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BOS 3 Report - M&S as a tool to bridge efficacy and safety data in special populations

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Summary

The development, registration and approval of novel medicines have traditionally been based on evidence arising from (large) prospective trials. Such an evidence-based approach is often unsuitable to evaluate benefit/risk (B/R) in special populations, ethnic groups or rare diseases. Inferential methods applied through modelling & simulation (M&S) can play a major role in the process of evidence synthesis and provide a strong basis for decision making during development, registration and therapeutic use of drugs.

The challenges for the systematic implementation of M&S in regulatory submissions and approval of label claims were introduced during a plenary session. The main issues faced by industry and

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regulators were illustrated with examples of successful and unsuccessful approaches across a range of diseases and conditions. Some of the Paediatric Committee's experiences were also shared to bring in the regulatory expectations. Among other things, it was clear that the degree of regulators' scrutiny in the use of M&S depends on the impact it has on clinical trials, label claims and on the implications for patients. The lack of a streamlined process and the need for a framework to assess assumptions and consequences for patients and other stakeholders was highlighted as the basis for better understanding and acceptance of alternative approaches for evidence synthesis of the benefit/risk of an intervention.

BOS3 was dedicated to discussing how developers and the EMA view the use M&S to support the design (i.e., protocol optimisation), as well as the analysis and interpretation of existing or new evidence. EFPIA was interested in understanding the degree of regulatory acceptability of M&S approaches to support indications in special populations, ethnic groups and rare diseases.

Consensus was obtained from all participants that M&S allows knowledge integration, enhancing the value of historical data for the assessment of pharmacokinetics, pharmacodynamics, efficacy and safety profiles in the populations of interest. The main challenge for regulatory and clinical acceptance of inferential methods remains, however, the lack of clarity about the assumptions and clinical consequences of inaccuracies or biases in M&S. **A standardised process to summarise assumptions and evaluate their impact was considered necessary in order to establish 1) the adequacy of the inferences, 2) the need for additional evidence and 3) the requirement for mitigation measures**. Of particular importance was the assessment of the consequences of assumptions used in M&S. Assumptions can be violated (this should be addressed accordingly e.g. , by additional evidence or by a better model), mitigated (e.g., by label restriction, dose titration) or managed as risk to patients and other stakeholders (e.g., regulator/sponsor).

Case examples were discussed to illustrate how assumptions are used and how their consequences are assessed from a clinical, pharmacological, statistical and regulatory perspective. Four main themes were identified for the purposes of the discussion:

Theme 1 focused on **t**he u**se of historical data from a reference population under the assumption of scalable ADME processes**. The position statement was that M&S should be routinely used to support dose finding in special populations and ethnic groups. The positive contribution of M&S for this purpose was unequivocally agreed. It was recognised that increased mechanistic understanding of drug disposition and pharmacodynamics offered considerable advantages over empirical methods, enhancing the accuracy and precision of model-based extrapolations (i.e., predictive power). The selected example (sugammadex) illustrated that such mechanistic considerations are also critical for the evaluation of pharmacokinetic and pharmacodynamic drug-drug interactions and assessment of dosing recommendations. Model-based predictions allowed evaluation of potential interactions and implications for the dose regimen in paediatric and renal-impaired populations. This example had high regulatory impact, as the simulations were used in lieu of in vivo interaction studies with drugs identified with a risk for displacement and provided a basis for SmPC wording. The model utilised allometric scaling for both sugammadex and rocuronium, both justified by their mechanism of elimination (mainly renal and biliary, respectively). Yet, uncritical, blanket application of allometric scaling must be avoided as additional factors may contribute to differences between populations, e.g. oral medications with variable (and less predictable) bioavailability. It was also pointed out here and for other examples that allometric scaling depends very much on the age range studied and must be considered carefully (e.g., in this case should not be extrapolated to children < 1 year and generally should not extrapolate beyond the age range used in model development). There are some subtleties that are only anticipated from an understanding of biological

processes and how they change in different populations (e.g. pharmacogenetic effects of acetylation are not apparent in neonates as a result of the immaturity of the enzyme responsible; sensitivity to drug-drug interactions is likely to change with age, as different cytochromes mature at different rates). Applying such mechanistic understanding to assess the biological plausibility of models can provide justification of the modelling approach and are supportive during regulatory assessment.

