

PERSPECTIVE

Modeling and Simulation in Clinical Pharmacology and Dose Finding

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The breakout session 2 of the European Medicines Agency/European Federation of Pharmaceutical Industries and Associations Modeling and Simulation (M&S) workshop focused on two topics: when and how M&S should be used and would be accepted by the authorities for the dose-regimen selection; and when and how M&S can be applied to register a dosing regimen without the need for a specific study. Each topic was introduced by an industry and regulatory perspective, followed by case examples for illustration (Table 1).

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THE USE OF M&S FOR DOSE-REGIMEN SELECTION

Optimal dose-regimen selection attempts to select a drug input profile that offers the best benefit/risk ratio for a given indication in a given population. Knowledge of the dose–exposure–response relationship is the key aspect for rational dose selection. The dose–exposure–response relationship is driven by the underlying pharmacology that characterizes the causal chain between administration of the dose and the observation of the response. Depending on the developmental state of a compound, response measures can be, e.g., measures for receptor occupancy, biomarker measurements indicating target engagement, surrogate end points, or clinical end points for efficacy or safety. Consideration of these pharmacology principles represents a first step in developing a rational approach to dose–response characterization. Mathematical models that allow integrating the available data under consideration of the pharmacological principles described above are well suited to characterize the dose–exposure–response relationship and predict a dosing regimen that offers the best benefit/risk ratio for the patient. A more accurate prediction of the right dose might lead to more efficient trials with a consequent saving in patients and costs (Table 1, IP1).

Although this approach is very attractive and was already often successfully used in the past,^{1,2} its application in clinical development is sometimes limited for various reasons. On the one hand, traditional dose ranging studies required by regulatory authorities, which involves pairwise comparisons, may not allow the elucidation of the nature of the dose–response relationship. On the other hand, the unavailability of suitable biomarkers, nonsensitive clinical end points, highly variable disease, or the absence of a causal relationship hamper the conventional dose-finding approach as well as the modeling approach. Moreover, one of the main reasons for not applying models more extensively for dose-regimen selection processes is the concern regarding model bias and hypotheses, i.e., doubts that the

model is a correct representation of the system (Table 1, RP1, CS1).

Despite these concerns and limitations, all participants of the workshop agreed that an M&S approach to dose-regimen selection may be helpful in providing insight into the “true” dose–exposure response relationship. Exploring pharmacokinetic–pharmacodynamic relationships in deeper detail by M&S has been helpful in regulatory decision making on the dose in the past (^{3,4}, Table 1, RP1, CS3), especially in situations in which 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 at which a limited number of patients are available or a condition is difficult to study (e.g., for orphan indications, pediatrics, or elderly with renal insufficiency), or if pharmacokinetic–pharmacodynamic relationships are very clear or straightforward (e.g., line extensions of accepted products, anti-infectives, or antidote drugs). Study designs that allow a better understanding of the pharmacokinetic–pharmacodynamic relationship are encouraged (Table 1, CS2); however, usually some Phase II parallel dose-finding studies are still required for new drugs.

From an industry perspective, which was confirmed by some regulators, the limited exposure of regulators to these M&S approaches and the limited experience with regard to evaluating the results hinder a more definite answer from regulators regarding what is expected from industry and give rise to variable responses for the modeling parts in submissions. 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 organization. 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 indeed considered pivotal in the process of regulatory assessment.

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Table 1 Presentations breakout session 2: modeling and simulation in clinical pharmacology and dose finding

Title	Presenter	Link to presentation
Dose–exposure–response relationships: the basis of effective dose–regimen selection—industry perspective (IP1)	Michael Lobby (Novartis)/Peter Miligan (Pfizer)	http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2011/11/WC500118276.pdf
Dose–concentration–response–relationship—regulatory perspective (RP1)	Elisabeth Rook (Medicine Evaluation Board)	http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2011/11/WC500118275.pdf
Dose finding under model uncertainty—a case study based on a multiregional clinical trial (CS1)	Chyi-Hung Hsu (Johnson & Johnson)	http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2011/11/WC500118274.pdf
Design of a model-based dose-finding study in diabetes (CS2)	Marie Sandstrom (Astra Zeneca)/Sofia Friberg Hietala (Astra Zeneca)	http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2011/11/WC500118277.pdf
Improvement of clinical benefit for a subgroup of pediatric sJIA patients utilizing model-based dose adjustment optimization (CS3)	Nicolas Frey (Hoffmann-La Roche)	http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2012/04/WC500126726.pdf
The integration of data (e.g., across studies or clinical and <i>in vitro</i> data) using modeling and simulation along with reasonable assumptions can provide evidence for evaluation of efficacy/safety risks without the need for a separate study—industry perspective (IP2)	Charles Benson (Eli Lilly)	http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2011/11/WC500118278.pdf
Integration of data using modeling and simulation can provide evidence for evaluation of efficacy-safety risks without the need for a separate study—regulatory perspective (RP2)	Marc Maliepaard (Medicine Evaluation Board)	http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2011/11/WC500118279.pdf
Modeling and simulation for dose adjustment in renally impaired patients (CS4)	Monica Edholm (European Medicines Agency, EMA)	http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2011/11/WC500118280.pdf
Modeling of drug-interaction mechanism and estimation of drug interaction in patients with renal impairment (CS5)	Monica Edholm (EMA)	http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2011/11/WC500118280.pdf
Assessing the probability of drug-induced QTc-interval prolongation during early clinical drug development (CS6)	Oscar Della Pasqua (Glaxo SmithKline)	http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2011/11/WC500118281.pdf

The framework of this session was “use of modeling and simulation with existing information (data, physiological/mechanistic knowledge) and reasonable assumptions will allow for improvements and efficiency in informed decision making to improve the outcomes for patient safety and efficacy in the clinical pharmacology arena.” Organizing committee: L.A., Norbert Benda, C.B., M.M., France Mentré, Krishna Prasad, Amin Rostami, E.R., and A.S.

