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PERSPECTIVE

Modeling and Simulation to Optimize the Design and Analysis of Confirmatory Trials, Characterize Risk–Benefit, and Support Label Claims

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The role of modeling and simulation (M&S) in the design and interpretation of phase III studies, from break out session 4 of the European Medicines Agency (EMA)/European Federation of Pharmaceutical Industries and Associations (EFPIA) M&S workshop, was divided into themes illustrated with case studies (Table 1): (1) M&S being conducted to support the design of confirmatory trials; (2) longitudinal model-based test as primary inferential analysis (biosimilarity and disease progression trials); (3) assessment of benefit–risk ratio, approval and labeling of an unstudied dose or dosing regimen, and development of future regulatory guidance.
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M&S BEING CONDUCTED TO SUPPORT THE DESIGN OF CONFIRMATORY TRIALS

Although no specific guidance exists, the role of M&S in designing and analyzing trials within the confirmatory phase of development has been encouraged by European regulatory colleagues.[1,2] The positive contribution of M&S for the purpose of designing confirmatory trials was unequivocally agreed during discussions. As listed in **Table 1**, the two presented case studies (case studies 1a and 1b) reflected dose selection in phase III using information from previous trials for the compound of interest and meta-analysis based on literature data using a drug–disease model for the efficacy endpoint. In contrast to the prospective examples, it was recognized that some decision makers within sponsor organizations do not realize that regulators also place considerable importance on the additional learning that can be gained from late-stage drug development, which can be enhanced through the application of M&S. It was agreed that regulators have an interest and responsibility to help guide dose selection and provide recommendations on dose selection for phase III studies. Regulatory review, whether at scientific advice or assessment of marketing authorization application, has generally focused on uses of M&S that were important for the regulatory decision, including exercises to "fill gaps" for questions that were not directly addressed in the clinical trial program. M&S contributions conducted predominately for the sponsor's internal decision making has received less attention. Engagement of companies with EMA before or during phase II would facilitate alignment with respect to the plan for confirmatory development and the expected impact level of the planned M&S activity discussed elsewhere.[3]

A LONGITUDINAL MODEL-BASED TEST AS PRIMARY INFERENTIAL ANALYSIS AND THE ROLE OF NONLINEAR MIXED EFFECTS MODELING APPROACHES IN THE ANALYSIS AND INTERPRETATION OF DISEASE PROGRESSION TRIALS

Case studies 2a and 2b were considered to have a "high impact" on the regulatory decision framework,[3] because they pertain to an analysis of pivotal clinical trial data that would affect the drug label. It was recognized that these approaches have scientific merit and discussion on implementation should continue. Case study 2a (**Table 1**) proposed a fully prespecified longitudinal model-based test for biosimilar equivalence assessment, with an illustration in rheumatoid arthritis. A number of methodological issues were highlighted for further discussion, not least the approach to controlling type 1 error through simulations and the various modeling and statistical assumptions that underpin the suggested approach. Case study 2b covered additional assumptions necessary to conclude drug-related disease progression modification via the application of a framework of hierarchical parametric (nonlinear mixed effects) models. Academic examples exist[4,5] but they were retrospective and were not submitted for a detailed review by the health authority. The potential regulatory acceptability of a modeling approach, in this case, would be enhanced because the potential for such modeling approaches is consistent with the principles expressed in relevant disease-related EMA documents (Guideline on Alzheimer's Disease[6] and Guideline on Parkinson's Disease[7]). Furthermore, it was agreed that inferential assessment of a disease progression change would require a longitudinal analysis approach to be used regardless of the selected statistical method used, be it a nonlinear mixed effects modeling or linear regression

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Table 1 Presentations of break out session 4: modeling and simulation to optimize the design and analysis of confirmatory trials, characterize risk–benefit, and support label claims

Title	Presenter	Link to presentation
1) Modeling and simulation to optimize the design of confirmatory trials		
a) Using totality of data for dose selection, phase III design, internal and regulatory decision making	Mike Smith (Pfizer)	http://www.emea.europa.eu/docs/en_GB/document_library/Presentation/2012/04/WC500126731.pdf (two case studies in one presentation)
b) PPAR phase III dose selection using a general PPAR drug–disease model based on a meta-analysis of more than 40 PPAR clinical trials	Valerie Cosson (F. Hoffmann-La Roche)	
2a) A longitudinal model-based test as primary analysis in phase III is appropriate provided it is prespecified and has been appropriately evaluated	Bruno Bieth (Novartis)	http://www.emea.europa.eu/docs/en_GB/document_library/Presentation/2011/11/WC500118295.pdf
2b) Mixed effect models for trials of disease-modifying treatments	Nick Holford (University of Auckland, NZ) and Mats Karlsson (Uppsala University)	http://www.emea.europa.eu/docs/en_GB/document_library/Presentation/2011/11/WC500118294.pdf
3a) Modeling and simulation to characterize risk–benefit and support label claims: decisive support of modeling and simulation for getting drug approval of nontested dosing scheme	Valerie Cosson (F. Hoffmann-La Roche)	http://www.emea.europa.eu/docs/en_GB/document_library/Presentation/2011/11/WC500118296.pdf
3b) Modeling to guide regulatory guidelines and decision making during development	Christian Sonesson (AstraZeneca)	http://www.emea.europa.eu/docs/en_GB/document_library/Presentation/2011/11/WC500118297.pdf
BOS4: plenary feedback	Scott Marshall (Pfizer)	http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2012/04/WC500126739.pdf
BOS4: summary and action plan	Organizing committee	http://www.ema.europa.eu/docs/en_GB/document_library/Report/2012/05/WC500127122.pdf

PPAR, peroxisome proliferator-activated receptor.

approach. Also, the investigation of the impact on disease progression would be secondary to establishing an overall treatment effect that would therefore lend plausibility to the findings. It was discussed that labeling claim statements indicating an impact on disease progression would additionally require linkage between the primary endpoint and the underlying pathology of the disease, illustrated by different measurements (e.g., biomarkers and brain imaging). Again, the scientific merit for increasing the use of modeling approaches is recognized and dialogue between regulators and industry for increased implementation should continue.

