

6th International Workshop on Regulatory Requirements and Current Scientific Aspects on the Preclinical and Clinical Investigation of Drug-Drug Interactions

May 3rd to 5th, 2015
Marbach Castle, Germany



MISSION STATEMENT

The overall objective of the International Marbach Castle DDI Workshop series is to improve and disseminate the scientific knowledge about drug-drug interactions (incl. food-drug and herb-drug interactions), to foster their

proper preclinical and clinical investigation and communication, thereby improving the safe use of drugs in the light of ageing populations and increasing poly-pharmacotherapy.

BACKGROUND, SCOPE AND AIM

In June 2010, the International Workshop on Regulatory Requirements and Current Scientific Aspects on the Preclinical and Clinical Investigation of Drug-Drug Interactions was held for the first time. The workshop was based on an initiative of experts in the field from academia and industry, intrigued by the notion that the field of drug-drug interactions (DDIs) is getting increasingly important and complex in view of continuously emerging new therapies, new drug combinations, complex treatment algorithms for many widespread diseases and ageing populations. These factors converge into poly-pharmacotherapy with increasing risk of clinically significant DDIs. Therefore, the meticulous investigation, informative labelling, and early recognition of DDIs represent substantial challenges for the pharmaceutical industry and regulatory bodies in the development, approval and post-marketing surveillance of new medicines. Failures in the early recognition, mechanistic elucidation (i.e. understanding) and proper clinical management of DDIs, in turn, have resulted in numerous drug withdrawals from the market in the past and continue to result in a significant health burden to patients as well as an economic burden on healthcare systems, rendering many DDIs serious public safety concerns.

Today, DDIs can be addressed in a more targeted and evidence-based fashion, because considerable progress has been made in the understanding of the underlying mechanisms of DDIs and the subsequent development of methodologies for the investigation of DDI susceptibility, and the extrapolation of outcomes of particular DDIs to other drug combinations. Apart from metabolism based DDIs, transporter based DDIs, DDIs involving therapeutic proteins, tools extrapolating *in vitro* results to predict clinical outcomes *in vivo* (IVIVE) as well as information technology guiding the detection and management of DDI have gained more importance over recent years. Furthermore, pharmacodynamic DDIs have gained increasing interest given the steady increase in drug combinations in clinical development.

Since its inception in 2010, the International Marbach Castle DDI Workshop has been designed to comprise all of the elements above, to foster a holistic view on the complex field of DDIs. In order to facilitate an intense exchange on the topic and networking across company and organizational borders, the Workshop is an exclusive event and it is limited to 70 participants from pharmaceutical industry, contract research organizations and drug regulatory agencies, thus providing a unique environment to learn and discuss about the current state-of-the-art in the investigation of DDIs.

In its sixth year, the Workshop will, as in previous years, cover a regulatory topic in depth. After the EMA, FDA, and PMDA have updated their DDI guidelines in recent years, the 2015 regulatory session comprises a number of topics spanning from the regulatory perspective of PBPK in assessing DDIs, the FDA's view on DDI studies and programs, and how to substitute ketoconazole in its role as a strong CYP3A4 inhibitor. As DDIs in the clinical setting go far beyond the effect of two co-administered drugs on each other, we have one lecture dealing with complex DDIs and a second one identifying the rate limiting processes of DDIs flanked by a presentation on how to extrapolate post-marketing identification of DDIs to clinical practice. Given the importance of intracellular drug concentrations for metabolism and transporter based DDIs alike and the limited knowledge of this critical parameter, we have devoted a complete session to this topic to provide insights on the processes that govern intracellular drug concentrations and how these can be measured.

The clinical session will comprise two presentations linking drug induced liver injury (DILI), a safety concern that is often discussed in isolation, with the respective role of DDIs, which as of to date has been largely neglected. In addition, we present an integrated approach on how to study the PK and PD effects on cardiac repolarisation (i.e. QT/QTc interval prolongation) by means of PBPK modelling.

We offer Tutorials as a new format to presenting information on practical aspects of DDIs. The 6th Workshop will contain a presentation on how to successfully submit PBPK data to regulatory authorities and an overview of clinical trial design that successfully examine DDIs in an environment of increasing complexity. Apart from the lectures and the tutorials, a poster session as well as short oral presentations of selected posters will provide you with an opportunity to get feedback on your work and address your current needs related to DDI issues.

