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Meeting Report

What Does it Take to Make Model-Informed Precision Dosing Common Practice? Report from the 1st Asian Symposium on Precision Dosing

Thomas M. Polasek,[1,2,11] Amin Rostami-Hodjegan,[1,3] Dong-Seok Yim,[4] Masoud Jamei,[1] Howard Lee,[5,6] Holly Kimko,[7] Jae Kyoung Kim,[8] Phuong Thi Thu Nguyen,[9,10] Adam S. Darwich,[3] and Jae-Gook Shin[9]

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Abstract. Model-informed precision dosing (MIPD) is modeling and simulation in healthcare to predict the drug dose for a given patient based on their individual characteristics that is most likely to improve efficacy and/or lower toxicity in comparison to traditional dosing. This paper describes the background and status of MIPD and the activities at the 1st Asian Symposium of Precision Dosing. The theme of the meeting was the question, "What does it take to make MIPD common practice?" Formal presentations highlighted the distinction between genetic and non-genetic sources of variability in drug exposure and response, the use of modeling and simulation as decision support tools, and the facilitators to MIPD implementation. A panel discussion addressed the types of models used for MIPD, how the pharmaceutical industry views MIPD, ways to upscale MIPD beyond academic hospital centers, and the essential role of healthcare professional education as a way to progress. The meeting concluded with an ongoing commitment to use MIPD to improve patient care.

BACKGROUND

The first section of this report provides background information on the clinical need for precision dosing, including the use of modeling and simulation (M&S). This summarizes the established knowledge on the topic prior to the 1st Asian Symposium on Precision Dosing held in December 2017. Subsequent sections describe the current status of MIPD, the individual presentations from the meeting, and our vision for the immediate future of MIPD.

Between Patient Variability in Drug Response—a Problem in Clinical Practice

Different patients often respond differently to the same drug at the same dosing regimen, usually a flat dose but sometimes a dose based on a metric of body size (kilograms or body surface area). This is called between patient variability (BPV). The causes of BPV in drug response are pharmacokinetic (PK), where drug concentration at the site of action differs between patients, or pharmacodynamic (PD), where response after drug binding to a molecular target differs between patients at the same drug concentration. Between patient variability in drug response is a problem in clinical practice because it is difficult to judge who will benefit most from drug therapy and who will suffer adverse effects. Trial and error with several drugs or doses may be required before finding the best "fit" for a particular patient. This is time-consuming and frustrating for healthcare professionals and their patients. In some disciplines of medicine, such as oncology and hematology, the clinical stakes are high for patients and their families, so getting the dose correct early in treatment is very important. Poor outcomes from drug therapy also represent a significant financial cost to

[1] Certara, 100 Overlook Center, Suite 101, Princeton, New Jersey 08540, USA.
[2] Centre for Medicines Use and Safety, Monash University, Melbourne, Australia.
[3] Centre for Applied Pharmacokinetic Research, University of Manchester, Manchester, UK.
[4] Department of Pharmacology, College of Medicine, The Catholic University of Korea, Seoul, South Korea.
[5] Department of Clinical Pharmacology and Therapeutics, Seoul National University College of Medicine and Hospital, Seoul, South Korea.
[6] Department of Transdisciplinary Studies, Graduate School of Convergence Science and Technology, Seoul National University, Seoul, South Korea.
[7] Janssen Research and Development, Lower Gwynedd Township, Pennsylvania, USA.
[8] Korea Advanced Institute of Advanced Technology, Daedoek Innopolis, Daejeon, South Korea.
[9] Department of Pharmacology and Clinical Pharmacology, Pharmacogenomics Research Center, Inje University College of Medicine, Busan, Republic of Korea.
[10] Faculty of Pharmacy, Haiphong University of Medicine and Pharmacy, Haiphong, Vietnam.
[11] To whom correspondence should be addressed. (e–mail: tom.polasek@certara.com)

healthcare systems. Waste of precious resources occurs when drugs lack efficacy, although there are no data to estimate the financial cost. However, it is known that drug-related harm costs about US $42 billion per annum globally (1).

