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High Scientific Level at the Second International Workshop about Drug-Drug Interactions at Marbach Castle, Lake Constance

The organisation team of the Second International DDI (drug-drug interactions) Workshop has expressed great satisfaction with the course of the scientific meeting. This was also confirmed by the outcome of a feedback survey given to the participants. Both the scientific level of the presentations and discussions as well as the breadth of the topics covered were judged positively. Many already expressed interest in the third DDI Workshop in 2012. Thus the DDI Workshop at Marbach Castle is on its way to become an established platform for the annual exchange between experts, scientists, members of the industry and regulatory bodies regarding DDI affairs.

This year more than 60 experts from 11 countries attended the meeting. Six of the 13 presenters traveled from the USA to the Marbach Castle which clearly highlighted the international character and the scientific standing of the meeting. The topics of interactions of biologicals (large molecules, e.g. proteins and antibodies), development of guidelines from the regulatory agencies in Europe and the USA, the influence of modeling and simulation for the regulatory assessment of complex interactions, pharmacokinetics and pharmacodynamics of drug-drug interactions in specific therapeutic indications and DDIs at the level of drug absorption were covered in five separate sections. In these sections drugs indicated against cancer, infectious- and cardiology diseases as well as immunosuppressants were discussed in more detail. Further the influence of food and formulation on drug absorption and transporter based DDIs regarding hepatic absorption and elimination were discussed.

For the second time the conference center at the Marbach Castle hosted an international workshop about drug-drug interactions. These interactions have gained increasing significance in clinical practice as well as in drug development. In his introductory presentation Robert Hermann presented the impressive and constantly growing numbers for the indications of drug-drug interactions and explained their development. The rising percentage of older patients, often with many chronic illnesses, in developed countries, combined with poly-pharmacotherapy in these patients is causing an increase in side effects of therapies in general and a drastic raise in the risk of unwanted drug-drug interactions in particular.

However, the discovered and documented cases are only representing the tip of the iceberg. Many unnoticed “silent DDIs” not characterized by recognizable side effects but only by a decreased or abolished efficacy of certain drugs, remain unnoticed. A well-established example for this is the concomitant treatment of breast cancer patients with tamoxifen and certain antipsychotic drugs, which inhibit the necessary metabolic activation of tamoxifen. The anti-tumor effects of tamoxifen can be entirely blocked by such antipsychotic drugs. Because of the increased frequency of this kind of drug interactions, experts have denoted the problem as a “silent epidemic”.

So the great significance the topic will have for medicine and drug development was established early in the meeting. Studies in the US have shown that 2.8 percent of all hospitalizations can be attributed

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to adverse drug effects of which 6 to 30% are represented by unwanted drug-drug interactions. No solid basis of information has been established for physicians, which would allow for the prevention of DDIs. Comparison between the most important standard compendia covering drug-drug interactions revealed significant differences and inconsistencies between these sources of reference. This situation has to be improved exigently to reduce the number of complications in the context of poly-pharmacotherapy.

More data from the US has revealed that roughly 30% of all patients over 60 years are receiving more than five prescription medicines. This does not include the number of over the counter medicines and supplements that many of these patients are taking on top of their prescribed medicines and which have been shown to display interactions with certain drug. For example the interaction of St. John's wort or grapefruit juice with a variety of drugs is well known.

A central topic, already much discussed last year, were the guidelines of the European and US agencies for the study of drug-drug interactions for regulatory approval of new molecules. Last year the newly developed draft of the new EU DDI guideline was presented and discussed. This year the comments regarding this guideline, collected by the workshop organizers, could be discussed. The comments received great approval by the participants in the discussion which reiterated that further modifications of the draft are desirable. The quite considerable „Safety Margins" for the assessment of in-vitro results were criticized. The participants noted that this could lead to an unnecessary number of clinical interaction studies with low information value, resulting in a misallocation of research budgets.

For the US a publication of the existing guideline is expected this year. This will allow the discussion of both the finalized version of the EU as well as the new draft version of the FDA guideline at the next DDI workshop.

Another important point, as indicated by the spirited discussion of the participants, was the coverage of drug-drug interactions of large molecules (biologicals). Much less data exists for those products compared to small molecule based medicines. Oliver von Richter impressively described the fundamental differences between large molecule and small molecule drugs, according to their pharmacokinetic properties. This also explains their respective potential to interact with other molecules and structures. In the meantime biologicals have come to represents 10 to 20 percent of newly approved drugs which highlights the importance of more thorough studies of their drug-drug interaction properties. Important approaches to study the interaction potential of biologicals in terms of cytochrome P450 enzyme suppression in vitro were presented by Andrew Parkinson in the form of the assessment of cytokine release from peripheral blood mononuclear cells (PBMCs) and the use of co-cultures of hepatocytes and hepatic macrophages (Kupffer cells).

