the remaining models. The model that has the relative root mean square error (rRMSE <20%) was selected as the generalizable model. Further, it will then undergo prospective evaluation using clinical data.

Results: Replication of all selected models was successfully completed, and cross-validation is currently in progress. The model developed by Chen et al. is being used as the reference in the initial cross-validation phase, with the remaining models to be evaluated subsequently.

Conclusion: Full cross-validation will identify the most generalizable model, which will then be externally evaluated and implemented clinically.


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