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 4 (BOS 4)

Room 2A

Organisers: Rob Hemmings (CHMP), Nick Holford (Uni of Auckland), Filip Josephson (MPA), Mats Karlsson (Uppsala Uni), Scott Marshall (Pfizer), Martin Posch (EMA), Jean-Louis Steimer (Novartis)

Aims:

- Improve how Companies and EMA interact with respect to the use of M&S in the design and interpretation of Phase 3 studies
- It is important for EMA to understand how EPFIA intends to apply M&S in the future including the confirmatory /risk benefit setting
- It is important for EFPIA to understand where application of M&S would be acceptable to the EMA in order to guide future activities in the following areas:
  - In Phase 3 design (dose, comparator, selection, N etc)
  - Model based primary or key secondary analysis
  - Acceptability in estimating risk benefit including where this replaces the need for further studies
  - In creation of development path guidance for novel or existing disease areas

General introduction (Agenda, Objectives) Scott Marshall	08:30-08:35

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Theme 1: M&S to optimize the design of confirmatory trials			08:35-09:25
Position statement	**Current key Template questions**	**Suggested additional Questions**	**Case Studies**
Understanding the totality of data and how it relates to prior information from Phase 2 (for example, through evidence synthesis of literature data) provides quantitative evidence to support Phase 3 design and dose-selection	How can industry get the required early regulatory feedback and agreement on the acceptability of these approaches, models, inferences to minimise the probability of EOP3 discussion around the Phase 3 study design, choice of doses? Best timing for seeking this input, feedback? How to ask the right question(s) to get appropriate feedback?	Under what circumstances would using this supplementary information (internal or external) be considered acceptable: For dose selection ? For Phase 3 design (number of doses , numbers of subjects, comparator arms)? For Phase 3 programme design: 1 study vs 2 studies ? When should this approach not be considered?	Pfizer4/Roche3 Mike Smith/Valerie Cosson (20 min)
Regulatory viewpoint			Filip Josephson (5min)
Discussion			20 min
Summary			5 min

Theme 2: M&S to analyse & interpret Phase 3 data			09:25-10:30
Position statement	**Current key Template questions**	**Suggested additional Questions**	**Case studies**
A Longitudinal model based test as primary analysis in phase III is appropriate provided it is pre-specified and has been appropriately evaluated	Do the regulatory agencies agree that the proposed longitudinal model-based test is appropriate to be considered as primary analysis? If the answer is "no" at this point in time, what would it take to get acceptance for the proposed approach? What do we need to do to address the type I error concern beyond simulating from extensive scenarios? Is it really better to pre-specify just one model with minimal assumptions than use model averaging approach ?	What situations could this type of approach be applied ? Range : Biosimilars to new compound in new disease area A number of other examples (see Novartis 5 slides)	Novartis 5 Bruno Bieth (15min)

Theme 2: M&S to analyse & interpret Phase 3 data: Disease Progression			
Position statement	**Current key Template questions**	**Suggested additional Questions**	**Case studies**
"A parametric NLME approach offers a useful framework to design and analyse confirmatory trials that assess the impact of a new treatment on "disease progression"	What is required to build greater acceptance of NLME approaches to analysis of disease progression trials within a regulatory environment? What would be required for an NLME approach to become a key secondary or primary analysis for assessing disease progression?		Disease progression Mats Karlsson (5min)
Regulatory viewpoint			Rob Hemmings (5min)
Discussion			35 min
Summary			5 min

~ Coffee Break ~

10:30-11:00

Theme 3: M&S to characterize risk –benefit and support label claims			11:00-12:30
Position statement	**Current key Template questions**	**Suggested additional Questions**	**Case studies**
Successful approval of non-tested dosing scheme using M&S techniques without further dedicated prospective studies	Would in general the EMA accept the principle of relying on M&S approaches to label an unstudied dose or dosing regimen? What information and evidence are needed by the EMA to consider to label an unstudied dose or dosing regimen based on M&S approaches? In what circumstances would the EMA accept exposure in a sub-population outside the range of previously tested exposure in that subpopulation but within the range of previously tested exposure in an other sub-population?	What General Guidelines can be offered with respect to when such approaches would be accepted in other situations ?	Roche 1&2 Valerie Cosson (15min)
Regulatory viewpoint			Filip Josephson (5min)
Discussion			25 min
Summary			5 min

Theme 3: M&S to facilitate creation of development path guidance for novel or existing disease areas			
Position statement	**Current key Template questions**	**Suggested additional Questions**	**Case studies**
M&S is important, not only in individual drug projects, but also to understand a disease area and how the Regulatory requirements determines the feasibility for clinical development of a new compound. M&S can help guide the development of future Regulatory Guidelines in terms of suitable endpoints in clinical trials (early & late stage) and requirements for registration and label claims.	At what stage of development is it suitable to have industry-Regulatory interactions? What should be the requirements of M&S work in such a situation? Is there a potential for collaboration across companies? How to facilitate discussions, based on M&S, between industry and Regulatory agencies regarding new Guidelines? What should be the requirements of M&S work in such a situation?		AZ2 (AZ2) Christian Sonesson (10min)
Regulatory viewpoint			Rob Hemmings (5min)
Discussion			20 min
Summary			5 min