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COMMENTARY

Commentary on the MID3 Good Practices Paper

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During the last 10 years the European Medicines Agency (EMA) organized a number of workshops on modeling and simulation, working towards greater integration of modeling and simulation (M&S) in the development and regulatory assessment of medicines. In the 2011 EMA – European Federation of Pharmaceutical Industries and Associations (EFPIA) Workshop on Modelling and Simulation, European regulators agreed to the necessity to build expertise to be able to review M&S data provided by companies in their dossier. This led to the establishment of the EMA Modelling and Simulation Working Group (MSWG). Also, there was agreement reached on the need for harmonization on good M&S practices and for continuing dialog across all parties. The MSWG acknowledges the initiative of the EFPIA Model-Informed Drug Discovery and Development (MID3) group in promoting greater consistency in practice, application, and documentation of M&S and considers the paper is an important contribution towards achieving this objective.
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What the MSWG perceives as a problem with the current applications of M&S is that they are often dissociated from clinical decisions on the design and objectives of clinical trials. Although in areas like pediatric drug development and dose selection the M&S, the clinical and the statistical objectives are all considered and taken into account in study design and analysis; these are otherwise often seen as standalone applications and reported as such. This *ad-hoc* application of M&S has implications for the strength of evidence supporting modeling assumptions and consequently may limit the weight of M&S in clinical and regulatory decision making. For instance, sometimes M&S analyses are not well integrated into a phase III study protocol since the rationale behind it has not been fully communicated and understood. Then, the collection of the data may become suboptimal and it will be hard to answer questions about the influence of intrinsic or extrinsic factors on exposure and response in patients. A better alternative is to clearly motivate the analysis, set up objectives that are relevant and understandable to the whole development team, and to plan the study and analyses accordingly.

A key element in the MID3 white paper[1] is the implementation strategy, i.e., a strategic plan that closely follows the drug development steps and lays out the knowledge gaps, the important questions and how these should be addressed through model-informed activities across the compound, mechanism, and disease level. The development of a strategic plan, as proposed by the MID3 group, is expected to improve communication between the different scientific disciplines involved in drug discovery and development and optimize utilization of quantitative tools and study designs. The MSWG considers that the regulatory review of models as part of Scientific Advice, Paediatric Investigation Plan (PIP), Marketing Authorisation Application (MAA), and other submissions would be very much facilitated by having access to the MID3 strategic plan.

Another proposal included in the MID3 paper that is important is the documentation of assumptions, how they are assessed, and what impact they have on decisions. The MSWG sometimes finds it challenging to discuss models with other disciplines. The modelers are often not well informed to evaluate the clinical assumptions included in the models. On the other hand, the clinicians often struggle to understand the mathematical language describing the clinical assumptions and the clinical impact of the data/mathematical/statistical assumptions. This creates a communication gap and unnecessarily prolongs the integrated discussion needed about how the drug product should be developed and utilized in the best way.

In the best case, the modeling assumptions can be assessed by model diagnostics, sensitivity tests, or plain reasoning. If this is the case, some level of reassurance can be provided on the model predictions and inferences. If not, the uncertainty on the assumptions adds to the overall model uncertainty. In the end, for those using models in the context of drug development and evaluation, it is important to manage uncertainties by evaluating their clinical consequences/impact.

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The assumptions table provided in the MID3 paper provides a good way to document assumptions, uncertainties, and impact in regulatory submissions. Such a structured approach is expected to improve the dialog between clinicians, modelers, and other disciplines.

Another important way to improve communication between different disciplines is the recommendation on the different sections of the analysis report. The targeted approach of sections according to audience (all readers vs. technical) is very much welcome.

The MID3 paper includes additional comments on practical aspects of conduct, documentation, and reporting of modeling and simulation. The proposals, which will not be elaborated here for the sake of brevity, are recognized by the MSWG and are clearly an improvement compared to what is currently seen in submissions.

The MSWG also notes that in the past few years the abundance and the quality (in terms of context of use, adherence to good practices, and reporting) of M&S in the submissions have increased. There has also been an increased focus on the development of good practice documents pertaining to modeling and simulation (Byon *et al*., 2013[2]; Dykstra *et al*., 2015[3]; Overgaard *et al*., 2015[4]; Nguyen *et al.,* 2016[5]; Jones *et al*., 2015[6]) from specific companies and industry groups (EFPIA) and professional bodies (ISOP, PSI SIGG); the list is not exhaustive. In addition, the interplay between modelers and statisticians (i.e., EMA extrapolation workshop,[7] EMA small population workshop,[8] ASA-ISOP statistic and pharmacometrics interest group) is gaining momentum. The MSWG finds these trends encouraging, in the sense that it is indicative that M&S is becoming more integrated within drug development. Common themes across all these initiatives are the improvements in communication and reporting. There is a desire from MSWG to keep the interaction ongoing with the MID3 EFPIA group, to initiate bilateral contacts with other groups developing good practices, and to act as a facilitator for further development and regulatory implementation of good modeling practice in general. Through its interaction[9] with the US Food and Drug Administration OCP pharmacometrics group, PMDA and Health Canada, the MSWG also envisages harmonization of good modeling practices across regulators.

To conclude, the MSWG considers that the MID3 white paper can potentiate the utility of modeling and simulation in regulatory review in moving from an *ad-hoc* problem-solving exercise, as it is often perceived, to an important source of evidence generation that influences development and benefit/risk decisions, labeling, risk management, and is crucial for the product lifecycle. The MSWG supports the principles included in the paper and invites other groups developing good practices documents to actively engage in discussions with regulators.

Conflict of Interest. The authors declare no conflicts of interest.

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