4 December 2014
EMA/341714/2014

Agenda - EMA EFPIA Workshop on the importance of dose finding and dose selection for the successful development, licensing and lifecycle management of medicinal products

04 – 05 December 2014, meeting room 3A
30 Churchill Place, Canary Wharf, London E14 5EU

Outline: Investigating and understanding dose-exposure-response (D-E-R) relationships and selecting a dose-range for confirmatory Phase III trials and licensing is among the most difficult problems that drug developers and regulators are called to solve. Regulatory experience indicates that dose finding is often confined to determining a single dose to carry forward in Ph3 based on the results of pairwise comparisons between a few dose levels in small trials on single efficacy parameters. This type of evidence tends to form a weak basis for decision making, increasing the risks associated with confirmatory trials. D-E-R information often is not available or not reported and questions of importance to product labelling are not precisely answered which complicates the licensing process. In addition, despite recommendations in the ICH E4 (Dose Response Information to Support Drug Registration) guideline, there is a common misperception that dose ranging/finding and D-E-R characterisation are limited to exploratory development.

The workshop will discuss the utility of methods for D-E-R relationship estimation and dose finding, and the implications for the sponsor, the regulator, the prescriber and the patient, when adequate information on important questions related to dose are not generated or are suboptimal. The impact that lack of these data might have on B/R assessment and post-approval studies will be examined. The goal of the meeting is to come with recommendations on which regulators and drug developers agree that will result in improved dose finding strategies and a more systematic D-E-R investigation in drug development. This should not only optimise the chances for successful development and approval, but should also result in improved dose recommendations (SmPC) and lifecycle management for the medicinal products.

Output: Agree on a toolkit of methods for the well informed drug developer and regulator and on a decision tree to guide the practical implementation of these methods in drug development. A common

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

EFPIA, EMA statement on the need to promote D-E-R characterisation and dose finding as an indispensable component of the development, submission and drug lifecycle management of the medicinal products.

Attendant profile: Clinical development, Regulatory, Modelling, Statistics, Post-Authorisation. Expertise in methods for dose-exposure-response characterisation is not necessary.

Day 1: 04 December 2014

Room 3A

~ Registration and Coffee ~

Dec 4

14:00 -15:00 **Session 1 Setting the scene**	
EMA (20')	Rob Hemmings (SAWP, MHRA) Efthymios Manolis (EMA)
EFPIA (20')	Richard Lalonde (Pfizer) Don Stanski (AstraZeneca)
FDA (20')	Vikram Sinha (FDA)
Deliverables: • Definitions • Objectives of dose finding/selection and D-E-R in drug development and beyond • Expectations from regulatory agencies, industry and academia	

15:00 -18:30 **Session 2 Designs and Methods** **Chairs: Rob Hemmings, Jose Pinheiro (J&J)**	
Opening the session	Rob Hemmings, Jose Pinheiro (J&J)
15:00-15:15 1. Pharmacometric principles: a solid basis for pharmacostatistical dose finding	Mick Looby (Novartis)
15:15-15:30 2. Selective androgen receptor modulator (SARM)	Charles Benson (Lilly)
15:30-15:40 Regulatory Discussants	Terry Shepard (MSWG, MHRA), Sofia Friberg Hietala (MSWG, MPA)
15:40-15:55 3. An adaptive dose-finding study in postoperative dental pain. MCP-Mod	Bjoern Bornkamp (Novartis)
15:55-16:10 4. Model Averaging	Andrew Hooker (Uppsala)
16:10-16:20 Regulatory Discussant	Norbert Benda (SAWP, BfArM)
16:20-16:50 Coffee break	

15:00 -18:30 **Session 2 Designs and Methods** **Chairs: Rob Hemmings, Jose Pinheiro (J&J)**	
16:50-17:10 5. Meta-analysis of clinical dose response in a large drug development portfolio by Pfizer	Neal Thomas (Pfizer) Regulatory Discussant: David Wright (BSWP, MHRA)
17:10-17:30 6. An Innovative Confirmatory, Dose-Range-Finding Trial for a new Treatment of Septic Shock.	Scott Berry (Berry Consultants - Ferring) Regulatory Discussant: Martin Posch (BSWP, Medical University of Vienna)
17:30-18:30 7. Key Learnings and Panel Discussion	Rob Hemmings, Jose Pinheiro Panel Discussion: Speakers/Discussants + Tomas Salmonson (CHMP, MPA), Vikram Sinha, Yaning Wang, Dionne Price (FDA), Efthymios Manolis (EMA)
Deliverables: • Methods definition • Pros and Cons • Which methods for the defined objectives e.g. consider how different factors like disease, BMs, clinical and practical considerations could impact methods of choice	

