PERSPECTIVE

Meeting Report: PMDA Public Workshop on Pharmacometrics at Japan

Shinichi Kijima[1,*], Yoshinori Ochiai[1] and Akihiro Ishiguro[1]

In recent drug development, applications of pharmacometrics and modeling and simulation (M&S) have become of increasing importance. A research group that consists of experts in academia, industry, and regulatory agency has been developing practical guidelines for pharmacometrics and M&S based on latest scientific findings. This paper outlines a public workshop to exchange opinions widely among stakeholders of draft guidelines on exposure-response analysis and physiologically-based pharmacokinetic model's analysis, which was held in Japan in July 2019.

Recent drug developments have paid attention to quantitative modeling and simulation (M&S) as a tool to examine study designs or optimize the dosing regimen of a drug. In Japan, the increasing number of drug approval applications have recently used results with M&S approach as rationales for establishing the optimized dosing regimen and precautions in the new drug application (NDA) documents. According to a survey on M&S utilization in NDAs of 38 drugs with a new molecular entities submitted to the Pharmaceuticals and Medical Devices Agency (PMDA) in fiscal year (FY) 2018, a population pharmacokinetic (PPK) analysis was studied in ~ 70% of NDAs, and a PPK/pharmacodynamic (PD) analysis or exposure-response (ER) analysis were studied in ~ 60% of NDAs (**Figure 1**). These data also indicate that assessments using empirical models, including PPK analysis, were increased yearly in Japan. In the 150 NDAs submitted between FY2014 and FY2016,[1] a physiologically-based pharmacokinetic (PBPK) model analysis was studied mainly to examine drug interactions in ~ 10% of NDAs.

A notification "Clinical pharmacokinetics of drugs"[2] issued by the Ministry of Health, Labour, and Welfare (MHLW) in 2001 had showed basic concepts of application of PPK analysis to evaluate on clinical PKs. With respect to ER analysis and PBPK model analysis, no relevant guidelines have been issued in Japan. Such unavailability of the guidelines and the current situation of M&S utilization in drug developments in Japan have led to increased needs to develop new guidelines for M&S to facilitate appropriate application of M&S for regulatory purpose. The Japan Agency for Medical Research and Development (AMED) funded research group consisting of experts from academia, industry, and regulatory authority started activities in 2014 to develop guidelines for M&S. The AMED research group has engaged in preparing three guidelines for PPK and PPK/PD analyses, and ER

analysis, as well as PBPK model analysis. As a first accomplishment of the research, the guideline for PPK and PPK/PD analyses entitled "Guideline for population PK/PD analysis"[3] was issued by the Pharmaceutical Evaluation Division of the MHLW on May 2019. This paper is aimed to outline the public workshop that was held on July 2019 to exchange opinions among stakeholders, including drug developers and regulators, as a part of preparation process of the second and third guidelines (i.e., guidelines or ER analysis and guidelines for PBPK model analysis).

PMDA PUBLIC WORKSHOP ON "UTILIZATION OF PHARMACOMETRICS IN DRUG DEVELOPMENT TO MEET UNMET NEEDS SUCH AS PEDIATRIC PATIENTS AND INTRACTABLE DISEASES"

On July 3, 2019, the AMED research group had a PMDA workshop "Utilization of pharmacometrics in drug development to meet unmet needs such as pediatric patients and intractable diseases" that is divided into two parts of which the first half provided presentations on ER analysis, and the second half provided presentations on PBPK model analysis. The workshop was attended by ~ 250 participants from industry, academia, and regulatory agency, and has made six presentations by speakers from home and abroad.

