SMi Presents the 13th Annual Conference on...

ADMET

Exploring the optimisation of ADMET modelling techniques, preclinical DMPK applications and development of biopharmaceuticals

HOLIDAY INN KENSINGTON FORUM, LONDON, UK

HIGHLIGHTS IN 2018:

• Discuss cutting-edge toxicology research strategies and how they enable early prediction of drug-induced liver injury (DILI)
• Understand the correlation between drug exposure, efficacy and toxicity in transporter-mediated drug interactions
• Hear about Genentech’s novel hepatocyte transporter assay used to predict the pharmacokinetic profiles of target compounds
• Explore unique applications of PKPD modelling in oncology
• Gain insight into the advances in models for the prediction of human drug metabolism

CHAIR FOR 2018:
• Eric Blomme, Vice President, Global Pre-Clinical Safety, Senior Research Fellow, AbbVie

FEATURED SPEAKERS:
• Justin Pittaway-Hay, Pharmacokinetic Assessor, MHRA
• Filipe Lopes, Laboratory Head, DMPK, Roche
• Nenad Manevski, Senior Scientist, DMPK Design Lead, UCB Pharmaceuticals
• Sheila Annie Peters, Head, Translational Quantitative Biology, Merck Serono
• Andreas Reichel, VP, Head of Research Pharmacokinetics, Bayer AG
• Laurent Salphati, Principal Scientist, Genentech
• Timothy Schulz-Utermoehl, Director of DMPK and Physical Sciences, Sygnature Discovery
• Kunal Taskar, Senior DMPK Investigator, GSK
• Robert Van Waterschoot, Head of Pharmacokinetics, Dynamics & Metabolism PDM Leaders, Roche Pharmaceuticals
• Ian Wilson, Professor, Drug Metabolism and Molecular Toxicology, Imperial College London
• Peter Littlewood, Director of DMPK, Vertex Pharmaceuticals

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09.10 Novel technologies and computational tools in discovery toxicology: opportunities and challenges

- Driving nonclinical safety-related attrition to sustainable levels
- Technologies to define target-related safety
- Computational prediction of off-target interactions
- Opportunistic use of in vitro models to tackle complex toxicity issues

Eric Blomme, Vice President, Global Pre-Clinical Safety, Senior Research Fellow, AbbVie

09.50 How advanced are our in vitro discovery toxicity assays for predicting DILI risks?

- Generating an understanding as to when predictive in vitro screening should be performed in discovery
- Use of case studies to qualify the predictability of the available in vitro assays
- Defining if potential metabolites should be screened alongside the active drug

Timothy Schulz-Utermoehl, Director of DMPK and Physical Sciences, Sygnature Discovery

10.30 Morning Coffee

11.00 Understanding the correlation between drug exposure, efficacy and toxicity in a transporter mediated drug-drug interaction

- Pushing towards more accurate and efficient drug testing in vitro, and most importantly leading the way towards a reduction in animal testing
- Examples of novel toxicity test platforms: embryonic stem cells
- Organ-on-a-Chip: CN Bio Innovations Limited’s collaboration with AstraZeneca to validate a new in vitro research tool that enables the high throughput evaluation of multi-drug dosing regimens
- Ex Vivo – The best design to establish causality and to detect effects?

Kunal Taskar, Senior DMPK Investigator, GSK

11.40 The importance of ADMET in medicines regulation: First in human studies and dose-exposure-response analyses

- Regulations concerning FHI studies and PBPK modelling and simulation: ADMET considerations
- Importance of demonstrating dose-exposure response relationships
- Extrapolation of PK and role in paediatric populations

Justin Pittaway-Hay, Pharmacokinetic Assessor, MHRA

12.20 Networking Lunch

13.20 Use of early dose prediction and ADMET properties to guide chemical design

- Early dose predictions can be used to guide chemical design and prioritise efforts.
- Multi-parameter design improves quality of drug-like properties.
- Metabolic stability, permeability, and solubility are linked with toxicological outcomes.