Of special interest was the application of physiologically-based pharmacokinetic (PBPK) modelling techniques, which provide a strong scientific basis for the description of potential impact of differences in physiology, metabolism, transporters, etc as a result of ethnicity, maturation, disease, etc. These processes may be of relevance when extrapolating from one well studied population to a new population and allow maximal utilisation of the existing PK data for a drug while minimising the impact of incorrect assumptions. It was discussed that PBPK could be complementary to empirical or allometric approaches, providing a basis for evaluating the sensitivity to model assumptions and also to anticipate covariates for incorporation into the population-PKPD model, to predict variability in PK beyond observed limits (i.e., beyond the small sample size normally utilised in paediatric or other small populations), to anticipate individuals who might have be exposed to higher risk due to pharmacokinetic differences and to support optimal study design. It was acknowledged that this is not current practice among companies and questioned whether we are ready as yet. A "predict-learn-confirm" paradigm would add confidence to the approach. For the few PBPK examples submitted so far in support of paediatric drug development, the confirmation step has been missing and is viewed as valuable to support the regulatory assessment of the entire paediatric data package. Particularly for children below 2 years of age, it is advisable to avoid oversimplification in extrapolation of PK while ignoring the maturational differences in these younger age groups.

The example also illustrated the use of literature models. Where a literature model is used for high-impact regulatory decisions, companies are advised to provide a critical assessment, justification and appropriate documentation for the model. Publication in a peer-reviewed journal is not normally considered adequate documentation.

It was agreed that the assumption of comparable pharmacokinetic-pharmacodynamic (PKPD) relationships across populations was an important point to consider. Often the use of bridging of pharmacokinetics in regulatory submissions lacks details or evidence supporting the assumption of similar PKPD relationships across populations. Early interactions with the PDCO or through the Scientific Advice procedures (EMA or national) were recommended to ensure clarification of the assumptions and overall approach to be used for the purpose of bridging. Companies are encouraged to provide detailed descriptions of their modelling approaches and underlying assumptions to best support useful discussions/advice.

Theme 2 considered the **use of data from another disease (indication) under the assumption of comparable pathophysiology and PKPD relationship across populations.** The position statement was that M&S should be used to extrapolate (PK, PD, efficacy or safety) data not only between different populations, but also across endpoints and diseases. Two examples were presented which can be considered as "moderate impact" on the regulatory decision framework, since they provided the basis for dose selection and inferences about efficacy in a new indication (the Pfizer case) as well as in a new population (the AZ case). It was recognised that extrapolation of pharmacodynamic endpoints, bridging across diseases as well as across different ethnic groups requires 1) a higher degree of understanding of the pathophysiology and 2) that M&S assumptions have to be scrutinised carefully and thoroughly. In fact, the number of cases available from regulatory submissions is rather limited, as the approach is not yet widely used by industry, despite its importance in areas such as

rare diseases. Allometric scaling of bioavailability was considered an area requiring further research in addition to a general understanding of the determinants of bioavailability in children.

There were a couple of useful lessons from the sildenafil case. Firstly, the assumed relationship between PK in adults and children was found not to be the case, which meant that less than optimal doses were used for confirmatory studies in children. The advice from this experience is to conduct a small PK study with PD evaluations prior to and to support confirmatory studies. Secondly, different PD endpoints may be necessary for very good reasons in adults and children. Where possible to consider this possibility in advance, bridging strategies can be built into the clinical development programme. In some cases limited data supporting bridging of PD endpoints between adults and children are available, as the data are difficult to generate. The question was raised as to whether a pragmatic approach is justified in this circumstance. The situation of sparse bridging data could potentially be solved by a collaborative approach within the pharmaceutical industry. There was a plea to stimulate the manufacturers to share knowledge on disease, physiological parameters and clinical endpoints especially in younger age groups. Also, there should be a possibility to obtain data from observational studies. Various approaches were discussed which have scientific merit and could be used to support pharmacodynamic bridging or extrapolation of drug response endpoints or across populations. However, when these approaches are applied in a regulatory setting, focus is often given to methodological issues rather than to the underlying assumptions. Both from a clinical and regulatory perspective, it is essential to understand which measures need to be in place to mitigate risks.

From this discussion, it also became evident that a regulatory process is lacking that supports the assessment of assumptions and their implications for the efficacy and safety claims in the target population. The availability of specific procedures would facilitate the evaluation of results and conclusions when M&S inferences are used as the basis for evidence synthesis (i.e., they are used *in lieu of* or *in conjunction with* new evidence). It was acknowledged that even as we improve our models, there will be occasions where the unexpected happens. This highlights the need to have in place a process that will allow a rapid identification of such deviations (i.e. continuous process control).