In the first session, Atsunori Kaibara, PhD, Eli Lilly Japan K.K., presented the impacts of ER analysis on approval review based on the results of a survey about review reports of new drugs that were approved from 2010 to 2019 in Japan. The survey indicated that ~ 80% of the NDAs in which the data on ER analysis were included were submitted by foreign-affiliated company. The speaker concluded that M&S utilizations in Japan are expected to be facilitated by the implementation of ER analysis guideline in preparation. Akiyuki Suzuki, MSc, Pfizer R&D Japan G.K., presented a development project of Revatio for treatment of pulmonary arterial hypertension as an example of utilization of ER analysis in drug development targeting pediatric patients and intractable diseases. Yusuke Tanigawara, PhD, Keio University, introduced the latest draft document entitled "Guideline for drug exposure-response analysis (draft)" being prepared at the AMED research group and major comments raised in response to the public consultation conducted by the MHLW from May to June 2019. One of the main comments to the latest draft document was that the limitation of data collection over a wide range of exposure in a single dose study
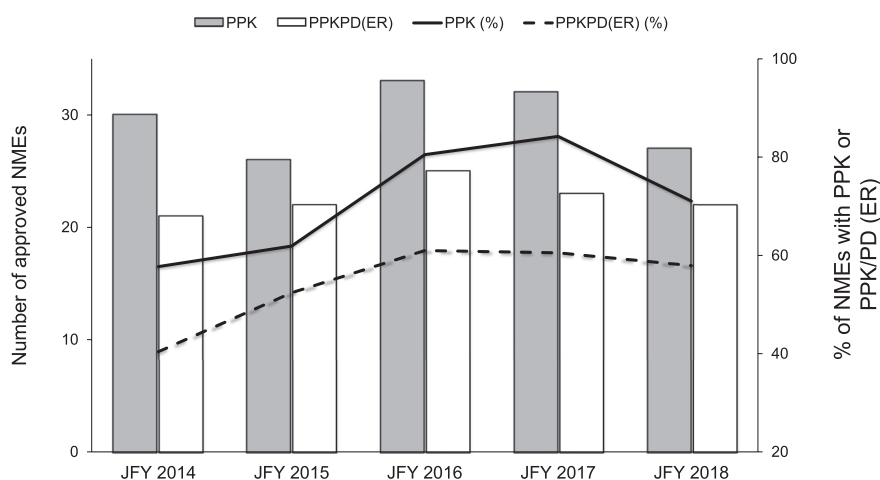
Figure 1 Characteristics of PPK or PPKPD (ER) analysis in NMEs for new active ingredients that were approved from JFY 2014 to JFY 2018 in Japan. Bars in gray and bars in white indicate the number of NMEs, which include reports on PPK analysis and reports on PPKPD (ER) analysis, respectively. The line chart with solid and dashed line indicate the percent of NMEs, which include reports on PPK analysis and reports on PPKPD (ER) analysis, respectively. PPK, population pharmacokinetic; PPKPD (ER) analysis, population pharmacokinetic/pharmacodynamics analysis or exposure-response analysis; NME, new molecular entity; JFY, Japanese fiscal year.

that is conducted in the late-stage of clinical development in some areas, such as oncology or rare diseases. The speaker replied that the importance of data collection depending on the purpose of ER analysis (e.g., an ER analysis to make an assessment of the safety of drug with the exposure data from a single dose study) will be described in the guideline.

In the second session, Tom Polasek, PhD, Certara/Royal Adelaide Hospital, Monash University, made a presentation titled "Virtual Twins Based on PBPK Models for Precision Dosing in Drug Development and Beyond," which described the potential use of the PBPK model approach not only in drug developments but also in clinical settings. Ping Zhao, PhD, of the Bill and Melinda Gates Foundation, made a presentation titled "Physiologically Based Pharmacokinetic model analysis for drug development and regulatory decision making: Past, Present, and Future," which covered the current reliability of PBPK model analysis and challenges for the future as well as further challenges for utilization of PBPK model analysis. Shinichi Kijima, MSc, PMDA, explained the current situation of PBPK model analysis for regulatory purpose in Japan and offered an overview of progress on development of guideline for PBPK model analysis at the AMED research group. The workshop became a first opportunity to present the scope or purpose of the guideline named "Guidelines for Analysis Report Involving Physiologically based Pharmacokinetic Modeling (draft)" as well as the table of contents of the guideline (**Table 1**).

In the last session of this workshop, a panel discussion entitled "Toward more efficient clinical development applied model based analysis" was presented with the participation of the six speakers along the line of three discussion points as follows: comments from stakeholders, academic researchers, drug developers, and regulators; usefulness and limitation of M&S in drug development to meet unmet needs, such as pediatric patients and intractable diseases; and significance of developing regulatory guidelines on pharmacometrics. Some remaining challenges were identified during the panel discussion of the workshop as follows:

Table 1 Table of contents for "Guidelines for Analysis Report Involving Physiologically based Pharmacokinetic Modeling (draft)"

1. Introduction
    1.1. Background and objectives
    1.2. Scope
2. Content of an analysis report
    2.1. Summary
    2.2. Objective
    2.3. Background information
    2.4. Methods of analysis
        2.4.1. Assumptions
        2.4.2. Information of system parameters
        2.4.3. Drug information related to modeling
        2.4.4. Simulation
        2.4.5. Methods for model validation
    2.5. Results
        2.5.1. Results of model validation
        2.5.2. Application of models
    2.6. Discussion
3. PBPK platforms
4. Electronic data submission0
5. Relevant guidance and guidelines
6. Glossary

PBPK, physiologically-based pharmacokinetic.

further activities toward proper implementation of the new guidelines for M&S through successive communications among stakeholders; and an international harmonization of guidances to foster consistency of applications of M&S for regulatory purpose across regions and facilitate discussions with and among regulatory authorities.

