DART Testing Strategies for Human Pharmaceuticals: Animal Models vs In-Vitro Approaches

Event #11116
10–11 October 2011
Hotel Holiday Inn, Leiden, The Netherlands

Programme Committee

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Continuing Education

DIA meetings are generally approved by the SwAPP (Swiss Association of Pharmaceutical Professionals) Commission for Professional Development (CPD) and SGPM (Swiss Society of Pharmaceutical Medicine) and will be honoured with credits for pharmaceutical medicine.
All participants are eligible for these credits and certificates are available on request from the registration desk.

Overview

For years there has been ongoing research into new approaches enabling alternative methods to replace animal studies. In the area of reproductive toxicity testing, a number of research programmes have provided important test strategies with regard to in-vitro testing methods.

The data might be insufficient to reach a complete replacement of in-vivo studies regarding developmental and reproductive toxicity (DART) by in-vitro approaches currently. However, it could be expected that the tests and combined test batteries developed and studied may contribute to alleviating the need for some of the animal studies required for reproductive testing (embryo-foetal toxicity) under ICH S5A guidelines. In order to achieve this goal, discussions between regulators, industry and the academic scientists involved are needed. An important aspect is the long time it takes to implement changes from this work on alternatives into regulatory measures.

Key Topics

- Rat and rabbit reproductive toxicity
- Embryonic stem cell test
- DART on development of human pharmaceuticals
- Validation and evaluation
- New developments

Who Will Attend

Pharmaceutical professionals with an interest in the following areas:

- Industry toxicology/teratology
- Non-clinical regulatory assessment
- Outsourcing non-clinical testing
- Regulatory affairs
- Research and development
- Medical writing

Objectives

At this workshop the following questions will be addressed and discussed:

- To what extent has either species (rat or rabbit) been retrospectively decisive in the evaluation of human pharmaceuticals? The focus is on the so-called ‘segment II studies’; the embryo-foetal developmental (EFD) studies covering the developmental stages C-D.
- Is this evaluation similar or different for various classes of human pharmaceuticals (e.g. antibiotics, dopamine-agonists)?
- Which developmental effects were crucial in the evaluation? How did sensitivity, incidence, severity and magnitude play a role in hazard identification? This knowledge is important to evaluate the usefulness of in vitro alternatives in view of their applicability domain.
- Will in-vitro methods (especially using mouse embryonic stem cells) be able to detect these crucial developmental effects? What type of data is available? Can recommendations be given for further evaluation of these in-vitro methods?

MONDAY | 10 OCTOBER 2011

08:00 REGISTRATION AND WELCOME COFFEE

08:45 **WELCOME AND INTRODUCTION - PURPOSE OF THE WORKSHOP**
Jan Willem van der Laan, Senior Non-clinical Assessor Medicines Evaluation Board, The Netherlands

09:00 Session 1

RAT AND RABBIT REPRODUCTIVE TOXICITY

Session Chair:
Robert E. Chapin, Senior Research Fellow Pfizer Global R&D, USA

Traditionally rats and rabbits have been used in the testing strategy for embryo-foetal toxicity. It is important to know the value of either species in the risk assessment of human pharmaceuticals. Parallel processes are ongoing in different areas of legislation evaluating the results of studies.

Rat vs Rabbit in Developmental Toxicology
Aldert Piersma, Professor of Reproductive and Developmental Toxicology, Laboratory for Health Protection Research, National Institute for Public Health and Environment RIVM, The Netherlands

Rats vs Rabbits and Alternatives for EFD for Pharmaceuticals
Abigail C. Jacobs, Associate Director, Pharmacology/Toxicology, ONDIO, CDER, FDA, USA

10:30 COFFEE BREAK

11:00 Session 2

EMBRYONIC STEM CELL TESTS

Session Chair:
Andrea Seiler, German Federal Institute for Risk Assessment, Center for Alternative Methods to Animal Experiment – ZEBET, Germany

Embryonic stem (ES) cells from mice are being used as an in-vitro approach to the testing of the developmental toxicity of chemicals and pharmaceuticals, mainly in the screening phase at the end of discovery. The ES tests themselves are still evolving and, increasingly, human ES cell tests are being developed and used.