Nenad Manevski, DMPK Design Lead, Senior Scientist, Biotransformation and Enzymology, UCB Pharma

14.00 PKPD – Strengths and limitations of compartmental modelling

- The making of a successful drug candidate
- Defining parameters in acute and chronic toxicity evaluations
- Drug safety testing – should we be aiming at more fluid constructs?
- Cost-benefit assessments

Sheila-Annie Peters, Head, Translational Quantitative Pharmacology, Merck Serono

14.40 Afternoon Tea

15.10 The use of precision-cut lung slicing model to study pulmonary disposition of a drug

- Assessment of the pulmonary CYP1A1 metabolism of mavoglurant in rat
- Functional assessment of rat pulmonary flavin-containing Monoxygenase activity
- Optimization of the precision cut lung slices (PCLS) as a useful tool for assessment of the pulmonary drug disposition in rat and human

Yildiz Yilmaz, Pharmacokinetics, ADME and Biotransformation, Novartis

15.50 Applications of PKPD modelling in oncology – an overview

- Binary safety/efficacy endpoints are simplifications and often based on relatively arbitrary thresholds of underlying biological longitudinal process
- Patients’ individual characteristics may have as big impact on e.g. safety response as solely a dose
- Processes underlying dose-limiting toxicities in oncology are often reversible therefore how do we best manage toxicity?
- PK and PKPD time-course described via a mechanistic model, thus may be used for predictions, where fixed AND random effects are estimated

Pau Aceves, Associate Director, Certara Strategic Consulting

16.30 Chairman’s Closing Remarks and Close of Day One

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Human PK and dose predictions for compounds with challenging physicochemical profiles

- Understanding the physicochemical properties of a compound: solubility, stability, form definition, solid-state properties, partition coefficient and ionization constants
- The optimization of these properties is fundamental to the drug discovery process, mainly due to their influence on absorption and distribution in vivo.
- Alterations of physicochemical properties such as molecular weight, log D, polar surface area or pKa may influence the absorption, distribution, metabolism or excretion (ADME) of a chemical series in a chemotype-dependent manner
- Application of mechanistic approaches to solving ADME issues provides insight as to why a change in properties causes a desired outcome in some cases, while leading to poorer outcomes in others.

Peter Littlewood, Director of DMPK, Vertex Pharmaceuticals

Biotransformation of biotherapeutics – impact on candidate selection

- Metabolism of small-molecule drugs vs. biotherapeutics
- Impact of protein biotherapeutics biotransformation on bioanalysis
- Workflows for studying protein biotherapeutics
- The future of the field

Filipe Lopes, Laboratory Head, DMPK, Roche

Impact of target interactions on small-molecule drug disposition: an overlooked area?

- Relevance of target-mediated drug disposition (TMDD) for small molecules
- Impact of TMDD on pharmacokinetic parameters
- Consequences of TMDD in human micro-dosing studies
- When and how to evaluate TMDD for small molecules?

Robert Van Waterschoot, Head of Pharmacokinetics, Dynamics & Metabolism PDM Leaders, Roche Pharmaceuticals

Distribution, Metabolism and Excretion – Hepatocyte transporters, a case study of Genentech

- In vitro and in vivo techniques used to predict pharmacokinetic profile of a compound at a pre-clinical stage
- Explore the use of an assay developed to measure the disposition of a compound from hepatocytes into the blood
- Transport systems include transporters for amino acids, monocarboxylic acids, organic cations, texoses, nucleosides, and peptides and most of these function in the direction of [mainly] efflux from liver to blood

Laurent Salphati, Senior Scientist, Genentech

Advances in models for the prediction of human drug metabolism

- Avoiding problems in drug development requires good methods for the prediction of drug metabolism/toxicology
- Accurate models that to predict liver-based metabolism in humans are needed
- Liver humanised models in rodents based on genetic modification or “chimeric” livers show some promise in this area
- The pros and cons of the use of each type of systems will be described and illustrated with examples

Ian Wilson, Professor, Drug Metabolism and Molecular Toxicology, Imperial College London

Intracellular pharmacokinetics: Emerging opportunities for tailoring project support

- Free drug levels in plasma are generally used as measure for drug concentrations at the pharmacologically active site, serving as appropriate exposure surrogate for setting-up PK/PD models of extracellular drug targets
- About 50% of therapeutic drug targets, however, are thought to reside in the inside of cells where unbound drug concentrations may be very different from those on the outside, i.e. in the interstitial space and in the plasma compartment
- The presentation will discuss i) mechanisms that control intracellular drug concentrations, ii) experimental approaches that are suitable to estimate unbound intracellular concentrations in selected cell types, and iii) their applicability to advance our understanding of intracellular drug-target interactions
- Initial case studies will be shown to illustrate how the field of ICPK can offer novel opportunities that can be used to address key questions in drug discovery projects, thereby enhancing our understanding of the intracellular fate of drugs - a topic of growing impact and interest

Andreas Reichel, VP, Head of Research Pharmacokinetics, Bayer AG

Towards a fully PBPK compliant ADME-MOC

- Introduction to Multi-Organ-on-chip (MOC) solutions
- The 4-Organ-Chip: A first proof of concept for ADME-studies
- A PBPK modelling approach for Multi-Organ-Chips
- Current and future applications

Reyk Horland, Head of Business Development, TissUse

Networking Lunch

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