The relevance of historical data from a reference group to support extrapolations between populations was the focus of **Theme 3**. The position statement was that model uncertainty and model misspecification must be evaluated when inferences are made about pharmacokinetics, pharmacodynamics or drug response in a new population. The challenges in the development of a fixed dose combination of anti-malarial drugs for the paediatric indication and for different ethnic groups were used to highlight the advantages and limitations of a model-based approach. The example illustrated how pharmacokinetic modelling can be used to select doses and ensure comparable exposure is achieved across populations. However, it became clear that the assumption of similar parameter-covariate relationships across populations is required to make inferences about the differences in pharmacokinetics between adult and children or across ethnic groups. Understanding of the physiological and pathophysiological mechanisms underlying ADME processes is critical for the accuracy of extrapolations in a new population. **The implications of unobserved covariates may not be anticipated from the data generated in a reference group of patients**. Despite such a limitation, the discussions also pointed out that empirical evidence of efficacy and safety does not warrant an accurate dose selection for drug combinations. The main lesson from this exercise is the need to account for a potential change in the benefit-risk ratio of a treatment when using fixed dose ratios in drug combinations in the presence of interacting covariates. The effect of the interaction between covariates (e.g. body weight, age and ethnicity) on drug disposition cannot be assumed constant for different compounds.

The extrapolation of PKPD from adults to children was endorsed for the anti-infective example, as the diseases are comparable in adults and children. It was pointed out that inferences about PD of anti-infective drugs *in vitro* data are likely to be sounder than extrapolation of the clinical response from adults. This is partly due to the lack of methods for scaling developmental differences, or extrapolation to immunocompromised special populations, which are not readily available at present. As no obvious differences were expected with regard to the mechanism of elimination of the example drug, the implications of ethnicity were not anticipated and inferences were made based heavily on data within the paediatric population, especially for the younger ages. On the other hand, points-to-consider in the evaluation of fixed-dose combinations do not include those differences may exist in developmental pharmacology for compounds which do not share the same elimination pathways. The expected standards for such an approach include transparency regarding the age ranges included and avoiding extrapolation beyond the observed age range (in this example limited to Asians > 2 years and Africans > 1 year). It was recommended to pay special attention to the specificities and differences of the younger age subsets in which allometric extrapolation do not work (avoid oversimplification). In addition, or additional role of organ functionality could have been considered in the analysis, as suggested in CL = CL (std) x F (size:allometry) x F(maturation) x F(organ) (Tod M, Jullien V, Pons G. Clin Pharmacokinet 2008; 47: 231–243). The modelling and simulation exercise as well as the limitations in the number of paediatric data in this example also illuminates the wealth of such an individual drug data set. A model-based approach allows data from different studies and sources to be embedded into a framework, yielding more sophisticated, clear conclusions about the benefit/risk ratio. Therefore, further work is needed to define standards for modelling and simulation, including the creation of a platform for the aggregation of knowledge that supports the use of extrapolations across populations. As there is simply no alternative solution because of the small number of patients in rare diseases and special populations, a closer and innovative collaboration between companies, with PDCO and academia is recommended, which can lead to more effective solutions, as it was demonstrated in the workshop itself.

Theme 4 focused on some important methodological considerations regarding the **sparse data, model uncertainty and parameter precision.** The position statement for the panel discussions was aimed at exploring statistical concepts and opportunities in support of the use of M&S as a tool for integration, analysis and interpretation of data as well as the basis for the optimisation of protocol design and decision making involving special populations, ethnic groups and rare diseases.

Topiramate was used as case study to illustrate the situation in which an extension of indication has been approved without any additional registration trials. The FDA's approval decision and dosing regimen for monotherapy of seizures for paediatric patients 2-10 years old with partial onset or primary generalized tonic-clonic seizures was primarily based on a pharmacometric bridging analysis similar to what was done for oxcarbazepine. Model development assumed similar disease characteristics and progression in adults and children. This assumption was viewed as justifiable in partial onset seizures and Lennox-Gastaut syndrome, but not necessarily in other infantile and juvenile epilepsies, which are specific to children and represent an important medical need due to their refractory nature and poor cognitive prognosis. Where specific claims are made from modelling (e.g. for topiramate, using the limited data available, it is claimed that there was no evidence of an effect of age or paediatric status on its PD characteristics), care should be taken to avoid generalisation when not supported by specific data (i.e. this statement may not apply to other infantile and juvenile epilepsies). Unfortunately, the FDA's decision tree does not explicitly capture these specific aspects of paediatric drug development due to oversimplification and therefore may not be the most useful/appropriate approach for guiding paediatric drug development.

The EMA contributed with two methodology presentations to highlight the current thinking around innovative approaches to support extrapolation. The first was an example of how historical trials in adults and children can be utilised to reduce sample size in a future paediatric trial. A Bayesian meta-analytic-predictive approach was used to determine the amount of evidence required in a future trial in conjunction with the historical data. This procedure generates a "prior effective sample size" of virtual subjects that reduce the number of actual subjects. An example on the use of anticoagulants for the treatment of acute venous thromboembolism illustrated how the suggested Bayesian meta-analytical approach may be a valuable tool for regulators, stakeholders, and experts. It should be noted, however, that despite the reduction in sample size requirements for comparative pivotal studies that can be achieved by using the proposed methods, in some special population studies it may still be almost impossible to recruit sufficient patient numbers. A call remains for the need of more inferential designs or methods in this field, which allow further reduction in sample sizes by adding in weighted assumptions and priors.

