

PERSPECTIVE

Quantitative Modeling and Simulation in PMDA: A Japanese Regulatory Perspective

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In Japan in October 2016, the Pharmaceuticals and Medical Devices Agency (PMDA) began to receive electronic data in new drug applications (NDAs). These electronic data are useful to conduct regulatory assessment of sponsors' submissions and contribute to the PMDA's research. In this article, we summarize the number of submissions of quantitative modeling and simulation (M&S) documents in NDAs in Japan, and we describe our current thinking and activities about quantitative M&S in PMDA.

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NEW DRUG APPLICATIONS' SUBMISSION OF ELECTRONIC DATA FOR MODELING AND SIMULATIONS (M&S) IN CLINICAL PHARMACOLOGY TO THE PMDA

Quantitative M&S has played an important role in decision-making in current drug development programs to efficiently and effectively develop new drugs having balanced efficacy and safety.^{1,2} The US Food and Drug Administration (FDA) and European Medicines Agency (EMA) have reported that quantitative M&S is useful for explanations of the underlying scientific rationales of experimental designs, selection of dosing regimens and patient populations, and for the use of the appropriate labeling language during the regulatory reviews for NDAs.^{3,4} Japan's PMDA has also been reviewing documents regarding population analyses (including population pharmacokinetics (PK) analyses, population PK and pharmacodynamic (PD) model analyses, exposure-response analyses) and physiologically based pharmacokinetic (PBPK) model analyses.

The Japan Revitalization Strategy (adopted by the Cabinet on June 14, 2013) indicated that it is essential to strengthen the PMDA system with respect to both the quality and quantity of regulatory review and consultations. The Healthcare and Medical Strategy (an agreement among relevant ministers, June 14, 2013) further states that PMDA shall promote its analyses and research by using study data (e.g., clinical data) and shall establish a rational and efficient process for making evaluations and decisions in its reviews and consultations (Document No. 1 in **Supplemental Table 1**). Since quantitative M&S can be helpful for various types of decision-making during drug development and regulatory reviews (e.g., dosing regimens and sample size in clinical trials, appropriate language in product label, etc.), these analyses by PMDA reviewers themselves are expected to help improve both the quality of the PMDA's reviews and consultations and contribute to improve the efficiency of new drug development. Especially, it is expected to facilitate the development of orphan drugs and pediatric drugs, which

may be more likely to face obstacles due to difficulties in collecting data for small numbers of patients and due to their unestablished evaluation methods.

With these changes, PMDA established the Task Force for Advanced Review and Consultation with Electronic Data on September 1, 2013. The Task Force was reorganized into the Advanced Review with Electronic Data Promotion Group on April 1, 2014, and specific processes for reviews and consultations that will further utilize the application data were discussed. After several notifications related to the electronic submission of study data were issued by Japan's Ministry of Health, Labour and Welfare (MHLW) and PMDA (**Supplemental Table 1**), the PMDA started accepting electronic submissions of study data in October 2016. Regarding the electronic data of quantitative M&S in clinical pharmacology, PMDA can receive the data of population analyses and PBPK model analyses. Specific content and formats of the electronic study data of these analyses, which have been opened on the Technical Conformance Guide on Electronic Study Data Submissions (Document Nos. 5 and 6 in **Supplemental Table 1**), are summarized in **Table 1**. In a population analysis, the analysis dataset and its definition file, the programs of models that were important in the model-building process such as the base model and the final model, and files with the output of major results should generally be submitted. If a simulation was performed, submission of the program used for the simulation and the program procedures are recommended. In a PBPK model analysis, files containing information such as the structure of the model used for the analysis, the set values of drug and physiological parameters, the analysis procedures, and the results of sensitivity analyses should generally be included in the submission. If necessary, the dataset of clinical studies containing the PK data used in the analysis and the definition file for that dataset are recommended to be submitted. Although we recognize that some commercial software for these analyses are well used by many researchers, the PMDA can receive data analyzed by any software. Sponsors can apply for a meeting with the

Table 1 Specific content of the electronic study data of clinical pharmacology analyses to be submitted to PMDA

Population analysis, including simulations	Physiologically based pharmacokinetic model analysis, including simulations
<ul style="list-style-type: none"> The analysis dataset file should preferably be in one of the following; <ul style="list-style-type: none"> SAS XPORT format (*.xpt) ASCII Format Data Files The dataset definition document should include at least the variable names and explanation of the variables. The program files should preferably be in the text file format. Files into which major results are outputted (such as NONMEM output). The file format is optional. The simulation file format is optional. The program procedures include the description of the detailed procedures of running the program. 	<ul style="list-style-type: none"> Files that contain information on the model structure used for the analysis, the set values of drug and physiological parameters, analysis procedures, and sensitivity analysis of the results. The file format is optional. Clinical study datasets, including blood concentration data. If the datasets were created or modified to be analyzed using a specific software for PBPK model analysis, the electronic files of the created or modified datasets should be submitted in the format for the specific software (Simcyp PE Data Files (xml format), etc.). If the datasets were not created or modified for a specific software for PBPK model analysis, the datasets can be submitted in an optional file.

PMDA entitled “Consultation on the Data Format for the Submission of Electronic Study Data” to explain and confirm the details of the data to be electronically submitted.