As in the previous years, the topics of the 6th International DDI Workshop will be covered by no less than 13 distinguished international scientists and experts from academia, pharmaceutical companies, contract research organizations, consultancies as well as government and regulatory agencies.

We are hoping to welcome you in Marbach in May of 2015.

The Workshop Organizers:
Hartmut Derendorf, PhD, FCP
Robert Hermann, MD, FCP
Amin Rostami-Hodjegan, PhD, FCP
Oliver von Richter, PhD, FCP

WHY YOU SHOULD ATTEND

- **Get informed** about strong CYP3A4 inhibitor alternatives to ketoconazole
 - **Discover** the effects of DDIs on QT/QTc prolongation and how these can be studied in an integrated fashion and using *in vitro* information on channel binding and PK
 - **Gain** insights into the role of DDIs liver injury (DILI)
 - **Update yourself** on tDDIs involving hepatic uptake transporters
 - **Focus** on intracellular drug concentration as a driver of DDIs
 - **Inform** yourself about permeability and plasma protein binding as important drivers of intracellular drug concentrations
 - **Get detailed explanation** of the EMA's perspective on the use of PBPK in the assessment of DDIs
 - **Realize** the physicochemical determinants of unbound tissue concentrations
 - **Enhance** your knowledge about managing complex DDIs in clinical setting
 - **Get to know** pharmaco-epidemiological aspects of DDIs
 - **Become familiar** with determining the rate-determining steps of DDIs
 - **Display and discuss** your recent work on DDIs during the poster session
- and most importantly Meet, Discuss and Network** with scientific and regulatory experts from pharmaceutical- and contract research-industries, international regulatory bodies and academia.



WORKSHOP PROGRAMME

May 3rd, 2015

Sunday

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| Afternoon | Individual Arrival & Check-in at Marbach Castle |
| 03:00 p.m. | Registration & Coffee |
| 04:00 p.m. | Come Together |
| 05:00 p.m. | Opening of the Poster Exhibition |
| 07:00 p.m. | Come Together Dinner |
| 09:00 p.m. | Concert: E3-Acoustic-Band (The Essence of Emotional Energy) Guitars and Vocals |

May 4th, 2015

Monday

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| 08:00 – 09:00 a.m. | Registration & Coffee |
| 09:00 – 09:05 a.m. | Welcome Address and Introduction into the Workshop <i>Amin Rostami-Hodjegan, PhD, FCP; University of Manchester, UK</i> |
| | Session I: Clinical Aspects of Drug-Drug Interactions Chair: Robert Hermann |
| 09:05 – 09:50 a.m. | Complex DDIs in the Clinical Setting <i>Yuichi Sugiyama, PhD; RIKEN Innovation Center, Yokohama, Japan</i> |
| 09:50 – 10:00 a.m. | Discussion |
| 10:00 – 10:45 a.m. | Exploring Drug-Drug Interactions in Real-World Clinical Practice <i>David Juurlink, MD, PhD; Sunnybrook Health Science Center, Toronto, Canada</i> |
| 10:45 – 11:00 a.m. | Discussion |
| 11:00 – 11:30 a.m. | Coffee Break |
| | Session II: Regulatory Aspects of Drug-Drug Interactions Chairs: Eva Gil Berglund and Hartmut Derendorf |
| 11:30 – 12:00 a.m. | The European Regulatory Perspective on the Use of PBPK in Assessing DDIs <i>Anna Nordmark, PhD; Medical Products Agency, Uppsala, Sweden</i> |

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| 12:00 – 12:10 p.m. | Discussion |
| 12:10 – 12:40 p.m. | Alternatives to Ketoconazole for Clinical CYP3A-Inhibition Studies to Quantify Victim DDI Potential <i>Alice Ke, PhD, Certara, Cary NC, USA</i> |
| 12:40 – 12:50 p.m. | Discussion |
| 12:50 – 02:00 p.m. | Lunch |
| 02:00 – 02:45 p.m. | Key Note Lecture I Current FDA Approaches to Food-Drug, Drug-Drug and Gene-Drug Interactions <i>Lawrence Lesko, PhD; University of Florida, Lake Nona, FL, US</i> |
| 02:45 – 03:00 p.m. | Discussion |

Session III:

