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Human Medicines Development and Evaluation

BOS 4 Report - M&S to optimise the design of confirmatory trials, to analyse Ph3 data and to characterise risk-benefit & support label claims

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Summary

BOS4 was dedicated to discussing how companies and the EMA view the use of M&S in the design and interpretation of Phase 3 studies. The EMA was interested in how EPFIA intends to apply M&S in the confirmatory /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. 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. Discussion focused on how particular M&S strategies might be implemented. An agreed common goal to improve standardisation, transparency and consistency of M&S packages in order to enable more productive and predictable regulatory review was established.

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Theme 1 focused on **M&S being conducted to support the design of Phase 3 trials**. The positive contribution of M&S for this purpose was unequivocally agreed. It was recognised that some decision-makers within sponsor organisations do not realise that regulators also value late-stage exploratory drug development and the associated use of modelling and simulation to quantify knowledge and assist in planning confirmatory development. It was agreed that regulators had both a role and a responsibility in guiding the optimal selection of dose based on available data, if approached by a sponsor. Regulatory review, whether at Scientific Advice or assessment of Marketing Authorisation Application, had 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 programme. Exercises conducted predominately for the sponsor's internal decision-making had received less attention. Engagement of EFPIA 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 work.

Theme 2 considered two proposals; 1) ***a longitudinal model-based test as primary inferential analysis*** *and 2) the role of* ***NLME approaches in the analysis and interpretation of disease progression trials*** . Both examples were considered as "High Impact" on the regulatory decision framework, since they pertain to the analysis of pivotal clinical trial data. It was recognised that these approaches have scientific merit and discussion on implementation should continue. 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 which underpin the suggested approaches. Proposal 2 covered additional assumptions necessary to conclude drug-related disease progression modification via the application of a framework of hierarchical parametric (NLME) models. The potential regulatory acceptability of a modeling approach, in this case, would be enhanced because the potential for such modeling approaches is already covered in disease related guidance EMA documents (Alzheimer's Disease & Parkinson's Disease). Furthermore, it was agreed that inferential assessment of a disease progression change would require a longitudinal analysis approach to be employed regardless of the selected method. Also the investigation of the impact on disease progression would be secondary to establishing an overall treatment effect. It was discussed that Labelling 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. brain imaging). Again, the scientific merit is recognised and dialogue for implementation should continue.

The first part of **Theme 3** 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 of the former, reference was made to the ongoing Benefit Risk (BR) methodology assessment project[1]. It was highlighted that M&S approaches can provide an important input into the BR assessment, allowing data synthesis through appropriate models and providing *what if* scenario answers via simulation. M&S approaches are valuable regardless of the more quantitative BR assessment approaches that are currently under discussion[1]. The acceptance of a 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 excluded. In addition, the regulatory approval of an unstudied dose would depend on the extent of associated circumstantial risk, the underlying benefit and medical need. Also

an appropriate risk mitigation strategy could be important 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 PK/PD for efficacy and safety could be extrapolated from the one subpopulation to the other was considered of pivotal importance.

Throughout the session, the question of how to ensure good practice and hence reliable M&S exercises was considered. It is recognised that, without appropriate planning and conduct, bias could easily be introduced. The possibility of regulators proposing (and perhaps pre-specifying to a certain degree) the use of M&S as an aid to understanding the risk benefit, as part of end of Phase 2 or Marketing Authorisation Application review, was discussed.

The second part of **Theme 3** 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 & late stage trials and requirements for registration and label claims) determine the feasibility for clinical development of a new compound. Given that this would be defining standards for design of 'pivotal' clinical trials, this example was considered to be of 'high impact'. Application of M&S in this case was viewed positively as it would add "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 programme was raised and, as such, the need for clear presentation and critique of underlying assumptions was stressed. Similarly, the need for regulatory agency to expect more requests of this nature in the future was emphasised.

1) Ref
   European Medicines Agency Risk Benefit methodology assessment project.
   http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/document_listing/document_listing_000314.jsp&mid=WC0b01ac0580223ed6

Actions

General

1) EMA, in conjunction with EFPIA, to define how alignment around the use of M&S in dose selection , design of confirmatory trials and reducing uncertainty in regulatory decisions can be discussed in advance of submission. This should consider how alternative meetings prior to Scientific Advice (such as Innovation Task Force (ITF), Qualification Meetings (QM)) can be used to facilitate early, non-binding, interaction on specific methodological topics. Consideration should also be given to increasing the prominence of M&S approaches within the Scientific Advice process.

2) EFPIA, in discussion with EMA, to lead the development of M&S best practice(s) which embraces the presented regulatory framework and includes the following: Identification and assessment of both statistical and pharmacological assumptions; and the need for clear appropriate pre-specification of modelling being conducted for medium to high impact drug development scenarios. Specific, targeted uses of M&S could subsequently be discussed with regulators to build standards for different types of M&S exercises.

Theme 2 (Model based testing / disease progression modelling)

3) EMA to give further consideration to the proposed model based testing approach and provide further guidance with respect to a way ahead which may lead to acceptance in the future. One possibility: EMA/EFPIA to initiate an ITF or a QM meeting on methodological aspects, e.g. role of longitudinal or NLME analyses, or simulation approaches for type-1 error control.

4) EFPIA to further develop the parametric model based framework for determining the impact on disease progression. Develop appropriate case studies for further discussion with regulators utilising existing partnerships e.g. IMI DDMORE and CAMD projects

Theme 3

Theme 3 (Risk Benefit and approval of unstudied dose)

5) EFPIA (in discussion with EMA) to consider how the quantitative M&S work, to capture and describe the benefits and risks in future Market Authorisation Application could be pre-specified in order to reduce the potential for bias.

6) EMA to consider how it could offer "advice" on the merits of undertaking M&S analysis (including causal linkage) as an output of the review of submitted End of Phase 2 packages or in review of Phase 3 packages.

7) EMA, in discussion with EFPIA, to provide further considerations on circumstances where M&S could be used for approval of a different dose or dose regimen to that originally studied. This would refer to risk-benefit assessment, risk-mitigation strategy with respect to new regimen, medical need, and additional evidence in support of the interpolated dose.

Theme 3 (Guide regulatory guidelines)

8) EMA /EFPIA to jointly consider how to encourage use of M&S to facilitate creation of development path guidance for novel or existing disease areas including outline of the route that should be used in order to attain regulatory advice and in-depth interaction e.g. ITF (Innovation Task Force) meetings / Scientific advice.