

PERSPECTIVE

Model Informed Drug Development and Regulation in China: Challenges and Opportunities

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Since 2016, the Center for Drug Evaluation, National Medical Product Agency has routinely received and reviewed modeling and simulation (M&S) analyses submitted at different stages of drug development. A series of related guidelines were released. The perspective identifies opportunities and challenges in applying M&S in drug regulations in China.

Model-informed drug development (MIDD) and regulation have played important roles in drug development worldwide. MIDD was defined as a quantitative framework for prediction and extrapolation, focused on knowledge and inference generated from integrated models of compound, mechanism, and disease level data, and aimed at improving the quality, efficiency and cost effectiveness of decision making.¹ The US Food and Drug Administration (FDA) and European Medicines Agency (EMA) have either used M&S methods or evaluated sponsor's models to address a variety of drug development and regulatory questions and to support regulatory decision making.^{2–4} The Pharmaceuticals and Medical Devices Agency in Japan also organized an internal discussion group and made efforts to use M&S techniques in regulatory decisions.⁵

In comparison, for several decades, drug development and regulation in China primarily focused on generic drug products. During this period, the application of quantitative analysis by sponsors and review staff at the Center for Drug Evaluation (CDE) in National Medical Product Agency (NMPA) was restrained to statistical assessment of bioequivalence. However, recognizing the importance of MIDD in drug development and regulation, the CDE established the Office of Statistics and Clinical Pharmacology in 2016. In essence, the Office is an integrated team responsible for conducting technical review of biostatistics, clinical pharmacology, and bioequivalence submissions in investigational new drugs, new drug applications, abbreviated new drug applications, and biologics license applications for both new and generic drugs, as well as Chinese traditional medicines. The Office is also responsible for developing regulatory guidelines and conducting regulatory research. So far, the Office has more than 60 staff members, consisting of clinical pharmacology reviewers, biostatistical reviewers, and pharmacometrics reviewers.

Since 2016, the CDE has routinely received and reviewed M&S analyses submitted at different stages of drug development. In some cases, the use of M&S approaches, such as pharmacokinetic/pharmacodynamic (PK/PD) analysis

and population PK (PopPK) analysis, has made significant impact on the CDE's review process. For example, the use of PopPK and exposure-response analysis in the review of new drug approval of Nemonoxacin Malate in the Chinese population has informed regulatory decisions of dose and regimen for various subpopulations in product label.⁶ In the meantime, a series of MIDD-related guidelines were released. This perspective identifies opportunities and challenges in applying M&S in drug regulations in China.

Similar to regulatory agencies from other countries, we realized that MIDD can play important roles in five broad areas: expediting drug development process by quantitatively translating nonclinical to early phase clinical results at the investigational new drug application stage, selecting doses for further clinical testing as the compound progresses to later development phases, optimizing design of clinical trials before and postapproval, determining dose and dosing regimen for special populations for labeling, and providing evidence of effectiveness and safety.² To this end, we summarized some review cases since inception of the Office in 2016 in **Table S1**, highlighting the assessment of M&S analyses submitted by sponsors. All examples used PopPK(PD) methods to determine dose regimen, primarily in Chinese populations. These methods were applied at different stages of drug development. Cases for drugs A to D represent routine use of PopPK(PD), model-based meta-analysis was implemented in drug E, and the example for drug F is rather unique. In the example of drug F, the sponsor estimated a safe starting dose in Chinese pediatric patients. The sponsor discovered a specific surrogate to evaluate occupancy of a target enzyme in the central nervous system in adult patients. A population PK/PD model was developed based on more than 100 adult volunteers from 4 clinical studies. Subsequently, this initial PopPK/PD model along with phase I safety results, was used to select the dose in pediatrics. As a result, twice-daily dosing of starting doses was selected according to body weight of pediatric patients who were stratified at an age cutoff of 9 years old. The sponsor first planned to enroll those patients who are 9 years and older, then modified the model based on the above quantitative analysis results and applied it to patients of younger ages. The sponsor's proposal was deemed acceptable.

