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Radolfzell, Germany, May 16th 2012

Valuable Scientific Discussions at the Third International DDI Workshop at Marbach Castle, Lake Constance

The organisation team of the Third International DDI (drug-drug interactions) Workshop has expressed great satisfaction with the course of the scientific meeting. The participants of the DDI Workshop commended the very high scientific level of the presentations and valuable and inspiring discussions of the different topics. Without a doubt, the DDI Workshop at Marbach Castle is a well established platform for the annual exchange between experts, scientists, members of the industry and regulatory bodies regarding DDI affairs. This year more than 80 experts from 14 countries attended the DDI Workshop. The speakers came from 6 different countries (USA, Germany, Great Britain, Finland, Sweden, and New Zealand), thereof 5 from the US. They presented scientific news, the content of the draft guidelines and state of the art lectures. The scientific sessions covered different aspects to current regulatory issues, UGT-based DDIs, transporter-based DDIs and pharmacodynamic DDIs.

The increasing share of seniors in all industrial societies triggers poly-pharmacotherapy. Hartmut Derendorf presented figures from Finland, where patients older than 80 years get 5 medicines on average. In the US 37 percent of the patients older than 65 years are receiving more than five prescription medicines and four additional OTC products, reported Larry Lesko. For the participants of the scientific DDI Workshop the social, medical and economic importance of drug-drug interaction is given and providers of health care and drug developers have to take the challenge for the achievement of an improved understanding and communication of drug interactions.

It's quite obvious that new medicines are underrepresented in standard compendia for drug-drug interactions. Often DDIs are only discovered after the introduction of a new medicine and respective information appears with the first revision of the labeling. There is definitely a gap in the information of health care professionals. Helen Winter specifically addressed this issue in her speech about the communication of drug-drug interactions. Additionally she talked about the appropriate format of the information which is also suboptimal.

The current revision of the DDI guidelines in Europe and the US expresses the increasing awareness and importance of drug-drug interactions. As expected, the discussion of the draft guidelines of EMA (European Medicines Agency) and FDA (Food and Drug Administration) was the central point of the DDI Workshop. Eva Gil-Berglund from the Swedish Medical Products Agency and the coordinator for the revision of the EMA DDI guideline presented the new parts of the draft guidance. She explained the main reasons for changing the existing guideline. One of the reasons is the increasing knowledge to transporter-based DDIs (tDDIs), which was an important topic of the workshop (presentations of Dietrich Keppler, Mikko Niemi, Caroline Lee, Sebastian Härtter, and Amin Rostami-Hodjegan). Many participants expressed in the forum discussion and in the polling session their unhappiness with the recommendations to tDDIs in the draft guidelines. The experts' fear is that new recommendations in the guidelines will trigger numerous – perhaps unnecessary – clinical studies. Larry Lesko, who assessed the recently published FDA draft guidance in his presentation, described this risk as a

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possible result of the current guideline revision. Larry Lesko was responsible for the evaluation of drug-drug interaction studies and held the position of a Director of Clinical Pharmacology in the FDA Center of Drug Evaluation and Research (CDER). He worked more than 20 years for the FDA. Today he is Director of the Institute of Pharmacometrics and Systems Pharmacology at the University of Florida. Beside the length of the FDA document (79 pages) Larry Lesko mentioned the number of decision trees with complex graphs and different possibilities of interpretation as critical points of the FDA draft guideline. Open questions are the review consistency, limited experiences with PBPK (physiologically-based pharmacokinetic) modeling of regulatory bodies as well as the application of new knowledge in useful recommendations to health care professionals. Drug developers from the pharmaceutical industry pointed out that the guidelines should not include too many obstacles.

The quite considerable „safety margins“ (e.g. 50 fold of maximum plasma concentration c_{max}) for the assessment of in-vitro results were criticized as in the year before. The “safety margins” define the necessity for clinical DDI studies based on in vitro data. False positive in vitro results could lead to an unnecessary number of clinical interaction studies with low information value, possibly resulting in a misallocation of research budgets.

In several presentations special attention was paid on pragmatic and affordable approaches for the investigation of DDIs. It’s a question of balancing the scientific requirement to investigate all aspects and the costs of drug development. “Nobody can study them all (DDIs) before a new medicine is approved”, said Larry Lesko and put emphasis on the fact to observe and document interactions with more effort after the launch of a new medicine.