Tutorials

Chair: Amin Rostami-Hodjegan

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| 03:00 – 03:30 p.m. | PBPK DDI Simulations in Support of Janssen Regulatory Submissions <i>Jan Snoeys PhD; Janssen, Beerse, Belgium</i> |
| 03:30 – 03:45 p.m. | Discussion |
| 03:45 – 04:15 p.m. | Coffee Break |
| 04:15 – 04:45 p.m. | Clinical Trial Designs to Successfully Examine DDIs <i>Robert Hermann MD, FCP; cr. appliance, Gelnhausen, Germany</i> |
| 04:45 – 05:00 p.m. | Discussion |

Presentation of Selected Posters

Chairs: Oliver von Richter and Amin Rostami-Hodjegan

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| 05:00 – 06:00 p.m. | Short Presentation of Selected Posters <i>Presentation of 4 selected posters with 10 minutes presentation and 5 minutes discussion</i> |
| 07:30 p.m. | Dinner |

May 5th, 2015

Tuesday

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| 07:00 – 08:30 a.m. | Breakfast |
| 08:30 – 09:15 a.m. | Key Note Lecture II Importance of Knowing the Rate-Determining Process in Predicting Complex DDIs from in vitro Metabolism and Transport Data. <i>Yuichi Sugiyama, PhD; RIKEN Innovation Center, Yokohama, Japan</i> |
| 09:15 – 09:30 a.m. | Discussion |
| Session IV: Determination of Intracellular Drug-Concentrations Chairs: Andrew Parkinson and Oliver von Richter | |
| 09:30 – 10:00 a.m. | Drug Concentrations in Tissue: Accounting for Permeability of Ionised Form and Implications for PD as well as DDIs <i>Avijit Ghosh, PhD; Johnson & Johnson, Pennsylvania PA, USA</i> |
| 10:00 – 10:15 a.m. | Discussion |
| 10:15 – 10:45 a.m. | Coffee Break |
| 10:45 – 11:15 a.m. | Coexistence of Passive Diffusion and Active Transport Controlling Intracellular Drug Concentrations <i>Bernard Faller, PhD; Novartis Institutes for BioMedical Research, Basel, Switzerland</i> |
| 11:15 – 11:30 a.m. | Discussion |
| 11:30 – 12:00 a.m. | Plasma Protein Binding and its Implications for Intracellular Drug Concentrations <i>Hartmut Derendorf, PhD, FCP; University of Florida, Gainesville FL, USA</i> |
| 12:00 – 12:15 p.m. | Discussion |
| 12:15 – 01:30 p.m. | Lunch |



Session V: DDI Influencing Drug Safety Issues

Chair: Robert Hermann

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| 01:30 – 02:15 p.m. | Hepatotoxic Consequences of DDIs: Case Studies and Possibilities to Predict Them <i>Daniel J Antoine, PhD; University of Liverpool, UK</i> |
| 02:15 – 02:30 p.m. | Discussion |
| 02:30 – 03:15 p.m. | Narrowing Down to the Channels for DDIs Leading to Cardiac Safety: A Combined PK and PD Problem and Promises of the IVIVE Approach <i>Sebastian Polak PhD; Jagiellonian University, Krakow, Poland & Certara, Sheffield, UK</i> |
| 03:15 – 03:30 p.m. | Discussion |
| 03:30 – 03:45 p.m. | Coffee Break |
| Q & A Session Moderators: Hartmut Derendorf and Oliver von Richter | |
| 03:45 – 04:45 p.m. | Q & A Session Involving all Workshop Topics |
| 04:45 – 05:00 p.m. | Concluding Remarks <i>Amin Rostami-Hodjegan, PhD, FCP; University of Manchester, UK</i> |
| 05:00 p.m. | End of Meeting & Departure |

Tuesday





WHO SHOULD ATTEND?

This international Workshop on drug-drug interactions is designed to meet the requirements and expectations of professionals from the pharmaceutical industry, contract research organisations, regulatory agencies and academia.

Department heads, project managers, scientists and consultants in R&D, in regulatory affairs, pharmacokinetics, clinical pharmacology, exploratory/translational medicine, clinical development, drug safety, biostatistics, business development, medical communications and so forth should attend. All delegates are invited to contribute actively to the scientific discussions.

LANGUAGE

English will be the language of the Workshop. No simultaneous translation will be provided.

VENUE & LOCATION

The Workshop will take place at the Marbach Castle Conference Centre (see the following web site: <http://www.schlossmarbach.de>) located close to the Swiss border amidst the beautiful surrounding of the Western shore of Lake Constance in close proximity to the historic town of Stein am Rhein. The old town centre of Stein am Rhein is characterised by striking medieval buildings such as the City Church, the former Monastery of St. Georgen, burghers' houses, gates and towers, as well as buildings dating from the early modern age, including the Town Hall and the Arsenal.

