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Highly Satisfied Participants at the Sixth International Drug-Drug Interaction (DDI) Workshop 2015 at Marbach Castle, Germany

Gelnhausen, Germany, May 21, 2015: At the sixth International Drug-Drug Interaction Workshop more than 80 experts discussed regulatory requirements and current scientific aspects on the preclinical and clinical investigation of drug-drug interactions. Several scientific highlights proved the high quality of this meeting and the DDI Workshop participants confirmed in the feedback protocols that they were highly satisfied with the 6th DDI Workshop at Marbach Castle.

The Drug-Drug Interaction Workshop series at Marbach Castle enjoys an unbroken popularity and the number of participants has remained consistently high over the years. The organizers of the DDI Workshop are highly pleased to see that the DDI Workshop is widely recognized and well established. This year the DDI Workshop was fully booked several weeks before the Workshop started.

Robert Hermann, member of the organization team, states: “Again the feedback of the participants was very positive and the organization team is very satisfied that the scientific programme was well accepted. All speeches and presentations of the meeting were scientifically on a very high level and the positive assessment of the Workshop participants generates a big challenge for the organization team to prepare such high quality meetings also in the upcoming years.”

Five scientific sessions were designed to focus on drug-drug interactions involving clinical aspects, regulatory aspects, determination of intracellular drug concentrations as well as influences on drug safety. The issues were covered by distinguished international scientists and experts from academia, pharmaceutical companies, contract research organizations, consultancies as well as governmental and regulatory agencies.

In Session I (Clinical Aspects of Drug-Drug Interactions) Yuichi Sugiyama from the RIKEN Innovation Center, Japan presented complex DDIs in the clinical setting and David Juurlink from the Sunnybrook Health Science Center, Canada talked about how to explore DDIs in real-world clinical practice. Sugiyama showed the clinically relevant DDIs between Cimetidine (CMD) and some OCT2/MATEs transporter substrates in the kidney. A broad variety of drugs have been identified as inhibitors of OCTs or MATEs transporters. Kinetic analyses based on the extended clearance concept indicated

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that the inhibition of MATEs, but not OCT2, is a likely mechanism underlying the drug-drug interactions with cimetidine in renal elimination.
Juurlink demonstrated how the understanding of the clinical relevance of DDIs can be advanced through the intersection of clinical epidemiology and clinical pharmacology. He showed that the availability of vast amounts of anonymized healthcare data has the potential to support research on the consequences of DDIs in clinical practice.

In Session II (Regulatory aspects of drug-drug interactions) Anna Nordmark from the swedish Medical Products Agency presented the European regulatory perspective on the use of PBPK in assessing DDIs. Alice Ke from Certara, USA presented alternatives to ketoconazole for clinical CYP3A-inhibition studies to quantify victim DDI potential of sensitive CYP3A substrates. Lawrence Lesko, from the University of Florida, USA presented as first key note speaker the current FDA approaches to food-drug, drug-drug and gene-drug Interactions. Nordmark discussed a concept paper with the title “Qualification and reporting of PBPK modelling and analyses”, which was released in 2014 as well as a corresponding guideline, which is under preparation. Case reports with PBPK modelling were presented. Lesko reported from a workshop ““Evaluating and Modernizing Approaches for Food-Effect Assessments” and presented a summary of this workshop, the recommendations of the Innovation and Quality Consortium (IQC, PhRMA).

In Session III (two tutorials) Jan Snoeys from Janssen, Belgium covered PBPK DDI simulations in support of Janssen regulatory submissions, and Robert Hermann from cr.appliance, Germany presented clinical trial designs to successfully examine DDIs. Snoeys gave an overview of the Janssen strategy with regard to applications of PBPK modelling and simulations for internal decision making and for regulatory interactions. The presentation of Hermann focused on general trial design considerations for mechanistic PK-studies, thereby considering recommendations of pertinent DDI guidelines as well as a set of DDI studies published over a 5 year period in three renowned international Clinical Pharmacology Journals.

Yuichi Sugiyama, the second key note speaker, addressed in his lecture “Importance of Knowing the Rate-Determining Process in Predicting Complex DDIs from in vitro Metabolism and Transport Data” the changes in pharmacokinetics due to genetic polymorphisms and drug-drug interactions. Transporters often can have an effect on the therapeutic safety and efficacy of many important drugs. He showed how to use the “Extended Clearance Concept” and to establish a PBPK model that includes the transporter-mediated membrane transport and enzyme-mediated metabolism processes.

