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Organizers of international workshop on drug-drug interactions register high acceptance from participants which are acknowledging the great benefit

The organisation team reports a big success regarding the drug-drug-interaction (DDI) workshop, which was held from May 30th to June 01st at Marbach Castle, Lake Constance in Germany. More than 60 experts from 11 countries and 5 participants at the industry exhibition joined the meeting on DDIs.
New methods and approaches for the investigation of drug candidates have become necessary due to the increasing complexity of this scientific area. Changes in the existing guideline on drug interactions must follow. Recently the European Medicines Agency (EMA) published a draft of the revised guideline, which was discussed in several talks at the DDI Workshop. In the US a new version of the existing FDA drug interaction guideline is under discussion but not published yet. Discussion of the current scientific status between representatives of the industry, regulatory bodies, and academia are of great importance and were successfully realized at the DDI Workshop.

More than 60 experts for drug development participated in the international DDI Workshop at Marbach Castle. Over a period of two days they listened to 14 expert presentations and discussed intensively the latest scientific and regulatory trends in the investigation of DDIs. Most of the participants were experts from the pharmaceutical industry. Almost all big companies were represented at the workshop. It was a big advantage that speakers and participants from regulatory bodies as well as academic institutions were also present generating useful and inspiring discussions and interdisciplinary exchange.

Besides the scientific aspects the discussion focused on regulatory requirements of the investigation of DDIs. What a lucky coincidence that EMA published the new draft of the guidelines exactly before the workshop started. Dr. Eva Gil Berglund from the Medical Product Agency (MPA) of Sweden, who is significantly involved in the preparation of the new guideline, had already agreed to speak at the workshop. Her speech together with the presentation of Professor Hartmut Derendorf showed that significant changes in the present draft of the guideline compared to the thirteen year old predecessor version will be implemented. New aspects like transporter-based DDIs will be included as well as interactions with food and OTC drugs, especially herbal drugs. Due to this additional sections within the European guideline there will be some differences between the respective US and European Guidance documents. However also various important commonalities are existing in terms of an international harmonization. Additionally the FDA is also planning to revise the existing guideline, which was published in 2006.

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Some industry representatives asked during the workshop for additional and sometimes more detailed guidance on how in vitro and in vivo studies should be conducted by pharmaceutical companies in the future to qualify their products for marketing approval in Europe. As always in the finalisation process of such guidance documents, the draft version of the guideline will be subject to expert comments from industry and academia and therefore most likely pass through several changes. Dr. Eva Berglund was very open for comments and asked the audience repeatedly for written feedback. Experts should send their comments to the EMA or place the comment directly on the EMA website. The new draft is open for discussion until the end of October this year. The final version of the guideline can be expected by end of 2011.

The increasing importance of DDIs was highlighted in almost all speeches. Dr. Robert Hermann showed in his introduction that demographic changes in the industrial nations will cause an exponential increase of poly-pharmacotherapy. Approximately 60 percent of older adults (elder than 65 years) take at least 5 or more drugs and/or supplements at the same time. The cost for the treatment of adverse drug reactions or drug interactions has, in the meantime, reached the level of the total costs for pharmacotherapy itself. The current challenge for industry, regulatory agencies and the society is to gather more scientific data on drug interactions, to be more efficient in the development process of drug candidates, and to transform the available knowlegde into useful information for physicians and patients. The existing expert systems, which should support physicians and pharmacists, are not yet sufficient.

The experts agreed that a total coverage of all possible drug interaction with clinical trials is impossible. Transporter-based DDIs (tDDIs), a main topic of the workshop, are good examples for the increasing complexity. The withdrawal of the cholesterol lowering drug cerivastatin from the market in 2002 due to fatal interactions with gemfibrozil marked a turning point and demonstrated the importance of tDDIs. In the meantime the knowledge in tDDIs has grown significantly and Dr. Oliver von Richter presented the current status. Currently 8 of 1100 so far identified human transporter proteins are known to be involved in active drug transport and hence, may play a role in drug interactions. At present robust methods and specific tool substances to study tDDIs in vivo in humans are limited. It is all the more important that in vitro methods are available to identify transporter substrates and inhibitors.

