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PERSPECTIVE

Report From the EMA Workshop on Qualification and Reporting of Physiologically Based Pharmacokinetic (PBPK) Modeling and Simulation

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On Nov 21, 2016, the European Medicines Agency (EMA) hosted a workshop to discuss its draft guideline on qualification and reporting of physiologically based pharmacokinetic (PBPK) analysis.[1] Published on July 21, 2016, the draft PBPK guideline is currently under the period of public comments.
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HIGHLIGHTS

The workshop was aimed at communicating the EMA's current thinking and receiving comments on the draft guideline. Attendees included stakeholders from regulatory agencies, pharmaceutical companies, academic institutes, and PBPK platform developers in the US and Europe. There were four sessions: 1) introduction and setting the scene to the draft PBPK guideline; 2) qualification of the PBPK platform for the intended purpose; 3) reporting and evaluation of predictive performance of the PBPK model; and 4) panel discussions with regulators (agenda and presentations can be found in ref. 2). The full-day event was opened by Dr. Enrica Alteri, head of the EMA's Medicines Evaluation Division. In Session 1, Dr. Anna Nordmark of the Swedish Medical Products Agency provided a brief introduction of the guideline. Dr. Nordmark also introduced the concept around the qualification of the PBPK platform for the intended use, which should aim at showing if there is enough scientific support for an intended use for the used PBPK platform. Session 2 was introduced by Dr. Efthymios Manolis of the EMA who overviewed CHMP (Committees for Medicines for Human Use) qualification procedure on novel methodologies and how it can be used for qualification of the intended purpose or application. Presenters from industry interest groups (Dr. Neil Parrott of Roche for International Consortium for Innovation and Quality in Pharmaceutical Development or IQC and Dr. Amy Cheung of AstraZeneca for European Federation of Pharmaceutical Industries and Associations or EFPIA) and PBPK platform developers (Drs. Viera Lukacova, Masoud Jamei, and Michael Block from Gastroplus, PK-Sim, and SimCYP) commented on the draft guideline with respect to how model qualification should be done. Because of its significant place in the draft guideline, the use of PBPK in pediatric drug development was specifically discussed in the session's last presentation (Dr. Rolf Burghaus of Bayer). The presenters also discussed areas in the guideline that require further clarifications. In Session 3, Europe and US regulators presented experiences in regulatory submissions of PBPK analyses (Dr. Susan Cole of UK Medicines and Healthcare products Regulatory Agency and Dr. Ping Zhao of US Food and Drug Administration) and the importance of assessing parameter sensitivity and model uncertainty (Dr. Ine Skottheim Rusten of Norwegian Medicines Agency). Professor Leon Aarons from the University of Manchester, UK, gave a short lecture on the concepts of sensitivity analysis. In Session 4, Dr. Eva Gil Berglund of the Swedish Medicines Product Agency summarized major comments the EMA has received to date. Sessions 2, 3, and 4 had panel discussions that engaged extensive discussions from the panel members and the audience. Below are major topics discussed with a focus on concerns raised by attendees.

Session 2 was devoted to platform qualification. Speakers from industry and platform developers centered their discussions on the following questions predefined by meeting organizers:

a. How would you qualify the PBPK platform for intended purpose, as outlined in the guideline?
b. Are the three practical qualification processes (via CHMP Scientific Advice, within a given submission, and through learned society) suitable?
c. What problems and benefits can you see with the outlined qualification approach in the guideline?
d. In a constructive way, what changes would you propose?

Several concerns were voiced by industry representatives. First, the guideline seemed to focus on PBPK applications or intended purposes with high regulatory impact. Examples of high regulatory impact analyses are simulations that affect the Summary of Products Characteristics (SmPC, EMA's equivalent to US prescribing information or labeling).[1] To drug developers, some applications are considered highly relevant in drug discovery and development, albeit these applications are of lower regulatory impact for the time being. A focus of a regulatory guideline on high-impact applications may imply discouragement of broader uses of PBPK. Second, industry attendees were not sure whether the latest version of a PBPK platform should always be used for regulatory submission. In fact, the guideline prefers submissions using the qualified version of a PBPK platform.

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This implies that analyses conducted using earlier, nonqualified versions during the development of an investigational drug need to be repeated for regulatory submission. Third, although the guideline mentioned that "If an in-house built computer program is used for high regulatory impact simulations (such as waiving of studies) the applicant is strongly encouraged to seek CHMP Scientific Advice," discussions were mainly around the use of commercial PBPK platforms. This may discourage the use of custom-built PBPK models. In addition to these concerns, presenters of both industry and platform developers sought clarifications on definitions such as "well-prediction" and "learned society," as well as the size of a large (qualifying) dataset.

The need for sensitivity analyses took center stage during Session 3. Some attendees debated whether a global sensitivity analysis is needed if one uses a commercial PBPK platform to develop a PBPK model, and the focus should be on parameters with less uncertainty. The EMA also sought advice on when a sensitivity analysis should be conducted and whether a "wish list" of parameters for a given application should be defined. For example, the reversible inhibition constant (Ki) should be tested when predicting the enzyme inhibition potential of an investigational drug is the purpose.

In recent meetings organized by regulators,[3,4] industry colleagues were interested in harmonization among agencies. This workshop is without exception. Besides recommendations in regulatory documents, industry attendees were interested in understanding differences in PBPK review and decision-making processes. Concerns were brought up by one company on different actions taken by the FDA and the EMA on one of its submissions that used PBPK to predict the effect of CYP3A inducers on the exposure of its investigational drug. The FDA allowed the prediction to be used for dosing recommendations, whereas the EMA did not allow such predictions.

CONCLUSION AND PERSPECTIVES

The workshop was well organized, with presentations being issue-driven and informative, and attendees actively engaged. Colleagues of both the EMA and the US Food and Drug Administration received valuable input related to issues to address such as modeling best practice, communicating predictive performance of the drug model, and platform qualification of an intended use.

Some concerns raised by industry colleagues at the workshop may not be an issue. For example, one should not be discouraged to use PBPK for applications that are of low regulatory impact for the time being, if the approach has proven useful in one's drug development tool box. Second, repeating modeling work using the latest version of a PBPK platform is not as time-consuming as one may have concerned. Sometimes, new features included in the latest version of a platform make it possible to explore additional mechanisms. It appears that uncertainty analysis is a more appropriate term than sensitivity analysis. In PBPK, sensitivity analysis has become a method to assess model uncertainty and to optimize model parameters when clinical data become available. To this end, an application-driven best practice needs to be defined before one can specify the timing and scope of such analysis. Establishment of such best practices also facilitates harmonization on regulatory recommendations.

Disclaimer: The content of this report does not reflect the views or policies of the US Food and Drug Administration (FDA) or its staff. No official support or endorsement by the FDA is intended or should be inferred.

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