One way to improve drug treatment is to consider BPV in drug response when prescribing. The first step is to select the most suitable drug for the patient from a range of drug options. The second step is to choose the most suitable dose. While drug selection is directed by indications and guidelines, dose selection is often more problematic, especially for complex patients, drawing heavily on the experience of the prescriber. Indeed, dosing can evolve after regulatory approval, so that the dose(s) used in routine clinical practice differ from those on which the approval was based. For drugs that are difficult to dose, the "start low and go slow" empirical approach is common. This works for some chronic medical conditions but is unsuitable acutely when prompt efficacy dictates clinical outcomes. Examples include the treatment of status epilepticus with anti-seizure drugs or achieving heart rate control in patients with rapid atrial fibrillation. Under the banner of "precision medicine," there is increasing interest in drug development and in clinical medicine to rationalize dose selection to improve the chances of development success and to improve patient care (2). We have previously defined "precision dosing" as dose selection by a prescriber for an individual patient at a given time (3). This definition covers all clinical settings, ranging from a clinical research unit conducting a first in human study, to acute medical care in the emergency room, and to the management of life-long chronic diseases by a general practitioner.

Precision Dosing Is Needed

Precision dosing should occur for many drugs with a narrow therapeutic index (TI). Examples include the antiarrhythmics, anticoagulants, antiepileptics, antineoplastics, aminoglycoside antibiotics, and immunosuppressants. Precision dosing should also occur for some drugs with large BPV in responses that are not typically considered as having narrow TIs. For example, when a rare genetic polymorphism of a drug-metabolizing enzyme predominantly responsible for clearance causes complete loss of efficacy or severe toxicity. Patients who belong to the "special populations" may also benefit from precision dosing because they are at increased risk of therapeutic failure and drug-related harm—pediatric patients, the elderly, those with renal or hepatic impairment, the fetus, the breastfeeding infant, the critically ill, and patients taking concomitant drugs that cause PK or PD drug-drug interactions (4). In drug development, a precision dosing requirement, for example, via the measurement of plasma drug concentration, routinely ends the development of new chemical entities (NCEs) for commercial reasons. Thus, many potentially useful drugs are lost, particularly for niche indications when getting the dose correct is important early in a clinical program.

At the bedside or in the clinic, the main factors that influence dose selection by prescribers are disease severity, age, an indicator of body size (*e.g.*, body weight), liver function, renal function, and whether a robust biomarker of drug effect is available, such as the international normalized ratio (INR) to monitor anticoagulation in patients taking warfarin. Suggestions for dose based on these "visible" factors are sometimes provided in prescribing information (PI) or by specific dosing and monitoring guidelines (3). However, the understanding of variability in drug response is rapidly expanding to include many "hidden" physiological and molecular determinants of PK and PD that are less familiar to prescribers (5). For example, pharmacogenomics (PGx) is used to avoid gene-drug combinations associated with increased risk of toxicity (*e.g.*, abacavir hypersensitivity in patients carrying the *HLA-B*5701* mutation) (6). Some PGx guidelines also address dose selection, including loading doses of warfarin in adults and pediatrics (7), and starting doses of various selective serotonin re-uptake inhibitor antidepressants (8). Non-genetic sources of drug response variability are increasingly recognized as important for narrow TI drugs and for patients who belong to the special populations. For example, there are many physiological and molecular changes that influence PK as children grow—ontogeny of drug-metabolizing enzymes and transporters (DMETs), hematocrit, organ blood flows etc. (9). Together, these factors need consideration to estimate the dose for a target steady-state plasma concentration (10).

Model-Informed Drug Development

Given that many factors influence drug response, computer M&S is an important way to consider such complexity when explaining dose-exposure-response relationships. The most widely used M&S approaches are population PK/PD (pop PK/PD) (11), physiologically based PK (PBPK) (12), quantitative systems pharmacology (QSP) and toxicology (QST) (13), clinical trial simulation, and model-based meta-analysis (MBMA) (14). Pharmaceutical companies accelerate drug development by applying these approaches to solve problems that would otherwise prevent or slow progress. This is called model-informed drug development (MIDD). Importantly, MIDD enables decision-making and saves time and money (15,16). It is now strongly supported by the major regulatory agencies (17). A nice example of MIDD is how PBPK M&S was leveraged to predict the extent to which ibrutinib, a kinase inhibitor used for several hematological malignancies, is sensitive as an "object" of PK drug-drug interactions (DDIs). The prediction of changes in ibrutinib exposure with M&S informed 24 potential interactions in the PI and decreased the number of clinical studies required for registration (18).