Overview of the Embryonic Stem Cell Test (EST)
Esther de Jong, National Institute for Public Health and the Environment (RIVM), Laboratory for Health Protection Research, The Netherlands

Overview of Embryonic Stem cell-based Novel Alternative Testing Strategies (ESNATS)
Jürgen Hescheler, President of the German Society of Stem Cell Research, Director of the Institute of Neurophysiology, University of Cologne, Germany

Development of a Multi-Faceted In-Vitro Approach to Predict Teratogenic Effects: Rat Whole Embryo Culture (WEC), mouse EST, human EST
Diane R. Umbenhauer, Associate Director, Merck Research Laboratories, USA

12:30 LUNCH

14:00 Session 3

DART ON DEVELOPMENT OF HUMAN PHARMACEUTICALS

Session Chair:
Aldert Piersma, Professor of Reproductive and Developmental Toxicology, Laboratory for Health Protection Research, National Institute for Public Health and Environment RIVM, The Netherlands

At some time during development of pharmaceuticals, companies have to evaluate the developmental toxicity. During the last decade companies have used in-vitro approaches in the screening phase (discovery phase) with a series of analogues to choose the compound with the lowest potency for inducing reproductive toxicity... What kind of ancillary assays improve predictability? Is it possible to use these assays to make regulatory decisions?

The Use of EST in Screening: Experience from Pfizer
Robert E. Chapin, Senior Research Fellow, Pfizer Global R&D, USA

The Roche Experience with the EST Assay: Improved prediction using a new algorithm and technology advances for full automation
Claudia McGinnis, Group Head, In-vitro Toxicology Screens, F. Hoffmann La-Roche AG, Switzerland

Industry Viewpoint
Jane Stewart, Director, Reproductive Toxicology, AstraZeneca R&D, UK

15:30 COFFEE BREAK

16:00 Session 4

VALIDATION AND EVALUATION

Session Chair:
Abigail C. Jacobs, Associate Director, Pharmacology/Toxicology, ONDIO, CDER, FDA, USA

The mouse embryonic stem cell test was validated by the European Centre for the Validation of Alternative Methods (ECVAM) as an alternative 3Rs approach. What does this mean? What has been the impact of this validation? To help assure the adequacy of ES tests from a regulatory viewpoint, what is an appropriate list of 'positive' and 'negative' compounds that should be accurately predicted?

The Validated Embryonic Stem Cell Test (EST) and its Applicability Domain
Andrea Seiler, German Federal Institute for Risk Assessment, Center for Alternative Methods to Animal Experiment – ZEBET, Germany

ECVAM Viewpoint
Susanne Bremer-Hoffmann, Institute for Health & Consumer Protection (IHCP) at the European Commission's Joint Research Centre (JRC), European Centre for the Validation of Alternative Methods (ECVAM), Italy

List of Teratogenic Substances in HESI-DART
George P. Daston, Research Fellow, Procter & Gamble Company, USA

17:15 **Introduction to Working Dinner**
Jan Willem van der Laan, Senior Non-clinical Assessor, Medicines Evaluation Board, The Netherlands

19:00 NETWORKING RECEPTION

19:30 **WORKING DINNER**
During dinner the participants will discuss a series of questions in small groups. The conclusions will be reported during the plenary session on Tuesday. The questions and the discussion will be used to reach consensus about further steps in implementing in-vitro approaches in developmental toxicity testing.

22:00 END OF DAY ONE

TUESDAY | 11 OCTOBER 2011

09:00 Session 5

NEW DEVELOPMENTS

Session Chair:
Bert Haenen, Senior Consultant, Non-Clinical Development, 3d-PharmXchange, The Netherlands

Beyond the current embryonic stem cell assays that are going through standardisation and validation, additional developments are appearing that could improve the prediction of developmental toxicity. This session highlights several aspects and assay designs that may be instrumental in further enhancing the predictability of in-vitro tests for developmental toxicity.

High Throughput Testing in EST
Sidney Hunter, Branch Chief, Systems Biology Branch, Integrated Systems Toxicology Division, NHEERL, ORD USEPA

Zebrafish Embryo Test
Karen A. Augustine, Research Fellow, Discovery Toxicology, Bristol-Myers Squibb R&D, USA

hES and iPS Metabolomics Based Assay for Developmental Toxicity Screening
Elizabeth LR Donley, CEO, Stemina Biomarker Discovery, Inc., USA

10:30 COFFEE BREAK

11:00 Session 6

PLENARY REPORT OF WORKING DINNER QUESTIONS - PART A
PLENARY DISCUSSION RATS VS RABBITS

Session Chair:
Aldert Piersma, Professor of Reproductive and Developmental Toxicology, Laboratory for Health Protection Research, National Institute for Public Health and Environment RIVM, The Netherlands

During the working dinner questions will have been discussed about the way to evaluate either species in the risk assessment of human pharmaceuticals

Formulation of recommendations for further research and regulatory steps.