The MIDD-related guidelines issued since 2016 have been released by the NMPA. These guidelines are technical by nature, including a draft guideline for PK/PD research of

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antimicrobials,⁷ and a guideline for determining the breakpoint of the antimicrobial susceptibility test.⁸ These guidelines provide detailed recommendations on the use of PK/PD and PopPK modeling during development of antimicrobials. Another important guideline is for extrapolation of pediatric medication strategy from data of the adult population, which requires the use of an M&S approach.⁹ The CDE stance on model-based extrapolation is consistent with current thinking published by International Conference on Harmonization E11(R1). The release of this guideline and the use of the model can accelerate the pediatric drug development and marketing in China. It has to be emphasized that the use of M&S in regulatory decision making has to be context specific.⁴ In addition, a series of guidelines on clinical trial data standardization, data management, and statistical analysis¹⁰ were released to ensure the quality of the data, which creates the fundamental basis of interpreting findings from clinical trial and exploring MIDD methods. Recently, the office is collaborating with academia and industry worldwide and discussing the first white paper in Chinese on the value and general consideration of pharmacometrics in new drug development.

It should be noted that M&S, as a tool, is very useful in analyzing clinical trials data in depth, rather than creating new data. At the same time, the validation of a PK/PD model and illustration of its assumptions need more attention. How much M&S can help to make decisions depends on the reliability of data used to build the model. Clinical trials data themselves are the basis for most parts of the decision making. In some cases, M&S can play more important roles. For example, for breakthroughs, if the clinical trial data is not sufficient yet, the MIDD approach may help a drug to be approved ahead of time based on simulation results, and, in such a scenario, it is generally recommended that the rest of the required clinical trials be continued after marketing.

In October 2017, the Chinese government provided opinions on deepening the reform of the regulatory review system and encouraging innovation in pharmaceutical research and development, promoting the structural adjustment and technological innovation for drug and medical device industries, enhancing the competitiveness of pharmaceutical industry in China, and meeting the clinical demand of the public. On one hand, a regulatory agency needs to conduct a review and approve the drug based on science; on the other hand, it should guide drug developers to carry out scientifically sound clinical trials.

In the near future, the CDE will formally receive electronic data. This will help our office to establish review and submission databases, summarize and standardize M&S analyses, and make generalizable knowledge open to the public. Applicants or organizations interested in applying M&S in research and development can discuss with our office and other offices in the CDE through advisory meetings.

We recognize that the CDE has made significant progress in advancing MIDD in the pharmaceutical industry in China. However, gaps between the NMPA and other regulatory agencies still exist. To name a few, reviewers are less experienced in using M&S techniques during product review, limited numbers of M&S cases submitted to the NMPA to

date, inadequate on-the-job training of advanced quantitative methods, and the lack of regulatory research capacity, which may take a toll on effectively developing a regulatory policy. China is not short of talents in mathematics and information science, but currently is lacking expertise and experience in applying mathematics and information science to medical research and development. The CDE is closely monitoring the rapid advancement of MIDD and its uptake by other global regulators and plans to incorporate applicable MIDD elements when revising current guidelines and developing new guidelines. In summary, the CDE is responsible for training the talented reviewers to apply scientific ideas to facilitate review and approval of new and generic drugs. The center is determined to narrow these gaps and to integrate with the rest of the global regulatory community.

As a regulatory agency, we also believe that ensuring the safety of medical products is of paramount importance. Providing guidance on the best practice of applying M&S in drug development and regulation requires continuous dialogs among global regulators and between regulators and pharmaceutical industries. We also believe M&S will play more and more important roles in drug development, and may lead to big changes in review and regulatory strategies.

Supporting Information. Supplementary information accompanies this paper on the *CPT: Pharmacometrics & Systems Pharmacology* website (www.psp-journal.com).

Table S1. Cases of modeling and simulation analyses submitted to the office of biostatistics and clinical pharmacology at the Center for Drug Evaluation (CDE), National Medical Product Agency (NMPA).

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