In Session IV (Determination of intracellular drug concentrations) Avijit Ghosh from Johnson & Johnson, USA discussed in his talk “Accounting for permeability of ionised form and implications for PD as well as DDIs” important determinants of tissue drug concentrations. Bernard Faller from Novartis, Switzerland showed the coexistence of passive diffusion and active transport controlling intracellular drug concentrations, and Hartmut Derendorf from the University of Florida, USA presented

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plasma protein binding and its implications for intracellular drug concentrations. Ghosh presented a systems pharmacology modeling approach, which allows to use physicochemical properties of a molecule to optimally drive unbound tissue distribution. In particular, the modeling can be used to maximize the therapeutic index of a target. Faller gave an overview of the relative importance of active transport versus passive diffusion in drug discovery based on experience accumulated with measurements of thousands of compounds in both biophysical and cellular uptake models. Derendorf demonstrated in his presentation that protein or other binding usually is of PK/PD-relevance. Furthermore, he showed experimental techniques to measure and to estimate the unbound, aqueous concentration near the target site.

In Session V (DDI influencing Drug safety issues) Daniel J Antoine from the University of Liverpool, UK, spoke about hepatotoxic consequences of DDIs: Case studies and possibilities to predict them, and Sebastian Polak from the Jagiellonian University Krakow, Poland talked about the narrowing down of channels for DDIs leading to cardiac safety: A combined PK and PD problem and promises of the IVIVE approach. Antoine showed that advances in the development of DILI (Drug-induced liver injury) registries have shown that typically 20% of patients with DILI are prescribed multiple agents and of the patients that die or require a liver transplant, 30% of these DILI patients are prescribed multiple agents. Clinical and pre-clinical studies of acetaminophen (APAP) overdose have shown the identification and development of circulating biomarkers that provide enhanced hepatic specificity (miR-122) and can inform on mechanistic events such as necrosis (keratin-18, HMGB1), apoptosis (caspase-cleaved keratin-18), mitochondrial dysfunction (glutamate dehydrogenase) and inflammation (acetylated HMGB1). The integrated use of these biomarkers and novel test systems were discussed in the context of understanding fundamental hepatology, mechanistic drug safety science and predicting relevant DDIs for DILI in man. Polak stated that cardiovascular toxicity remains one of the leading causes of early and late attrition during drug development process and presented the IVIVE approach combining mechanistic PK and PD models, which offers new possibilities in the field of drug-drug interactions prediction. He discussed a Cardiac Safety Simulator simulating pseudoECG signals which were further analyzed to calculate QT/QTc and presented results indicate that mechanistic IVIVE can be used to predict clinical effects resulting from drug-drug interactions at both PK and PD level.

This year the poster presentation was on the first day and selected posters were presented orally in an additional session on the second day.

This year's DDI Workshop Marbach Castle can be considered again as a top-class international scientific event and the Organization Team is highly motivated to work on a new programme for 2016. The DDI Workshop 2016 is scheduled for May 29 to 31, 2016.

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About the DDI Workshop

The DDI Workshop is an initiative of cr.appliance in cooperation with Hartmut Derendorf, Amin Rostami-Hodjegan, and Oliver von Richter. The meeting will take place at Marbach Castle Conference Centre, located at the Lake Constance, Germany.

The organizers of the DDI Workshop are:

- Hartmut Derendorf, PhD FCP; College of Pharmacy, University of Florida, USA
- Robert Hermann, MD FCP; cr.appliance, Germany
- Amin Rostami-Hodjegan, PhD FCP; Faculty of Medical and Human Sciences, University of Manchester, UK
- Oliver von Richter, PhD FCP; Dept. Exploratory Medicine, Merck Serono, Germany

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The team of experts has undertaken successful project work in the pharmaceutical industry as well as work in the service sector (CROs), hospitals and academia. The team has a wealth of well-founded, up-to-date expertise.
This, combined with many years of professional experience in a number of specialist fields and areas of work, enables them to provide high-quality consultancy, create sustainable and viable development concepts and offer customer-specific services in various aspects of drug development.

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