RECENT SUBMISSIONS OF M&S REPORTS IN NEW DRUG APPLICATIONS TO PMDA

In this section, recent submissions of PBPK M&S reports and population analysis reports are introduced. This is the first time for the PMDA to introduce submissions of PBPK M&S reports. Regarding the population analysis reports, PMDA has introduced the results of a survey of the NDAs that included population analyses during a recent period in Japan.¹⁰

The use of PBPK M&S data in regulatory reviews and decisions has become a hot topic.^{5,6} In 2016, both the US FDA and EMA published draft guidance/guidelines on the reporting of PBPK M&S results.^{7,8} The numbers and content of PBPK M&S reports submitted to the US FDA in a recent year were also introduced.⁹ Here we summarize the numbers and content of PBPK M&S reports submitted to the PMDA that were part of NDAs for new molecular entities (NMEs) approved in 2014, 2015, and 2016 in Japan. During those 3 years, PBPK M&S reports were included in 17 NDAs (**Figure 1**). In these submissions, drug–drug interactions (DDIs) were mainly evaluated. The PBPK M&S reports in those applications were used 1) to simulate the concentration–time profiles of drugs in plasma under DDI scenarios in which a set of drugs that had not been tested in a clinical DDI study were administered; 2) to predict the exposure of the drug in pediatric patients in order to set the dosing regimen prior to conducting the first clinical pharmacokinetic study for a pediatric population; or 3) to understand the impact of intrinsic factors such as ethnic differences and disease states on the PK of a drug. Considering the impact of PBPK M&S results on the proper use of the drug, area under the plasma concentration–time curve (AUC) values calculated from PBPK analysis in an untested scenario are described on Japanese product labels and used as a basis of dose adjustments in some cases: e.g., the labels for Cerdelga, Farydak, and Imbruvica (**Supplemental Table 2**). As such, PBPK M&S results have been

utilized in Japan to explain dose adjustments and to provide information about the proper use of the drug.

Based on the results of the recent survey, among the NDAs for NMEs approved in the period from April 2012 to March 2014, population PK analyses were conducted in more than 50% of the applications.¹⁰ The numbers of PK/PD or exposure–response analyses have also increased. Although this type of analysis was included in 30% of the NDAs in 2012, it increased to 50% of the NDAs in 2014. These population analyses including PK/PD and exposure–response analyses were conducted mainly in the field of oncology, followed by metabolic disorders and antibiotics.

CURRENT ACTIVITIES AND FUTURE PERSPECTIVES ON QUANTITATIVE M&S IN PMDA

As noted above, in recent years several PBPK M&S reports were submitted to the PMDA as an attachment for NDAs, and those M&S results have been utilized in regulatory reviews. At this time, we have not yet examined in detail the numbers and content of new NDAs that include a population analysis, but we have also received several M&S reports based on population analyses that were conducted to evaluate the necessity of dose adjustments in special

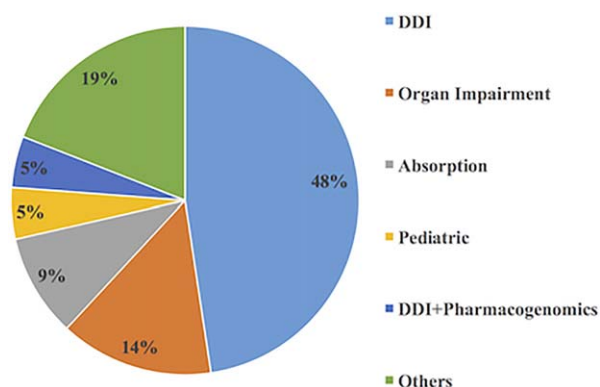


Figure 1 PBPK application in the 17 submissions in NDAs of NMEs received by the PMDA from 2014 to 2016. In some cases, multiple PBPK M&S reports were included in one submission.

populations (including organ impairment patients) and to determine the dose and dosing regimens in confirmatory clinical trials. In consideration of this situation at the PMDA, where the number of M&S reports has been increasing, we organized an internal discussion group consisting of clinical pharmacology reviewers, biostatistical reviewers, and medical reviewers to discuss the utility of M&S results in regulatory decisions in new drug reviews and consultations at the PMDA.

Since it is also very important for regulatory agencies to understand the thinking regarding the utility of M&S reports in regulatory reviews of new drugs and to harmonize our practices and activities in this area, the M&S discussion group members at PMDA have joined cluster activities with the US FDA, EMA, and Health Canada by holding regular teleconferences to exchange information and perspectives on quantitative M&S through guidelines, workshops, and publications. Moreover, PMDA is playing the major role in creating the guideline on population PK and PD analysis in Japan. This guideline will provide general guidance based on current scientific knowledge in order to ensure that evaluations based on population analyses in drug development are appropriately conducted. PMDA has also been contributing to the finalization of a draft guideline on drug interactions for drug development and labeling recommendations in Japan. In this draft guideline, points to be considered in PBPK model analyses for the prediction of DDIs are described in detail (as of February 2017, published only in Japanese). These guidelines will be issued in the near future after some modifications based on public comments have been incorporated.

In response to the recent drug development efforts that use M&S techniques and to facilitate effective and efficient drug development, we realize it is important to establish the utility and in the meantime understand the limitations of quantitative M&S in drug development and in regulatory reviews. This greater understanding of quantitative M&S can then be shared with industry, academia, and regulators. Since the utility and limitations of quantitative M&S may differ depending on the applications of M&S, the PMDA's knowledge obtained from review experiences of various NDAs including quantitative M&S will be very useful. We feel that it is important for PMDA to generate information and knowledge regarding points to be considered when quantitative M&S data are utilized in new drug development and reviews, based on the knowledge and experience obtained through both new drug reviews and cross-product

analyses of accumulated clinical data using M&S techniques.

Conflict of Interest. The authors declare no conflicts of interest.

Disclaimer. The views expressed in this article are the personal views of the authors. The content of this article does not reflect the views or policies of the Pharmaceuticals & Medical Devices Agency (PMDA) or its staff.

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