Marbach Castle is within easy reach of the major cities in the area (Zurich, Basel, Stuttgart,). The distance to Zurich International Airport (ZRH) is about 60 kilometres. Airport taxi shuttles for Workshop attendees will be organised on Sunday May 3rd and Tuesday 5th. Taxi from and to the Airport is approx. 100 Euros. Please find detailed itinerary descriptions posted under the Contact/Travelling item of the Marbach Castle web site, if you arrange the travel yourself.

POSTER EXHIBITION

The Workshop will comprise a poster session for topics related to all aspect of non-clinical and clinical DDI investigations including IVIVE or other pharmacometrics approaches, regulatory, pharmaco-epidemiological as well as labelling aspects of DDIs. Poster presenters need to submit an abstract to karen.grave-hermann@cr-appliance.de. The deadline for abstract submission is on Tuesday March 31st 2015.

The abstract must be structured, including the following headings: Aim(s), Methods, Results (some numerical data, including confidence intervals on differences, when appropriate, must be included), and Conclusions. The abstract should be a maximum of 250 words. In addition authors should provide a written statement on:

What is already known about this subject

A summary of the state of scientific knowledge on this subject before you did your study and say why this study needed to be done in up to three short bullet points (not more than 50 words in total)

What this study adds

A simple answer to the questions "What do we now know as a result of this study that we did not know before?" and "What take-home-message do you want to impart to the readers?" in up to three short bullet point sentences (not more than 50 words in total)

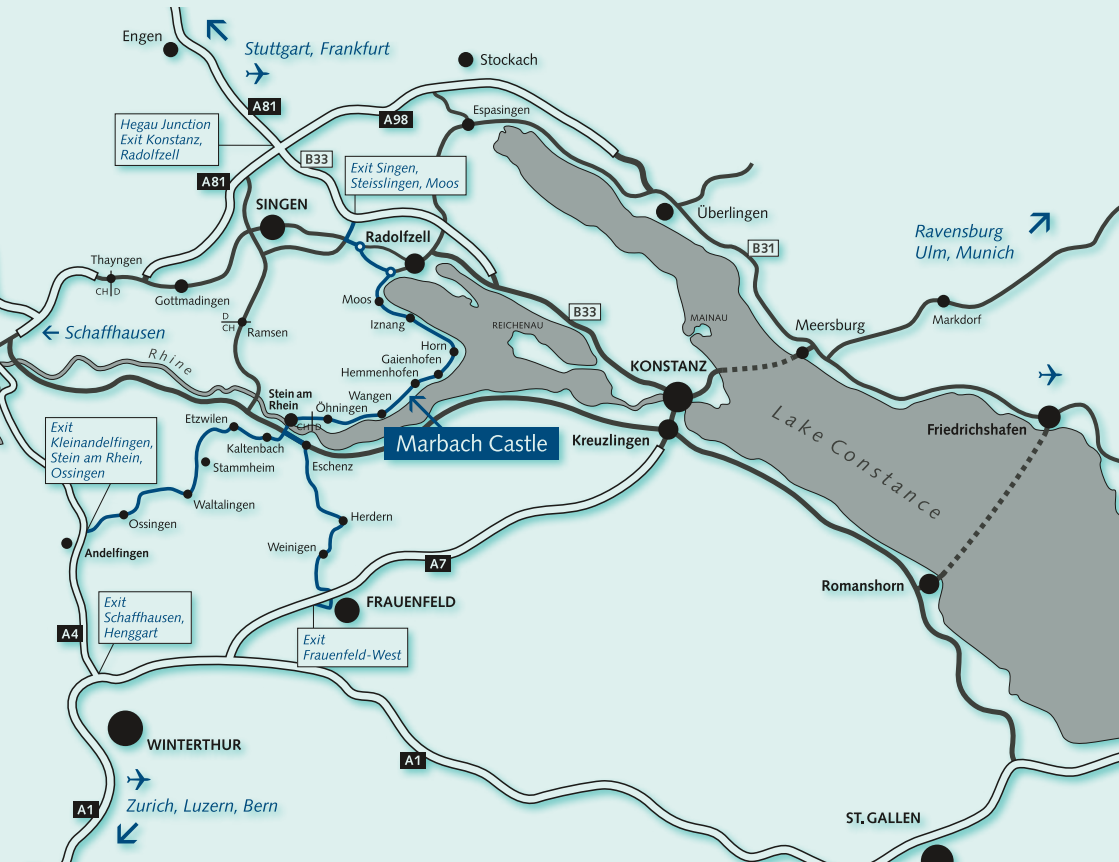
The posters will be displayed on Sunday May 3rd from 05:00 p.m. – 07:00 p.m., Monday May 4th from 08:00 a.m. – 05:00 p.m. and on Tuesday May 5th from 08:00 a.m. – 01:30 p.m. The poster format and size must meet the following: portrait format; 120 x 140 cm (47,24 x 55,12 inch).