Model-Informed Precision Dosing

Model-informed precision dosing (MIPD) re-purposes the M&S techniques used successfully in drug development to the healthcare setting. The goal is to improve drug therapy for better patient care. We previously defined MIPD as "M&S in healthcare to predict the drug dose for a given patient based on their individual characteristics that is most likely to improve efficacy and/or lower toxicity in comparison to traditional dosing (19)." The advantage of MIPD is superior dose selection based on broader consideration of the many factors that influence drug exposure and response—the traditional "visible" factors seen at the bedside or in the clinic plus the "hidden" factors that may

require additional tests and interpretation, *e.g.*, genotype of DMETs. The concept of MIPD is not new. However, enthusiasm for MIPD has increased in recent years for several reasons. (1) The growing clinical awareness that dosing requires fine-tuning to achieve the desired effects in specific patients and medical conditions. (2) The emergence of rapid and affordable genetic testing. (3) The rise of "multi-omic" technologies to identify novel biomarkers suitable for monitoring drug effects. (4) The increased computing power to analyze large volumes of patient data. (5) The blueprint of success created by M&S in drug development (*i.e.*, MIDD), such as guidance on dose selection at all stages of clinical development (20) or the prediction of PK in special populations such as children (21).

STATUS OF MIPD

Building on the First Meeting on MIPD

A healthcare summit was held in the UK in May 2016 to discuss for the first time the opportunities and challenges of MIPD. This meeting resulted in a "state of the art" paper that addressed the status of MIPD, the requirements of a MIPD tool, the future landscape of MIPD, and the legal/regulatory considerations of MIPD (22). The key points from the meeting have been updated here to "set the scene" for our report on the 1st Asian Symposium on Precision Dosing.

There are pockets of successful clinical implementation of MIPD but these are largely restricted to local collaborations between academia and healthcare. Examples include the dosing of chemotherapy in serious pediatric illnesses (23), the use of immunosuppressants in transplant medicine (24), dose optimization of anti-microbial drugs in intensive care (25,26), and personalized dosing of metformin based on renal function (27). A notable exception to the academic nature of these examples is the commercial application of a companion MIPD tool that personalizes the dose of octocog alfa (recombinant coagulation factor VIII) in hemophilia A. This tool was approved in December 2017 by the US Food and Drug Administration (FDA) via the 510 (k) medical device pathway. Taken together, these cases provide evidence that MIPD works, and that interest from healthcare professionals is strong when there are clear benefits to patients. In addition, there are many examples where good models are available for drugs but translation into clinical practice has not yet occurred (28).

Ways that MIPD Is Used in Clinical Practice

The clinical implementation of MIPD occurs in three ways:

1. Real-time MIPD. Prospective use of M&S is based on live measures from the patient of drug exposure (*e.g.*, therapeutic drug monitoring (TDM) of aminoglycoside plasma concentrations) or efficacy (*e.g.*, INR for warfarin). A pop PK/PD model uses a Bayesian approach to estimate the PK parameters for an individual patient once dosing has started, and these PK parameters are then used to tailor subsequent doses that have an increased chance of achieving the target concentration or response compared with "blind dosing." This approach is used by bespoke in-house M&S applications (29) and several commercial platforms that have aggregated published pop PK/PD models into a user-friendly interface (DoseMe, Insight Rx, PK-PD Compass etc. (30,31)).
2. Model-derived dose banding. Dose is selected based on the patient's unique value(s) of empirically identified covariates known to impact PK/PD. This pragmatic strategy for MIPD includes pediatric dosing of narrow TI antibiotics such as vancomycin (32) and amikacin (33), and the selection of biologic drug doses in oncology. For example, in the National Health Service in England, patients receive fixed doses within 10% of their milligram per kilogram doses, thus decreasing the waste of high-cost drugs such as pembrolizumab and nivolumab (34).
3. Mechanistic M&S using PBPK. Increased knowledge of individual patient covariates that impact PK, such as activities of the key DMETs, allows for the generation of "virtual twins" within the framework of verified PBPK models (35,36). This approach is promising for MIPD because (i) it is independent of TDM and its associated costs, (ii) dose can be estimated prior to drug administration, and (iii) predictions of dose are possible for patients with covariates known to impact PK/PD that have not been studied in clinical trials analyzed by pop PK/PD.