DISCUSSION

The draft guideline for ER analysis has been finalized based on views exchanged in the workshop that was held just

after the completion of public consultation on "Guideline for drug exposure-response analysis (draft)" conducted by the MHLW. The guideline describes basic concepts applied to drug development using ER analysis, which covers practices such as planning clinical studies, handling related data, performing these analyses, reporting analysis results to the regulatory authorities, and providing information on the analysis results after marketing. The finalized guideline has been issued by the MHLW on June 2020.[4]

The guideline for PBPK model analysis summarizes considerations and basic principles in reporting the results of PBPK modeling, so that assessment results obtained by using PBPK modeling in drug development are appropriately reported to the regulatory authority. The objective of this guideline is to maintain the consistency of data presented to the regulatory authority, to facilitate timely decision making in clinical trial consultations and regulatory reviews, etc., and to standardize the content of PBPK modeling reports for appropriate provision of information. After the workshop, a draft document titled "Guideline for PBPK model analysis and analysis reports (draft)" was subjected to the public consultation conducted by the MHLW from September to October 2019, and is aimed to be finalized in 2020.

It is important to provide general considerations that are scientifically valid as the Japanese regulatory authority because the underutilization of M&S by domestic companies in Japan was pointed out by the industry speaker in session 1 of the workshop. Comments to these two draft guidelines (i.e., guidelines or ER analysis and guidelines for PBPK model analysis), were solicited from experts in overseas regulatory authorities, including the US Food and Drug Administration in the United States and the European Medicines Agency that have provided guidances for M&S.[5–9] The new guidelines that have been developed by the AMED research group are expected not only to promote appropriate utilization of M&S for regulatory purpose in Japan but also to serve as an agenda for future harmonizing activities.

Conflict of Interest. All other authors declared no competing interests for this work.

Disclaimer. The views presented in this article are those of authors and do not necessarily reflect the official position of the Pharmaceuticals and Medical Devices Agency.

1. Sato, M. *et al.* Quantitative modeling and simulation in PMDA: a Japanese regulatory perspective. *CPT Pharmacometrics Syst. Pharmacol.* **6**, 413–415 (2017).
2. Ministry of Health, Labour, and Welfare, Pharmaceuticals Medical Safety Bureau, Evaluation and Licensing Division. Clinical Pharmacokinetic Studies of Pharmaceuticals. <http://www.nihs.go.jp/phar/pdf/ClPkEng011122.pdf> (2001). Accessed March 13, 2020.
3. Ministry of Health, Labour, and Welfare, Pharmaceutical Safety and Environmental Health Bureau, Pharmaceutical Evaluation Division. Guideline on Population Pharmacokinetic and Pharmacodynamic analysis. <https://www.pmda.go.jp/files/000230073.pdf> (2019). Accessed March 13, 2020.
4. Ministry of Health, Labour, and Welfare, Pharmaceutical Safety and Environmental Health Bureau, Pharmaceutical Evaluation Division. Guideline on Exposure-Response Analysis of Drugs. <https://www.pmda.go.jp/files/000235382.pdf> (2020). Accessed July 6, 2020.
5. US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER). Guidance for Industry: Physiologically Based Pharmacokinetic Analyses —Format and Content. <https://www.fda.gov/media/101469/download> (2019). Accessed March 13, 2020.
6. European Medicines Agency, Committee for Medicinal Products for Human Use. Guideline on the reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation. <https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-reporting-physiologically-based-pharmacokinetic-pbpk-modelling-simulation_en.pdf> (2019). Accessed March 13, 2020.
7. US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER). Guidance for Industry: Exposure-Response Relationships – Study Design, Data Analysis, and Regulatory Applications. <https://www.fda.gov/media/71277/download> (2003). Accessed March 13, 2020.
8. US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER). Guidance for Industry: Population Pharmacokinetics. <https://www.fda.gov/media/128793/download> (2019). Accessed March 13, 2020.
9. European Medicines Agency, Committee for Medicinal Products for Human Use. Guideline on reporting the results of population pharmacokinetic analyses. <https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-reporting-results-population-pharmacokinetic-analyses_en.pdf> (2008). Accessed March 13, 2020.