The second EMA contribution proposed therefore a scepticism factor to justify a more liberal significance level in paediatric subpopulations, borrowing strength from evidence in other populations. The more liberal significance level seems to be justified scientifically and ethically since before starting trials in paediatric subpopulations usually evidence is already existing from adults (similar considerations can be made from children in higher ages or across ethnic groups). In this context, the requirement for a controlled clinical trial can be seen as a validation study to "safeguard" for the possibility that the extrapolation paradigm does not hold. The scepticism factor is therefore defined as the "probability" that the treatment is not effective in the sub-population, i.e. that the extrapolation assumptions are incorrect. The scepticism factor can be quantified by expert opinions or potentially by M&S. Where "scepticism" is very small, extrapolation of efficacy without clinical studies in children could be justified. Instead a "case series of x patients" may be requested for subpopulations. Where "scepticism" is very high, a study with full significance level would be required. In the extreme case, where there is no existing pre-evidence from adults in diseases only affecting children, the two pivotal studies paradigm may be applied. The approach provides a formal link of extrapolation to the relaxation of significance levels in subgroup validation studies. It adds understanding to the delicate decisions taken under uncertainty. Although presented in a quantitative framework, it is acknowledged that justification of extrapolation remains a complex exercise far beyond pure statistics.

A number of methodological issues were raised which reflect the challenges regulatory agencies and reviewers face when appraising the use of M&S approaches. The lack of mechanistic models, the lack of a standardised process and appropriate documentation on the underlying assumptions and predictive performance of a model constitute one of the major hurdles for evaluating the robustness of the approach. From a statistical standpoint, it was noted that simulation techniques (including clinical trial simulations) are underutilised or not carefully considered when evaluating the predictive performance of a model and what-if scenarios in the target population. It was also highlighted that the scientific soundness and biological plausibility of the M&S assumptions are equally critical for regulatory decision making. The decision to extrapolate pharmacokinetics, pharmacodynamics, safety or efficacy does not rest on quality and statistical properties alone. In conclusion, the use of a standardised template to support the assessment of M&S assumptions, clinical implications, risks and mitigation measures was recommended for accurate business and regulatory decision making.

Actions

The participants called for the **development of a framework supporting the use of M&S in clinical development plans, which would facilitate the regulatory approval process and therapeutic use of medicines in special populations**. Of particular interest are 1) the sharing of

standards for evidence synthesis using inferential methods (e.g. assumptions, model building, and validation) and 2) the feasibility of M&S approaches for the joint evaluation of safety and pharmacodynamics /efficacy as the basis for subsequent assessment of the benefit- risk ratio for concerned population(s).

Proposed action items:

1) Sharing of examples of guidelines for model-based data analysis currently used in industry. Such practices can support the creation of standards for the use of inferential methods for the evaluation or extrapolation of pharmacokinetics, pharmacodynamics, safety and efficacy data.

2) Explore the advantages and requirements for the implementation of the 'scepticism factor' during the regulatory evaluation of M&S approaches in rare diseases, paediatric indications, other special populations (elderly) or across ethnic groups.

3) Undertake a pilot project with a few examples (starting from those presented during the workshop) to demonstrate the benefits of a standardised evaluation template for the assessment of M&S assumptions, clinical implications, risks and mitigation measures. Subsequently, assess the impact of such a standardised template on regulatory views (e.g. PDCO) by comparing decisions with and without assessment of M&S assumptions.

4) Delve into the issue of "ownership" of data and explore mechanisms or processes to ensure that all available data about a drug can be used to optimise its utilisation across populations or indications. This concern is particularly important for small companies, which were cited as example of organisations that are developing drugs for children and rare diseases, but have very limited access to data.

5) Evaluate the feasibility of ranking M&S approaches based on their potential predictive or prognostic value, with particular focus on mechanistic modelling (e.g. PBPK and PBPKPD), which could contribute for better understanding of PK, PD or disease assumptions.

6) Promote the views and conclusions from this workshop with a publication on the objectives and outcome from BOS3. The timelines and contributing authors will be defined in due course.

7) Work towards a proposal on the points-to-consider for evidence synthesis based on inferential methods and seek agreement on the use of common template for the assessment of M&S assumptions, clinical implications, risks and mitigation measures.