4 April 2012
EMA/143473/2012
Human Medicines Development and Evaluation

BOS1 Report - M&S in early development

EMA-EFPIA Modelling and Simulation Workshop, 30 Nov – 1 Dec 2011, London.

Organising Comittee: Thomas Kerbusch (MSD/Merck), Sandra Visser (AZ), Efthymios Manolis (EMA), Meindert Danhof (Leiden University), Beatriz Silva Lima (University of Lisbon), Markku Pasanen (Kuopio University), Walter Janssens (FAGG), Antti Poso (Kuopio University), Jean Marc (EMA)

Chairs: Thomas Kerbusch (MSD/Merck), Sandra Visser (AZ), Efthymios Manolis (EMA)

Disclaimer

The views expressed in this Report are the personal views of the participating experts and may not be understood or quoted as being made on behalf of or reflecting the position of the European Medicines Agency or one of its committees or working parties.

Summary

Three main topics were addressed. The first theme considered M&S in preclinical development. Two case studies on prediction of safety signals in humans based on preclinical data in the area of thyroid hormone changes and QT prolongation were discussed. A common ground was the wish for sharing data and building descriptor-based open databases with which quantitative models could be developed that describe pharmacological and in particular safety systems. This would imply a need for agreement on prioritization of modelling platforms to be developed (e.g. which toxicity signals, DILI, QT, others) and agreement on scientific aims. In long term, backbones of (systems) models will need to be developed and reused. Confirming experimentally the system specific parameters and gaining experience through use of models in real case scenarios would be able to build confidence on these models. The ultimate goal would be to use M&S and in vitro experiments to predict accurately the activity and toxicity profile of a new compound with minimal animal experimentation.

The second theme considered the use of M&S for first in man (FIH) dose selection. A case study was presented on how M&S could support the MABEL approach. It was recognized that M&S could be an important tool to aid the prediction of safety margins. FIH dose selection and escalation could be supported by M&S activities provided sufficient confidence in the model and adequate safety margins are taken into account for unexpected events. Safety may be increased during dose escalation when

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7040
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

lower dose level observations are added to the original model predictions and in certain cases dose escalation steps may be larger. For specific PK and PKPD and other type of system pharmacology models, there is a desire to qualify the models by building the level of confidence by predictions and confirmations using multiple compounds and mechanisms. Microdosing could be a way to allow for early refinement of models.

It was discussed that the documentation would require an adequate description of the assumptions made, and preferably a sensitivity analysis which allows for quantifying the risks of the assumptions. To date, mainly PK analysis and simulations are provided in documentation, but the aspiration is that clinical trial applications would include even M&S contributions on predictions of safety and efficacy. It was also indicated that increasing M&S contributions within the documentation packages might increase the workload for the regulators significantly and regulatory training and capacity building on this area will be needed. The current variation in terms of methodology used and validation, seen in models submitted, increases the regulatory uncertainty around model predictions. Regulators acknowledge that 'one size fits all' solution will not be feasible in this evolving field; nevertheless they would like to see models adhering to some basic principles, or qualify some backbone models. This will raise the confidence on the use of models in FIH. It was noted that regulatory model qualification is not limited to the scope of model validation (verification that the model describes the data and that the model assumptions are valid). Qualification would evaluate modelling and simulation in the context of a wider algorithm for predicting first in man pharmacokinetics together with safety and pharmacology related responses.

In the third theme of the session, a number of case studies were used to illustrate the number of ways how M&S could be used for optimal use of all available information including in vitro, preclinical (translational M&S), literature and in house data to optimize clinical development and help early selection of safe and efficacious drug. An example was given on a successful industry-academia consortium (TI Pharma: mechanism-based PKPD modelling platform) where systems models have been developed in a number of therapeutic areas. It was also highlighted that there a number of different modelling approaches that can be taken. Quantitative systems pharmacology was highlighted as a multidisciplinary contribution of modelling skills which can carry quantitative knowledge forward along the value chain and be used to rationalize decision making. Three examples were presented to illustrate how M&S could be used for dose selection in Ph2A, Ph2B and for go-no go decision making. The use of literature and competitor data to inform decisions and support dose selection was considered of value with transparency on assumptions made. It was shown that existing public domain data on comparators and standard-of-care is playing an increasing role of importance alongside clinical trial data generated for the investigational compound in making drug development decisions. The discipline of systems pharmacology is expected to grow fast in the future. Similarly to the themes discussed above the importance of sharing data and models and regulatory capacity building was highlighted. Regulators are eager to play a bigger role in early stages of drug development. The notion that exploratory development is the company's risk is wrong and regulators have a clear assignment in addressing the high attrition rates by facilitating new approaches to drug development. Modelling and simulation is a promising tool in this respect.

General concluded aspirations/Actions

Best Practices of Model-Based FIH Dose-Escalation.

What: Develop Best Practices (or Points-to-Consider) on the use of model-based (PK-PD) approaches (in parallel to NOAEL) for dose-escalation in First-in-Human trials including a focus on MABEL.

How: collect use-cases and identify common themes.

Grow EU regulators Capability in M&S.

What: Increase capability of EMA to assess model-based approaches ("going beyond popPK") through focused training conducted in partnership with EFPIA and Academia.

How: All partners share presentations on typical examples and Best Practices during training sessions at EMA.

M&S reporting in CTDs.

What: Provide guidance on preferred location of reporting of model-based approaches in regulatory documents (e.g. CTD modules).

How: EMA guidance document providing suggestions for typical locations in CTD modules for typical model-based approaches (FIH dose escalation steps, Phase 3 dose-selection, covariate effects and impact on dosing, etc).

Pre-competitive data and model sharing.

What: Initiate focused effort on pre-competitive sharing of systems data and toxicology signals.

How: Prioritize and identify key gaps and opportunities for pre-competitive sharing (e.g. DILI, QTc, etc.) based on need (other initiatives), feasibility and availability, with the aim of development of systems models and model qualification.