THE USE OF M&S TO REGISTER A DOSING REGIMEN WITHOUT THE NEED FOR A SPECIFIC STUDY

For a specific compound, it might not be possible to provide comprehensive safety and efficacy data for each (sub)population of interest or specific therapy condition due to ethical considerations and feasibility of studies. In such situations, M&S approaches could be used to integrate suitable data (e.g., across studies or inclusion of *in vitro* data) and give the possibility to simulate (investigate) situations that cannot be tested or should be avoided. This together with reasonable assumptions might provide enough evidence for efficacy/safety without the need for a separate study (Table 1, IP2, RP2).

The participants were, in general, more comfortable using a modeling approach for interpolation rather than extrapolation.⁵ With respect to pharmacokinetics and pharmacokinetic–pharmacodynamic relationships, nowadays, interpolation is quite commonly used (e.g., when estimating exposure in case of renal or hepatic impairment (Table 1, CS4)). However, confidence in extrapolation can be increased by the use of external data, prior information, mechanistic understanding and at least some sparse data. From a regulatory perspective, experience with translational M&S, e.g., extrapolation of *in silico* drug–drug interaction data to the actual clinical situation seems promising; however,

current regulatory experience leading to dose advice on Data Documentation Initiatives is limited (Table 1, CS5).

One important question was how M&S can be used to improve the approach to QT prolongation risk. Data were presented (Table 1, RP2, CS6) that showed how the totality of evidence significantly improves the negative and positive predictive values of the characterization of QT vs. using any one QT study in isolation.^{6,7} Characterization in this case refers to the ability of the combined assays to appropriately identify the potential risk of a clinically significant drug-induced change in the QT interval.

Potential hurdles could be inconsistent preclinical or clinical data acquisition/analysis. Two main approaches could be identified: empirical approach—collect data set demonstrating ability of Phase 1 to predict TQT. The empirical approach simply follows a retrospective (or prospective) correlation of early phase data to TQT studies. This provides no incentive for companies to provide improved data in preclinical or early clinical studies; or incentive approach—written guidance that allows sponsors to delay TQT until Phase 3, or omit TQT altogether, if appropriate preclinical or clinical data are acquired and used for prospective predictions of QT liability. To be noted, in Europe, this decision is the local ethical committees’ responsibility, as the European Medicines Agency does not decide on initiation of Phase III trials. An incentive approach

rewards companies that design studies optimally and perform and evaluate them excellently with the opportunity to avoid the TQT study.

It might be necessary to perform first a “totality of evidence” approach to QT assessment to predict reliably negative and positive early phase data before an incentive approach can be taken. To convince the regulators completely, a number of “totality of evidence” data sets need to be provided to them for thorough evaluation. To achieve this, possibilities of precompetitive sharing of data should be evaluated.⁸ For example, a proposal is currently being put forward for a study of a set of well-characterized compounds to describe the ability of non-clinical and early clinical assays to find (or not find) a QT signal at the threshold of regulatory interest. If this approach is successful, regulatory agencies may agree that if nonclinical and early clinical data are generated in a similar fashion and rule out significant risk, a TQT study will not be required.

In general, it can be concluded that the acceptability of M&S approaches instead of observational data for registration of a dosing regimen in an untested population/condition is difficult to state in general terms as it is influenced by many factors. Important requirements will be that the clinical and pharmacological assumptions of the model are adequately supported by both empirical evidence and the underlying mechanistic understanding; in addition, a suitable risk mitigation strategy should be implemented.

For all kinds of M&S analyses discussed in this break out session, it can be stated that key points for appropriate and efficient regulatory assessment are clear communication, informing assessors adequately on the justification of the model, and on assumptions made by the modelers. Adequate validation, with an assessment of robustness (sensitivity analysis) and predictive performance of the model is a prerequisite for regulatory acceptance.

COMMON OBJECTIVES AND PROPOSED NEXT STEPS

Industry, regulators, and academia were aligned in that M&S is an important tool to support dose-regimen selection for a target population as well as to dosing recommendations for an untested population/clinical condition (see **Table 2** in ref. 9). Although it will be very difficult to come up with an universally applicable and definite criteria when and how these approaches are accepted, all participants agreed that this can be facilitated by developing a framework for acceptance. As a first step, the development of a guideline that endorses the use of M&S in general was proposed, or/and an update of relevant documents such as the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use dose-finding guideline¹⁰ were found crucial to further advance the role of M&S in clinical development. In the development of such documents, it should be noted that the guidelines should not be too restrictive so as to hinder this innovative field.

With regard to QT prolongation, it should be defined 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 a replacement of a TQT study (e.g., precompetitive sharing of data, combination with other initiatives).

In addition, interaction between regulators and industry regarding M&S approaches should be intensified using either already existing possibilities (e.g., project-specific scientific advice, innovation task force, or qualification process) and/or new ways that can be discussed, e.g., at further European Medicines Agency/European Federation of Pharmaceutical Industries and Associations workshops. As a third objective, additional training of assessors to allow a comprehensive evaluation of the M&S approaches/results was identified as an important factor to promote these approaches.

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