The talk of Professor Uwe Fuhr covered so-called cocktail drug interaction studies (simultaneous investigation of several drugs in one study), which can help to gain a first overview and to reduce the number of studies for the assessment of the drug interaction potential of a drug candidate. Despite the well-known and addressed limitations, cocktail studies have achieved acceptance by regulatory agencies.

In addition to clinical in vivo studies, which produce the most reliable results, a broad spectrum of in vitro test systems like isolated recombinant enzyme systems, human microsomes or liver cells (hepatozytes) is available. The use of in vitro systems has recently become more popular and sophisticated due to the known limitations of predicting metabolism based DDIs (mDDIs) in humans based on animal data. Professor Amin Rostami-Hodjegan gave a state-of-the-art lecture about mDDIs and presented the characteristics of the different in vitro systems. Professor Andrew Parkinson demonstrated very impressively that different in vitro test systems can also deliver controversial data. In principal only the observance of the complete data set allows a solid assessment of the results. Inconsistant data from in vitro tests will have to be rechecked in clinical trials.

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Modelling and simulations are increasing in industry and sciences due to the increasing complexity and number of drug interactions. Representatives from the industry confirmed that modelling and simulations are the sectors undergoing the most impressive changes within R&D and teams for these methods are growing above average. It is obvious that the industry is running into a problem to get qualified experts for these groups. In Germany the demand to adapt the education in natural sciences and medicine to this situation appears more pronounced than in other relevant countries.

Professor Isabelle Ragueneau-Majlessi talked about pharmacogenetic aspects (i.e. the role of the individual genetic make-up of drug metabolizing enzymes and transporters) of DDIs. This relatively new area is gaining increasing importance and experts are expecting more advances towards different reactions of individuals on multiple medication as well as individualized treatment (selection of the most suitable medicines as well as the adequate dosage for individuals) from phamacogenetics.

“Timing” of DDI studies within the development program was the focus of Dr. Robert Hermann in the last presentation of the workshop. In pharmaceutical companies the right “timing” of DDI studies is sometimes underemphasized and the design and conduct of DDI studies is executed too late in the clinical development programs. Cost saving in the early development phase as well as fear to increase the development risk due to data that is difficult to interpret may be the reasons for this kind of mindset. It is a fact that the early investigation of possible drug interactions allows for a better planning of the costintensive phase III development. To have the information on drug interactions readily available in an earlier stage of the development allows for a more focused patient recruitment based on knowledge-driven rules for allowed and disallowed concomitant medications. The patient’s safety as well as the opportunity to secure the access to the study for more patients will improve. All in all the probability of positive results in phase III will increase.

Speakers
Dr. Eva Gil Berglund, PhD, Medical Product Agency, Schweden
Professor Isabelle Ragueneau-Maijlessi, MD, University of Washington, USA
Professor Hartmut Derendorf, PhD, University of Florida, USA
Professor Uwe Fuhr, MD, Universität Köln, Germany
Dr. Robert Hermann, MD, cr.appliance, Radolfzell, Germany
Professor Andrew Parkinson, PhD, XenoTech, Lenexa, USA
Dr. Oliver von Richter, PhD, MerckSerono, Darmstadt, Germany
Professor Amin Rostami-Hodjegan, PhD, University of Manchester, UK

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 was held in Marbach Castle Conference Centre, located at the Lake Constance, Germany.
The workshop event combined a regualtory update on the investigation of drug interactions along with a scientific update. The meeting offered the opportunity to discuss and network with scientific and regulatory experts from Pharma- and CRO-industries, international regulatory bodies, and academia.
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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About cr.appliance

cr.appliance is an independent team of experts that supports its clients in the healthcare industry with counseling, development concepts and services during the early stages of clinical drug development and throughout the licensing process. 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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