M&S APPROACHES TO ASSESSMENT OF THE BENEFIT–RISK RATIO, APPROVAL AND LABELING OF AN UNSTUDIED DOSE OR DOSING REGIMEN, AND IN DEVELOPMENT OF FUTURE REGULATORY GUIDANCE

The first part of Theme 3 (**Table 1**, Theme 3a) considered the "high-impact" potential of the regulatory acceptability of M&S approaches to assessment of the benefit–risk ratio and to approval and labeling of an unstudied dose or dosing regimen. In respect to the former, it was highlighted that M&S approaches can help to inform the risk–benefit assessment, allowing quantitative data integration through appropriate models and providing "what if" scenario answers via stochastic simulation. Reference was made to the ongoing risk–benefit methodology assessment project,[8] whereas the M&S approaches discussed here could potentially provide inputs into the risk–benefit decision framework that is under discussion; this topic was beyond the scope of the break out session.

The acceptance of an M&S approach, or indeed in providing justification for an unstudied dose, is influenced by many factors and hence acceptability is difficult to state in general terms. However, it was discussed that the clinical and pharmacological assumptions of the model would need to be adequately supported by both the empirical evidence and the underlying mechanistic understanding. The resultant drug exposure from the unstudied dose being within the empirically studied range for the compound would be easier to accept from a regulatory point of view, though the possibility of extrapolation was not principally excluded. The validity of the model for extrapolation, the estimated benefits and risk, the medical need, and, importantly, the rationale for the acceptance of a model-based prediction rather than further empirical investigation of the proposed dose would also need to be provided. An appropriate risk mitigation strategy could be crucial to the acceptability of an unstudied dose/dose regimen, e.g., use of titration, flexible dosing, appropriate patient monitoring. The session also considered extrapolation between populations. For these exercises, the assumption that pharmacokinetic/pharmacodynamic–-clinical response relationship could be extrapolated from the one subpopulation to the other was considered of pivotal importance for inference to be based on a modeling approach (BOS 3 paper[9]).

Throughout the session, the question of how to ensure good practice and hence reliable M&S exercises was considered. It was recognized that, without appropriate planning and conduct, bias could easily be introduced. Although this is true for all M&S exercises, in the confirmatory setting, this represents the biggest investment risk for companies and the possibility of false-positive licensing decision by regulators. The possibility of regulators proposing the use of M&S to drug companies as an aid to understanding the risk–benefit, as part of scientific advice or marketing authorization application review, was discussed. Depending on the context, and in particular for use as confirmatory evidence, a prospective approach may well require an increased degree of prespecification, preplanning, and early engagement with regulators.

Theme 3b (**Table 1**) focused on the high-impact use of M&S to guide regulatory guidelines and decision making during drug development. It was agreed that M&S was important in helping understand a new disease area and how regulatory requirements (e.g., the suitability of endpoints, populations in early- and late-stage trials, requirements for registration, and label claims) determine the feasibility for clinical development of a new compound. Given that such definitions would be defining standards for design of "pivotal" clinical trials, this example was considered to be of "high impact." Application of M&S to help quantify and appraise the feasibility of drug development in a particular therapeutic area was viewed positively as it would add, as stated by one regulatory colleague, "objectivity to an otherwise predominately subjective exercise." The potential for a conflict of interest having an influence on the scope of a prospective clinical development program was raised and, as such, the need for clear presentation and critique of underlying assumptions was stressed on several occasions. Similarly, the need for the regulatory agency to expect more requests of this nature in the future was emphasized. It was agreed that the role of consortia in developing disease-level model libraries and engaging with regulators in the "approval" of drug discovery and development of M&S tools should be encouraged (BOS1 paper[10–12]).

COMMON OBJECTIVES AND THE NEXT STEPS PROPOSED

Break out session 4 captured the current practice in the application of M&S in the confirmatory stage of development through case studies that have either been submitted to European regulators or would be considered to be of high impact within the new EMA regulatory framework. The EMA was interested in how EPFIA intends to apply M&S in the confirmatory and risk–benefit setting in the future. EFPIA was similarly interested to understand the degree of regulatory acceptability of M&S approaches applied within the confirmatory setting for ultimate regulatory approval to guide future activities in the following areas: (i) in phase III design (dose, comparator, selection, *N*, etc.); (ii) model-based primary or key secondary analysis; (iii) acceptability in estimating risk–benefit, including where it may replace the need for further studies; and (iv) in the creation of development path guidance for novel or existing disease areas. The shared opinion that M&S was an important tool in improving R&D efficiency and decreasing late-stage failure underpinned the valuable discussion that occurred both before and during the workshop. There was alignment on the need for clear technical and practical standards for best practice application of M&S principles. Discussion focused on how particular M&S strategies might be implemented within the regulatory process. An agreed common goal was established between the EMA and EFPIA to improve standardization, transparency, and consistency of M&S packages to enable more productive and predictable regulatory review. This will include, for instance, the identification and assessment of both statistical and pharmacological assumptions and the need for clear appropriate prespecification of modeling being conducted for medium- to high-impact drug development scenarios. Further actions are detailed in BOS4: summary and action plan (**Table 1**).

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