In the area of specific indications particularly interesting discussions about drug-drug interactions were conducted in the field of oncology. Alex Sparreboom unmistakably stated that due to several reasons not enough attention is paid to drug interactions in this particular field. This is true for the treatment with established compounds as well as for the development of new drug candidates. Often, the ethics committees, fearing a loss in efficacy, are opposing systematic studies of drug-drug interactions of oncology drugs. Here new study designs are necessary of which ethics committees have to be convinced of. In his presentation Karthik Venkatakrishnan introduced several scenarios for the integration of drug-drug interactions in the drug development process. Without a doubt the difficulties in the oncological drug development stem from the lack of Phase 1 clinical trials with healthy volunteers. This complicates a systematic and inclusive study of drug-drug interactions in the context of the particular challenging ethical circumstances of oncological diseases.

Apart from oncology, drug-drug interactions in the fields of immunosuppressants, anti-infectives and cardiology were introduced by Uwe Christian, Hartmut Derendorf and Wilhelm Haverkamp

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respectively. Special attention was paid to the unwanted QT/QTc interval in the ECG for cardiology drugs and its significance for poly-pharmacotherapy was highlighted. A lengthening of the QT interval in the ECG is a risk marker for the development of life threatening ventricular arrhythmias, e.g. Torsade de pointes.

The discussions at this year's DDI workshop put emphasis again on the fact that drug interactions could become a critical point in drug development and are also gaining strategic impact. First of all, considering an increasing public sensitivity towards drug safety, it is becoming ever more important for the pharmaceutical industry to determine the correct deployment of new substances even before the regulatory approval through controlled clinical studies. This will help to prevent the occurrence of unforeseen safety risks immediately after product introduction. Secondly, the requirement of too many small DDI studies, following the interpretation of in-vitro and Phase 1 data, would result in longer development times and higher research expenditures. Therefore M&S (modeling and simulation) are gaining importance to keep the effort in a reasonable balance. This is being accepted by the regulatory agencies and the FDA has recently addressed this problem in particular with complex interactions. Amin Rostami-Hodjegan explained that PBPK (physiologically-based pharmacokinetic) models can give conclusive results regarding inhibition, induction or suppression of certain enzymes and transporters which in many cases allow for quantitative estimation of drug-drug interactions.

Michael Bolger, in his presentation, stressed the importance of models for food – and formulation interactions in the context of intestinal absorption. The presented studies showed how closely the simulations corresponded to data later collected from in-vivo studies.

Thomas Gramatte´ also explained the mechanism of drug-drug interaction influencing intestinal absorption. The demonstrated variability of absorption, in particular of molecules with low bioavailability, has immense consequences for the efficacy and safety of these drugs. The presentation also covered the issue of existing „absorption windows" for different drugs along the intestinal tract.

An interesting tool agent might also be NRL 972 (Cholyl-L-lysine-fluorescein) with which the transporter-based hepatic uptake and biliary excretion of respective transporter substrates can be determined. This was presented by Christian de Mey in his talk covering transporter based drug interactions influencing hepatic uptake and elimination.

As last year, the DDI Workshop at the Marbach Castle was accompanied by an industrial exhibition. Five specialized industry providers in the area of drug development attended the meeting.

Presenters at the Second DDI Workshop

Michael Bolger, PhD, Simulations plus Inc., Lancaster, USA
Uwe Christians, MD, PhD, University of Colorado, Denver, USA
Hartmut Derendorf, PhD, PhD, FCP, College of Pharmacy, University of Florida, USA
Thomas Gramatte´, MD, PhD, Drug Development Consulting, Munich, Germany
Wilhelm Haverkamp, MD, PhD, Department of Cardiology, Charite Berlin, Germany
Robert Hermann, MD, FCP, cr.appliance, Radolfzell, Germany
Krishna Machavaram, PhD, Symcyp Ltd., UK
Andrew Parkinson, PhD, XenoTech LLC, Lenaxa, Kansas, USA
Christian de Mey, MD, PhD, ACPS, Applied Clinical Pharmacology Services, Main-Kastel, Germany
Oliver von Richter, PhD, FCP, MerckSerono, Germany
Amin Rostami-Hodjegan, PharmD, PhD, FCP, Faculty of Medical and Human Sciences, University of Manchester, UK

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Alex Sparreboom, PhD, St. Jude Children's Research Hospital, Memphis, TN, USA
Karthik Venkatakrishnan, PhD, Millennium, Cambridge, MS, USA

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 took 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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cr.appliance uses its well-documented, recognised expertise to the benefit of its clients.
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.

More information about cr.appliance: http://www.cr-appliance.com

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