Day 2: 05 December 2014

Room 3A

Dec 5

08:30-12:10 **Session 3 Gap analysis by different therapeutic area** **Chairs: Tomas Salmonson (CHMP, MPA) & Charles Benson (Lilly)**	
08:30-09:10 **1. CNS:** *Target Occupancy*	**Chair:** Luca Pani (SAWP, AIFA)
• Phase 2a dose selection based on PKPD to ensure an optimal coverage of the receptor occupancy range	Mona Alamedine (Roche)
• A Systems Pharmacology Perspective on the Clinical Development of Fatty Acid Amide Hydrolase Inhibitors for Pain http://www.nature.com/psp/journal/v3/n1/full/psp201372a.html	P H van der Graaf (Leiden University)
• EMA View and Panel Discussion	Luca Pani, Valentina Mantua (SAWP, AIFA)
09:10-09:50 **2. Infectious Disease:** *PK-PD for antibiotics*	**Chair:** Filip Josephson (CHMP, MPA)
• PK/PD of antibiotics (15min)	Shampa Das(AZ)
• EMA View (5min)	Mair Powell (SAWP, MHRA)
• Mechanism-based PKPD-models (10min)	Lena Friberg and Elisabet Nielsen (Uppsala University)
• Key Learnings and Panel Discussion (10min)	Filip Josephson & Mair Powell

09:50-10:10 Coffee break

10:10-10:50 **3. Oncology:** *MTD-Exposure/Response* • Cabozantinib (Cometriq) (10min) • Shifting the MTD paradigm in Oncology (10min) • Systems Pharmacology example (10min) • Key Learnings and Panel Discussion (10 min)	**Chair:** Bertil Jonsson (SAWP, MPA) Frans Opdam (NKI, MEB) Kevin Smart (Roche) James Yates (AZ) Bertil Jonsson
10:50-11:30 **4. Cardiovascular:** *Focus on anticoagulants* • Novel oral anticoagulants (15min) • Key Learnings from Otamixaban Development (15min) • Key Learnings and Panel Discussion (10min)	**Chair:** Peter Mol (SAWP, MEB) Antonio Gomez (CVSWP, AEMPS) Christophe Gaudin (Sanofi-Aventis) Peter Mol Robert Temple (FDA) via TC
11:30-12:10 **5. Immunology:** *Liver Transplantation* • Tacrolimus/Everolimus combination therapy in liver transplantation • Regulatory View and Panel Discussion (10min)	**Chair:** Michael Looby (Novartis) Thomas Dumortier (Novartis), Yaning Wang (FDA) via TC Lisbeth Barkholt (EMA,MPA), Flora Musuamba (MSWG, UCL), Yaning Wang (FDA) via TC
Deliverables: • Gap analysis by therapeutic area	

Lunch break

13:00-14:00 **Session 4** **The importance of D-E-R characterisation in dose selection, labelling and B/R assessment** **Chairs: Terry Shepard (MSWG) & Solange Rohou (EFPIA)** Focus in children & elderly	
Children (30')	**Presenters:** Ine Skottheim Rusten (PDCO, NOMA), Anne Brochot (J&J) **Panel:** Dirk Mentzer (PDCO, PEI), Joe Standing (MSWG, UCL), Efthymios Manolis (EMA), Cecile Olivier (EMA), Ralf Herold (EMA)
Elderly (30')	Susan Morgan (SAWP, MHRA), Terry Shepard (MSWG, MHRA), Francesca Cerreta (EMA), Amy Cheung (AZ)
Deliverables: • How to scale the dose/exposure response information available in adults, to the specific groups? • How to confirm dose/exposure response relationship in the specific groups? • What is unique in these groups? • What are the minimum requirements for dose selection, labelling and B/R assessment?	

14:00- 15:00 **Session 5** **Impact on licensing decisions, post-authorisation commitments and lifecycle management of medicinal products** **Chair: Tomas Salmonson (CHMP)**	
EMA (20')	Falk Ehmann (EMA)
FDA (20')	Yaning Wang (FDA)
PMDA (20')	Dr Yabana and Dr Nagai (PMDA)
Deliverables: • Define the place and impact of D-E-R information in regulatory submission, approval and post authorisation commitments and lifecycle management.	

15:00-15:30 **Session 6 Conclusions and Directions for the future**
Tomas Salmonson (CHMP, MPA) Rob Hemmings (SAWP, MHRA) Richard Lalonde (Pfizer) Don Stanski (AstraZeneca)