COMMENTARY

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Pharmacometrics for Regulatory Decision Making

Status and Perspective

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As a methodology to rationalize and inform drug development, pharmacometrics (modelling and simulation) is widely appreciated by industry, academia and regulators in general. However, the integration of pharmacometric analyses into regulatory decision making is not formally established and has been the subject of discussion in many scientific and regulatory fora. The article by Lee et al.[1] published in this issue of the journal provides instructive case studies of how pharmacometrics can be used by regulators to help decision making, interaction with companies, reviewing and labelling. Their case studies indicate that pharmacometrics is not a tool reserved only for companies for internal decision making, but also is a powerful platform that regulators may use to compile and analyse data in order to support approval and labelling. This is considered to have beneficial effects for both industry, in terms of resource optimization, and for prescribers and patients, who obtain more precise labelling instructions and optimal therapeutic interventions, respectively.

The increasing impact of pharmacometrics on US FDA approval and labelling (see table I in the article by Lee et al.[1]) indicates the success of the methodology and the need to make best use of all available data during regulatory decision making, especially in controversial cases or when data are scarce (e.g. in orphan diseases or paediatrics).

In Europe, modelling and simulation was identified by the European Medicines Agency (EMA) Think-Tank Group on Innovative Drug Development and Committee for Medicinal Products for Human Use (CHMP)[2] as one of the key methodologies to overcome bottlenecks in drug development. There is no EMA guideline that generally defines how pharmacometrics should be used in regulatory decision making. Indeed, it is difficult to discuss this methodology outside a specific context (e.g. the clinical condition, feasibility of trials, availability of good biomarkers for safety and efficacy, availability of clinical efficacy and safety data from other groups, and stage of development).

In general, the hurdle for regulatory acceptance of modelling and simulation seems lower in the exploratory phases than in the confirmatory phases of medicine development. On the basis of information compiled from various clinical efficacy/safety and methodological EMA guidelines, and discussions by the EMA Scientific Advice Working Party (SAWP) and Paediatric Committee (PDCO), we have identified the following cases to exemplify the spectrum of current thinking in the European regulatory setting.

Examples where the use of modelling and simulation is well appreciated are:

- hypothesis generation and learning throughout drug development;
- use of models to minimize the burden of pharmacokinetic/pharmacodynamic evaluations in current studies and to optimize future experiments;
- use of models for selection of doses to be further tested in clinical trials.

Examples where the use of modelling and simulation could be accepted if properly justified are:

- use of models for final recommendation of intermediate doses that were not specifically tested in phase II/III trials;
- population pharmacokinetic analysis in phase II/III to support regulatory claims (e.g. the absence of suspected drug-drug interactions[3] and the effect of pharmacogenetics on exposure[4]);
- modelling and simulation to bridge efficacy data.[5-8]

Examples where the use of modelling and simulation is generally seen as controversial are:

- model-based inference as the 'sole' evidence of efficacy/safety, notwithstanding exceptional scenarios;[9]
- approval based on simulated data for efficacy and safety.

An important criterion that regulators check when assessing the weight of modelling and simulation in a given submission is the quality of the exercise. The principles of transparency, traceability, parsimony, external validity and internal validity,

as well as biological/clinical plausibility, are very important. Also, results of pre-specified modelling and simulation-based analyses of clinical trial data are more convincing than *post hoc* analyses. When pharmacometrics are used to support labelling and approval, a high degree of adherence to these principles is expected.

Although European regulators acknowledge the regulatory impact of modelling and simulation similarly to their FDA colleagues, there are differences in the practical approach of triggering pharmacometric regulatory assessments as part of scientific advice, paediatric investigation plans and marketing authorization applications. The FDA may conduct a pharmacometric review irrespective of whether the sponsor has submitted one or not. The EMA assesses a pharmacometric exercise only if it is included in the submission; additional pharmacometric analyses can be requested, but it is the responsibility of the sponsor to conduct them.

In their scientific discussion, Lee et al.[1] acknowledge the need to move from a customized approach to more standardized implementation of modelling and simulation in drug development and regulatory decision making. For this purpose, the need to develop standards for data collection, analysis, reporting and assessment has been emphasized. Collaboration of all stakeholders (academia, industry and regulators) is essential for providing best-practice examples and for contributing to regulatory guidance. Also, examples and uses of pharmacometrics may be warranted for understanding and learning from failed developments.

We also recognize the need for consolidation and dialogue on pharmacometrics methodology. As a first step, a further international workshop[10] on modelling and simulation at the EMA is planned.[1] We continue to suggest[7,8] that the procedure for qualification of novel methodologies[11] is a suitable forum for such discussions. The objective is to engage in a broad dialogue with all relevant stakeholders and to contribute to pre-planned and formal integration of pharmacometrics in drug development and regulatory decision making.

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