Induced by the guideline revisions, the discussion of tDDIs was very intensive. The decision process in clinical development is not sufficiently supported as yet by in vitro models. So presentations focused on PBPK modeling as a supplemental approach to in vitro models. Amin Rostami-Hodjegan presented new approaches for the investigation of DDIs and showed that PBPK modeling information as part of NDA submissions increased dramatically (12 fold) in the last years. Additionally Mikko Niemi talked about active drug uptake by liver cells and what that means for drug-drug interactions. A closely related topic was covered by Dietrich Keppler from the German Cancer Research Center (DKFZ) in Heidelberg. He highlighted active drug excretion processes of liver cells. Caroline Lee gave an overview to methodological challenges connected with the FDA recommended in vitro models. She discussed the importance and role of K_i und IC_{50} values in defining the basis of "safety margins". She recommended the use of IC_{50} as a basis for further considerations. It was quite obvious that some uncertainties exist which must be solved in the upcoming years.

The participants discussed not only the increasing knowledge to tDDIs but also drug-drug interactions based on UGTs (glucuronyltransferases enzyme family). Andrew Parkinson presented specific challenges in characterizing UTG-based interactions in vitro. Additionally Robert Hermann summarized the current status to UGT-based interactions and illustrated how this knowledge should be considered in clinical development plans. The synthesis of glucuronides by glucuronyltransferases is one of the most important metabolic pathways for the elimination and detoxification of drugs as well as the inactivation of highly active body’s own metabolites and messengers (e.g. hormones). The possible influence on this kind of biochemical reactions by medicines, administered at the same time, is extremely important. This knowledge is not sufficiently considered in the development plans as well as in the guidelines. He showed some impressive examples of drug-drug interaction as well as the interaction of drugs with endogenous messengers based on an interference with glucuronyltransferases.

Oliver von Richter focused on interactions based on displacement in plasma protein binding. These types of interaction are often considered as clinical irrelevant. They are not described on the FDA draft guidance. However recent studies demonstrate drug-drug interactions based on a combination of

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displacement in protein binding and inhibition of drug elimination. It was emphasized that one cannot detect this kind of interactions with conventional analytical methods like plasma concentration measurements.

Another topic of the workshop was the significance of pharmacodynamic studies in the investigation of drug-drug interactions. It is unfortunately often the case that pharmacodynamic interactions are detected only after the launch of a new medicine. This is probably based on the fact that the existing guidelines are very much focused on pharmacokinetic DDIs. Based on the assumption of a linear dose-response the impact of pharmacokinetic alterations on the efficacy will be estimated. Hartmut Derendorf unmistakably stated that this assumption is definitely misleading. He called for a more rigorous planning of the investigation of pharmacodynamic DDIs, which are essential for an appropriate assessment of the clinical relevance of interactions. Larry Lesko showed in his presentation that almost all recommendations in the FDA draft guidance are based on pharmacokinetic approaches. The new perspective to investigate pharmacodynamic DDIs more proactively was one important message of the workshop.

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

Presenters at the Third DDI Workshop

Dr. Eva Gil-Berglund, PhD, Medical Products Agency, Sweden
Prof. Dr. Hartmut Derendorf, PhD, FCP, College of Pharmacy, University of Florida, USA
PD Dr. Sebastian Härtter, PhD, Boehringer Ingelheim, Biberach, Germany
Dr. Robert Hermann, MD, FCP, cr.appliance, Radolfzell, Germany
Prof. Dr. Dietrich Keppler, MD, German Cancer Research Center, Heidelberg, Germany
Dr. Caroline A. Lee, PhD, DMPK Solutions, USA
Prof. Dr. Larry Lesko, Center for Pharmacometrics and Systems Pharmacology, University of Florida, USA
Prof. Dr. Mikko Niemi, PhD, Pharmacogenetics, University of Helsinki, Finland
Prof. Dr. Andrew Parkinson, PhD, XPD Consulting, Shawnee, Kansas, USA
Dr. Oliver von Richter, PhD, FCP, MerckSerono, Germany
Prof. Dr. Amin Rostami-Hodjegan, PharmD, PhD, FCP, Faculty of Medical and Human Sciences, University of Manchester, UK
Dr. Manuela LT Vieira, PhD, University of Florida, USA
Dr. Helen Winter, PhD, University of Otago, New Zealand

About the DDI Workshop

The DDI Workshop series 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 series 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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