Discussant: Edward J. Fisher, Pharmacologist, CDER, FDA, USA

12:30 LUNCH

14:00 Session 7

PLENARY REPORT OF WORKING DINNER QUESTIONS - PART B
PLENARY DISCUSSION ON IN-VITRO APPROACHES

Session Chair:
Jan Willem van der Laan, Senior Non-clinical Assessor, Medicines Evaluation Board, The Netherlands

During the working dinner questions will have been discussed regarding the implementation of in-vitro approaches.

15:00 SUMMARY OF RECOMMENDATIONS AND DISSEMINATION OF THE REPORT

15:30 END OF WORKSHOP

HOTEL INFORMATION

The DIA has blocked a limited number of rooms at the following hotel:

Hotel Holiday Inn
Haagse Schouwweg 10
P.O. BOX 9004
Leiden 2332 KG
The Netherlands

http://www.holidayinn.com/hotels/us/en/leiden/ldnnl/hoteldetail?sitrackingid=172700882&siclientid=1952

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Fax: +31-71-5355553

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Important: Please complete your reservation by **11 September 2011**. Reservations received after this date will be subject to hotel availability and room rate may vary.

In case of cancellation:
Cancellation of the hotel booking must be made in writing directly to the hotel. Cancellation or changes are free of charge until 11 September 2011. Cancellations received after this date may result in a (full reservation) charge. se of cancellation, please ask the hotel for your cancellation number.

TRAVEL INFORMATION

Arriving by plane
Leiden is only 20 minutes by train from the main Dutch airport 'Schiphol Amsterdam International Airport': Please visit Netherlands Railways for more information. www.ns.nl

Other Dutch airports relatively close to Leiden, mainly used by low-cost european carriers, are Rotterdam Airport and Eindhoven Airport.

From Rotterdam Airport: busses from Rotterdam Airport to the Rotterdam Central Train Station depart frequently and takes about 20 minutes. From Rotterdam Central Train Station it will take you about 30-40 minutes to travel to Leiden Central Train Station. www.rotterdamthehagueairport.nl

From Eindhoven Airport it will on average take you 2-3 hours to get to Leiden.

By train
Leiden's Railway Station connects Leiden directly with the major Dutch cities (Amsterdam, Rotterdam, Utrecht and The Hague). When arriving with an international train at one of these stations you can find trains directly to Leiden at all hours of the day. Trips can be planned online on the website of the Dutch Railroad Company. www.ns.nl

Opposite the Leiden Central Train Station you will find the Leiden Visitor Centre, they can provide you with further directions for your visit to Leiden. http://portal.leiden.nl

By car
Leiden is reachable via the Dutch highways A4 (Amsterdam - The Hague) and A44 (Amsterdam – Delft)

REGISTRATION FORM

DART Testing Strategies for Human Pharmaceuticals: Animal Models vs In-Vitro Approaches
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ID # 11116

DIA www.diahome.org

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TOTAL AMOUNT DUE: €_____ **NOTE: PAYMENT DUE 30 DAYS AFTER REGISTRATION AND MUST BE PAID IN FULL BY COMMENCEMENT OF THE EVENT**

STUDENT RATES, GROUP DISCOUNTS, SMEs AND OTHER SPECIAL RATES ARE AVAILABLE! PLEASE CONTACT DIA EUROPE FOR MORE INFORMATION. 11116DIA

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PLEASE COMPLETE IN BLOCK CAPITAL LETTERS OR MAKE REGISTRATION EVEN SIMPLER BY ATTACHING THE ATTENDEE'S BUSINESS CARD HERE

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Payments must be net of all charges and bank charges must be borne by the payer.

CANCELLATION POLICY: All cancellations must be in writing and received with DIA Europe by 17:00 CET on 30 September 2011

Cancellations received by the date above are subject to an administrative fee:
Full Meeting Cancellation: Industry (Member/non-member) = € 200.00. Government/Academia/Non-profit (Member/non-member) = € 100.00. Tutorial cancellation: € 50.00. Regretfully, if you do not cancel by the date above and do not attend, you will be responsible for the full registration fee. You are responsible for cancelling your own hotel reservations. DIA Europe reserves the right to alter the venue and dates if necessary. If an event is cancelled, DIA Europe is not responsible for airfare, hotel or other costs incurred by yourself.

Transfer Policy

You may transfer your registration to a colleague prior to the start of the event but membership is not transferable. Substitute attendees will be responsible for the non-member fee, if applicable. Please notify DIA Europe office of any such substitutions as soon as possible.

IMPORTANT: Hotel and travel reservations should be made ONLY after receipt of written registration confirmation from DIA Europe. If you have not received your confirmation within five working days, please contact DIA Europe.

HOW TO REGISTER

The DIA Europe Customer Services Team will be pleased to assist you with your registration. Please call us on +41 61 225 51 51 from Monday to Friday between 08:00 and 17:00 CET.

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