REGISTRATION INFORMATION

Date, Time and Venue

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|----------------------------------|--|------------------------|
| Date | Workshop May, 3 rd to 5 th , 2015 | |
| Venue | Marbach Castle | +49 (0)7735 – 8130 |
| | D-78337 Öhningen | info@schlossmarbach.de |
| Times | May 3 rd 2015 | |
| | Afternoon: individual arrival, come together, come together activity, come together dinner | |
| | May 4 th 2015 | |
| | Start 09:00 a.m. – Finish 06:00 p.m. | |
| | May 5 th 2015 | |
| | Start 08:30 a.m. – Finish 05:00 p.m. | |
| Registration & Coffee | May 3 rd 2015 | 03:00 p.m. |
| | May 4 th 2015 | 08:00 a.m. |

MAP



Registration Form

Please print your details

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| Title | First name |
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| E-mail | |
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| Date | Signature |
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You may register by:

Mail: cr.appliance
Heinrich-Vingerhut-Weg 3,
D-63571 Gelnhausen
Fax: +49(0)6051-97 166 93
Internet: www.cr-appliance.com
E-mail: karen.grave-hermann@cr-appliance.com

For further information please contact Karen Grave-Hermann
Phone: +49(0)6051-97 166 91

Cancellation Policy

- Over 30 days prior to the Seminar: Cancellation fee of 200,00 €.
- 14–29 days prior to the Seminar: 50 % of the fee.
- Less than 14 days or if no notification received:
Registrant liable to pay FULL seminar fee.

**NB: Cancellation must be addressed in writing to
karen.grave-hermann@cr-appliance.com**

In the event circumstances beyond control, cr.appliance reserves the right to alter the programme, the speakers, the date or the venue.

Workshop Fee (incl. Lunch, Dinner & Coffee Breaks, incl. 19 % VAT)

Please tick

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|--|------------|--------------------------|
| Participation from May 3 rd to 5 th , 2015 | 1.830,00 € | <input type="checkbox"/> |
| Participation from May 3 rd to 5 th , 2015 (Discounted rate for Members of ACCP, DMDG, ISoP or BioLago) | 1.730,00 € | <input type="checkbox"/> |
| Participation on May 4 th and 5 th , 2015 only | 1.730,00 € | <input type="checkbox"/> |
| Participation on May 4 th to 5 th , 2015 only, in combination with Membership of ACCP, DMDG, ISoP or BioLago | 1.630,00 € | <input type="checkbox"/> |

Accommodation (incl. Breakfast and 19 % VAT)

A limited number of bedrooms are available

at Marbach Castle (further Hotel capacities in close proximity available upon request):

| | 1 night | 2 nights |
|--|--------------------------|------------------------------------|
| Category A: single room (175,00 € per night) | <input type="checkbox"/> | <input type="checkbox"/> (= 350 €) |
| double room (250,00 € per night) | <input type="checkbox"/> | <input type="checkbox"/> (= 500 €) |
| Category B: single room (127,00 € per night) | <input type="checkbox"/> | <input type="checkbox"/> (= 254 €) |
| double room (202,00 € per night) | <input type="checkbox"/> | <input type="checkbox"/> (= 404 €) |
| No hotel accommodation required: | | <input type="checkbox"/> |

Application to Register

To ensure the personal workshop character of the event and provide maximum knowledge transfer benefits for the attendees, the overall number of participants is limited. Workshop participation will be assigned in the sequence of receipt of registration applications. Full confirmation of registration will occur by receipt of the Workshop fees.

Discounted Rates

Discounted rates may be granted for a limited number of participants on individual application for students, personnel from non-profit organizations and registered charities.