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# BOS 2 Report - M&S in clinical pharmacology and dose finding

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

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### Summary

BOS 2 focused on two topics 1) when and how M&S should be used and is accepted by the authorities for the dose regimen selection process and 2) when can the integration of data (e.g. across studies or clinical and in-vitro data) using M&S along with reasonable assumptions provide enough evidence for evaluation of efficacy/safety risks without the need for a separate study. Each topic was introduced by an industry and regulatory perspective, followed by case examples for illustration.

Regarding the dose regimen process for new drugs the following discussion points can be summarized. There is a perception that scientific evidence is being restricted by the nature of the studies required by regulatory authorities. For example, in a dose ranging study which only involves pairwise comparisons, it may not be possible to elucidate the nature of the dose-response relationship.

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Modelling potentially can lead to greater precision in the detection of the signal from the background noise in clinical trials. This in turn leads to more efficient trials with a consequent saving in patients and costs. Of course this is only the case when the model is an acceptable representation of the system. Model bias and hypotheses are the main issues which have dissuaded some people from using a modelling approach.

For the general questions whether the dose regimen selection process is the sole responsibility of the sponsor and whether it is sufficient for the regulators if efficacy and safety for the selected dose is shown in phase 3, there was no unambiguous answer. All participants agreed that an M&S approach to dose regimen selection may be helpful in providing insight in the “true” dose-response relationships. Regulators indicated that although some challenges in the “classical” way of dose finding may not be solved by M&S per se (e.g. in case of lack of suitable biomarkers, highly variable disease or non-sensitive endpoints), it is still considered a useful approach. Exploring PK-PD relationships in deeper detail by M&S have been helpful in regulatory decision making on the dose in the past, especially in situations where parallel studies did not provide a clear distinction between different dose levels.

In general, regulators will be more willing to accept dose regimen finding by M&S in situations where patients are sparse (e.g. for orphan indications and paediatrics), or if PK-PD relationships are very clear or straightforward (e.g. line extensions of accepted products, or antidote drugs). But usually, some Phase II confirmatory parallel dose-finding studies are still required for new drugs.

From an industry perspective, which was supported by some regulators, the limited exposure of regulators to these M&S approaches and the limited experience with regard to evaluating the results hinders a more definite answer from regulators regarding what is expected from industry. On one hand this lack of predictable regulatory acceptance hinders the further implementation of M&S driven dose regimen selection approaches in the pharmaceutical industry. On the other hand, M&S scientists of companies might have to deal with skepticism regarding M&S approaches within their own organisation. Some decisions actually based on M&S may not end up in the Clinical Overview, a key document for regulatory assessment, thereby reducing the chance that the models are considered pivotal in the process of regulatory assessment.

To promote M&S further clear regulatory endorsement by developing new guidelines or update existing guidelines (e.g. on dose finding) are considered essential.

In the second session we discussed how integration of data (e.g. across studies or clinical and in-vitro data) using M&S along with reasonable assumptions provide enough evidence for evaluation of efficacy/safety risks without the need for a separate study.

In general, the participants were more comfortable using a modeling approach for interpolation rather than extrapolation. With respect to pharmacokinetics, interpolation nowadays is quite commonly used (e.g. when estimating exposure in case of renal or hepatic impairment). However confidence in extrapolation can be increased by the use of external data and prior information. An acknowledged advantage of M&S is the possibility to investigate situations that cannot be tested or should be avoided. From a regulatory perspective, experience with translational M&S, e.g. extrapolation of in silico DDI data to the actual clinical situation seems promising, however, current regulatory experience leading to a dose advice due to DDIs is limited.

Key points for appropriate and efficient regulatory assessment of submitted M&S analyses are clear communication, and informing assessors adequately on the justification of the model, and on assumptions made by the modelers. Adequate validation, with an assessment of robustness and predictive performance of the model is a pre-requisite for regulatory acceptance.

We asked what M&S can do to improve our approach to QT prolongation risk. We saw presentations that demonstrated how totality of evidence significantly improves the negative and positive predictive values of the characterization of QT versus using any one QT study in isolation. There were questions raised around the potential inconsistent preclinical or clinical data acquisition/analysis and multiple approaches were suggested: 1) Empirical approach - Collect data set demonstrating ability of Phase 1 to predict TQT; 2) Incentive approach – Write guidance that allows sponsors to delay TQT until Phase 3, or emit TQT altogether, if appropriate preclinical or clinical data are acquired. A number of the breakout session participants believed that they were ready to trust a combined, 'totality of evidence,' approach to QT assessment including trusting concentration response models to predict negative and positive early phase data. To convince also the regulators completely a number of "totality of evidence" datasets need to be provided to them for thorough evaluation.

There was common mutual agreement that modelling and simulation is driven by and informs the underlying science. Therefore consistency and substantiation of the underlying science is a requirement for the acceptance of modelling and simulation. This is equally true for approaches that do not use modelling, although we would contend that there is no such thing as a truly model independent approach.

There was agreement that the **three following actions are needed to happen to advance the role of M&S in clinical pharmacology:**

Develop a guideline that endorses the use of M&S (but being not too restrictive to hinder this innovative field), or update relevant documents such as the dose regimen finding guideline

To develop a framework for interaction between regulators and industry regarding M&S approaches (including how best data and the M&S analyses results can be shared)

Additional training for assessors to allow comprehensive evaluation of the approaches

**Concrete action points regarding the content of the session are:**

**Rational dose regimen selection:** Define when and how M&S should be used and is accepted by the authorities for the dose regimen selection process

**QT:** Define what has to be done so that a combined "totality of evidence" approach to QT assessment can be applied and accepted for delay or as replacement of a TQT study