EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

efpia
European Federation of Pharmaceutical Industries and Associations

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EMA-EFPIA Modelling and Simulation Workshop

Break Out Session 3 (BOS3)

Room 2G

Chair: Terry Shepard and Oscar Della Pasqua
Organisers/Panellists: Lutz Harnisch, Ralf Herold, Chyi Hung Hsu, Trevor Johnson, Matts Kågedal, Huub Jan Kleijn, Stephanie Läer Solange Rohou and Joe Standing

Framework:
An evidence-based approach is often unsuitable for the evaluation of pharmacokinetics, pharmacodynamics, safety and efficacy in special populations, ethnic groups and rare diseases. Inferential methods (M&S) should underpin evidence synthesis and knowledge integration in the development of drugs for special populations, ethnic groups and rare diseases.
Case examples will be discussed to illustrate how inferences can be used to support evidence synthesis during the design stage (i.e., protocol optimisation), as well as during the analysis and interpretation of existing or new evidence. We will highlight the importance of assessing the consequences of assumptions for the implementation of a model-based approach. Assumptions can be violated (this should be addressed accordingly e.g. , by additional evidence or by a better model), mitigated (e.g., by label restriction, dose titration) or pertain as risk to patients and other stakeholders (e.g., regulator/sponsor).

Welcome by Terry Shepard, MHRA, UK 08:30-08:35

Introduction 08:35-08:55
Scene seen by PDCO and Paediatric Medicines at EMA - Ralf Herold, EMA Scene seen by EFPIA member - Oscar Della Pasqua, GSK

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Theme 1			08:55-09:35
Position statement	**Past experience, proposed use by industry and regulatory status**	**Open questions**	**Case studies**
M&S assumptions about ADME processes *"M&S should be routinely used to support dose finding in special populations and ethnic groups."*	• M&S can be used to define the dose to be included in PK, PK/PD, or/and safety efficacy trials in these populations. • M&S can be used to inform the label following the analysis of the results from studies in these populations • M&S to inform the label in lieu of new evidence	• Concerns of sponsors about regulator's attitudes • What research is required before implementation • Current standards for assessing the impact of assumptions and model validity • What is required for future use of model-based approaches (tools and methods)?	08:55 -09:05 Semi-mechanistic population PKPD model for sugammadex mediated reversal of rocuronium induced neuromuscular blockade across a wide range of patients (Huub-Jan Kleijn, MSD)
Regulatory Discussant		Terry Shepard, MHRA (15min)	
Panel Discussion		(15min)	

Theme 2			09:35-10:25
Position statement	**Record Industry Use and Regulatory Status**	**Open questions**	**Case studies**
Assumptions about PKPD relationships, pathophysiology and disease *"M&S should be used to extrapolate (PK, PD, efficacy or safety) data across different populations and diseases".*	• M&S supported/validated by limited observed data in a new population. • M&S approach as stand alone without requirements for data in these populations."	• Concerns of sponsors about regulator's attitudes • What research is required before implementation • Current standards for assessing the impact of assumptions and model validity • What is required for future use of model-based approaches (tools and methods)?	09:30-09:40 Revatio in Paediatric Pulmonary Arterial Hypertension (PAH, orphan indication) (Lutz Harnisch, Pfizer) 09:40-09:50 Bridging of PKs across Ethnic Groups (Japanese submission) (Matts Kågedal, AstraZeneca)
Regulatory Discussant Christopher Male PDCO (10min)			
Panel Discussion (15min)			

~ Coffee Break ~

10:25-10:45

Theme 3			10:45-11:15
Position statement	**Record Industry Use and Regulatory Status**	**Open questions**	**Case studies**
Assumptions about parameter-covariate relationships *"Model uncertainty and model misspecification must be evaluated when M&S tools are used for prediction and optimisation of studies across populations."*	1) M&S supported/validated by limited observed data in a new population. 2) M&S approach as stand alone without requirements for data in these populations."	• Concerns of sponsors about regulator's attitudes • What research is required before implementation • Current standards for assessing the impact of assumptions and model validity • What is required for future use of model-based approaches (tools and methods)?	10:45-10:55 Challenges in dose selection for fixed dose combinations in paediatric indications and across ethnic groups. (Oscar Della Pasqua, GSK)
Regulatory Discussants Gerard Pons, PDCO and and Stephanie Läer, University of Düsseldorf (10min)			
Panel Discussion (10min)			

Theme 4			11:15-12:10
Position statement	**Record Industry Use and Regulatory Status**	**Open questions**	**Case studies**
Validity of assumptions (sparseness of evidence, priors, accuracy, variance and other statistical aspects) *"M&S should be used as a tool for data integration (preclinical and clinical historical data) to support analysis and interpretation of oncoming data, to optimise protocol design and enable decision making involving special populations, ethnic groups and rare diseases."*	1) M&S inferences supported/validated by limited observed data in a new population. 2) M&S approach as stand alone without requirements for data in new populations."	• Concerns of sponsors about regulator's attitudes • What research is required before implementation • Current standards for assessing the impact of assumptions and model validity • What is required for future use of model based approaches (tools and methods)?	11:15-11:25 PKPD assessment of topiramate dosing regimens for children with epilepsy from 2 years to less than 10 years of age (Chyi Hung Hsu, J&J) 11:25-11:35 Sample size estimation in a planned paediatric clinical trial utilising external information of historical trials in adults and children (Wolfgang Köpke, EMA) 11:35-11:45 Some statistical issues of modelling and extrapolation (Martin Posch, Peter Bauer)
Regulatory Discussants Gerard Pons, PDCO and Stephanie Läer, University of Düsseldorf (10min)			
Panel Discussion (15min)			

Wrap up, presentation of key points raised during the discussion panels by Stefanie Läer, Solange Rohou and Ralf Herold	12:10-12:25
Closing Remarks by Terry Shepard	12:25-12:30