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The 5th Drug-Drug Interaction (DDI) Workshop at Marbach Castle is highly rated by participants

Gelnhausen (Germany), 20th June 2014 – More than 70 experts in drug development and drug-drug interactions from 14 countries took part in the scientific meeting entitled "DDI 2014 – 5th International Workshop on Regulatory Requirements and Current Scientific Aspects on the Preclinical and Clinical Investigation of Drug-Drug Interactions" at Marbach Castle on Lake Constance between 25 and 27 May. Feedback on the workshop from participants was consistently positive. The DDI Workshop is now confirmed as a scientific platform that has proven itself as an event for the exchange of ideas between representatives from academic, regulatory health authorities and industry. This was also evident at the anniversary event this year, which focussed on new approaches to studying drug-drug interactions in drug development, the significance of transporter based interactions, and the new draft of the Japanese guideline. These areas were also complemented by the topic of food-drug and herb-drug interactions. The new addition of a poster presentation was well received and is to be included in the programme again next year.

This is now the fifth year in which experts in drug development and drug-drug interactions have met at Marbach Castle on Lake Constance to discuss the latest scientific findings and developments concerning regulatory authorities and in the pharmaceutical industry. The meeting enjoys an unbroken popularity and the number of participants has remained consistently high over the years. Some participants and speakers have been involved from the start and attend the workshop every year. It is therefore no surprise to the organisers that this year's feedback on the 5th DDI Workshop was decidedly positive and that there was demand for this series of events to be continued.

Robert Hermann, member of the organisation team explains: "Over the years we have been able to show that at Marbach Castle we bring together experts who guarantee a high scientific standard in the lectures. We have also succeeded in making advances with internationalisation of the event. The participants this year came from 14 countries. They gave presentations and discussed topics such as the work on the new Japanese guideline, which was linked with a higher proportion of participants from Asia. This combination of science and regulatory framework conditions for drug development is what makes the workshop series so unique and attractive for participants from academic, health authorities and the industry. We are thrilled that this has been such a success in the last five years."

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In the key note lectures, Lloyd Stevens from Nottingham (UK) and Andrew Parkinson from Shawnee (USA) spoke about the current level of knowledge on mass balance and metabolic versus transporter based DDIs, Akihiro Hisaka and Kazuya Maeda from Tokyo (Japan) presented the work on the new PMDA guideline, and Werner Weitschies from Greifswald (Germany) and Veronika Butterweck from Basel (Switzerland) discussed the influences of food and the impact of herbal drugs on the bioavailability of concomitant medications.

Lloyd Stevens assessed the various study methods in bioanalysis for determining the pharmacokinetic parameters of an active ingredient and underlined the importance of high-resolution mass spectrometry in conjunction with chromatographic separation. The use of the microdosing method as an elegant way of rendering some toxicological studies needless was also highlighted.

Andrew Parkinson added transporter proteins to the pharmacokinetic world of ADME (absorption, distribution, metabolism, elimination) to produce an ADMET world. A physicochemical assessment of an active ingredient can be used to evaluate whether metabolism or transport is at the forefront. The logP and TPSA (total polar surface area) of the substance are used as parameters here. This assessment will aid decision-making for upcoming in vitro and in vivo studies.

Akihiro Hisaka and Kazuya Maeda focussed in particular on the differences between the Japanese draft DDI guideline and the FDA and EMA guidelines. The three guidelines have great similarities in large parts – something that is very much welcomed by the industry. The draft of the PMDA guideline, however, contains some new scientific findings, in particular for transporter based DDIs. In Japan, value has also been placed on improving the drug labeling and thus producing greater drug safety. In this regard, DDIs found in the contraindications of a drug are of particular significance. As already seen in the other guidelines, PBPK (physiology based pharmacokinetic) modelling is becoming increasingly important in the PMDA guideline too.

Werner Weitschies gave an overview of the influences of food on the bioavailability of drugs and in particular went into recent therapeutic agents for cancer that can be administered orally, for which the influence of food and the dosage recommendations need to be re-assessed due to the evidence available today. For therapeutic agents with significant food-drug interactions, the previously recommended intervals of one hour before a meal and two hours after a meal may be insufficient. This must be checked on a case-by-case basis.

Veronika Butterweck reiterated that the evidence from the current studies on herb-drug interactions is very weak. In most cases, the current data for evidence-based assessment cannot be used. There is a lot of catching-up to be done here. Reliable data on interactions of herbal drugs with active ingredients that have a narrow therapeutic window and are used in at-risk patients with cancer, HIV or organ transplants is key.

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Oliver von Richter from Darmstadt (Germany) expanded on Butterweck's key note lecture with his discussion of the study of herb-drug interactions. He too pointed to the large gaps in knowledge, which despite a rising number of studies have remained unresolved for some time. Suitable clinical studies remain few and far between and focus on CYP enzymes. There has been virtually no systematic study of transporter based interactions thus far.

Beyond the key note lectures of the 5th International DDI Workshop, presentations on transporter based DDIs (tDDIs) played a major role. Henriette Meyer zu Schwabedissen, Martin Fromm and Robert Hermann spoke about this topic.

Henriette Meyer zu Schwabedissen from Basel (Switzerland) reported on tDDIs in the liver. Using the example of statins, she demonstrated how influences on hepatic uptake by OATP1B transporters affect the pharmacokinetics of various statins. ABCB11 (BSEP) was explored in more detail as another key hepatic transporter protein. This protein is responsible for the active efflux of substances from the hepatocytes in the bile.

Martin Fromm from Erlangen (Germany) reported on tDDIs in the kidneys. Here, transporters such as OAT are responsible for the cellular uptake through the basolateral membrane and transporters such as MATE are responsible for the cellular efflux of a drug into the urinary compartment via the apical membrane. The effects of tDDIs on the systemic exposure to metformin and digoxin were presented.

Robert Hermann reported on the consideration of endogenous substances in tDDIs. Changed plasma levels of safety parameters such as serum creatinine and serum bilirubin during the course of drug development as finding for a new active ingredient are always challenging. Many discussions and studies follow such finding and a clear assessment and clarification of the causative mechanisms is still down to the developer team in such cases.

Lawrence Lesko from Gainesville, Florida (USA) reported again on how much work has gone into the new FDA guideline, which is yet to be published in its final version. This investment is however necessary to further improve drug safety and ensure that the scientific findings now available are adequately assimilated. The importance of PBPK modelling was highlighted yet again, as not all issues can be resolved by means of clinical studies. Simulations on the basis of in vitro and in vivo data are necessary and practical. Amin Rostami-Hodjegan from Manchester (UK) summarised the current state of the discussion on PBPK modelling and reported a total of 80 submissions and 4 changes in drug labeling for which PBPK modelling had been applied. In his lecture, Dietmar Schwab from Basel (Switzerland) emphasised the needs of the industry and advocated extensive harmonisation of the various guidelines in individual countries. He viewed strict compliance with the guidelines in the early development phase of a drug as a risk. Here, a quantitative and integrated understanding of the active ingredient and its properties may be the better precondition for assessing and predicting potential drug-drug interactions.

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The success of this year's excellent event has motivated the organisation team to continue the series of events. The 6th DDI Workshop at Marbach Castle will take place on 3-5 May 2015. The poster presentation introduced this year was well received and will also be held next year.

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 in 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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