It should be emphasized that only select clinical scenarios will benefit from MIPD. There are several characteristics of the patient, the disease, and the drug that make MIPD more likely to improve clinical outcomes than traditional dosing (22). The patient should belong to a vulnerable group, typically a specific subpopulation in the target population for whom the physiology is well characterized, but where clinical data for efficacious drug therapy are lacking. The impact of treating the disease should be large, *i.e.*, there is a significant unmet medical need. This includes direct benefits to patients from improved health and indirect benefits to the broader community via cost savings that flow to other areas of healthcare. A relevant biomarker of disease status should be available to establish a therapeutic target. Characteristics associated with the drug that indicate a high impact case for MIPD include a narrow TI, significant morbidity or mortality from under- or over-dosing, high cost, well-characterized drug properties and target exposure, and inadequacy of other dosing strategies such as empirical dosing (22).

Legal and Regulatory Framework

The legal and regulatory framework for MIPD is complex and evolving. Any recommendations from a MIPD tool should be used to guide clinical decision-making, with prescribers legally responsible for sensible use, and developers and regulators required to ensure sufficient performance. Applications to regulators for a MIPD tool would come under the medical devices guidance. New drugs could be co-developed with a companion MIPD tool, with initial marketing authorization based on clinical trials conducted with MIPD. Alternatively, a MIPD strategy in the post-marketing phase showing superior clinical outcomes to traditional dosing may result in supplemental marketing

authorizations for the MIPD tool. This may require "dynamic" prescribing information to allow greater flexibility in dose selection, offsetting the concern of liability when prescribing outside a static dose range (19).

On this background, the 1st Asian Symposium on Precision Dosing was held on the 15th of December 2017 in Busan, Korea. The Symposium was organized to build on discussions at the Manchester healthcare summit, but also to gain insight into the Asian perspective of MIPD. The theme of the day was the question, "What does it take to make MIPD common practice?" There were 74 attendees from Korea, India, Thailand, Singapore, Australia, Zimbabwe, and the USA, with representation from academia (academics and students), the pharmaceutical industry, healthcare (doctors, pharmacists, nurses), and government agencies. The remainder of this report describes the individual presentations, summarizes the important messages from the panel discussion, and presents the immediate vision for progress with MIPD.

SUMMARY OF INDIVIDUAL PRESENTATIONS

The symposium had three theme-based sessions of speakers, with each presentation opened for questions from the audience after completion.

Session 1: Genetic *vs.* Non-Genetic Sources of Drug Exposure and Response Variability

The first session highlighted the distinction between genetic and non-genetic sources of variability in drug exposure and response. Rather than considering PGx alone, superior dose selection may be achieved by considering all the covariates influencing PK/PD. In some cases, it may be possible to distill complexity into relatively simple instructions for dosing. For example, CYP3A4 activity is the major factor explaining BPV in axitinib exposure (>90%) (3). Knowing CYP3A4 activity may be all that is needed for MIPD of axitinib. However, this is one of the major challenges for MIPD, since there has been no way to accurately estimate gut and hepatic CYP3A4 activity for individual patients without taking a selective probe IV and then orally, which is inconvenient and impractical in clinical practice. To this end, plasma exosome-derived biomarkers of CYP3A4 were recently shown to correlate well with oral midazolam clearance, offering the potential to assign CYP3A4 activity in an individual patient following a simple blood test (37).

Professor Amin Rostami-Hodjegan (University of Manchester and Certara) opened the session with the message that stratifying patients to one of a limited number of doses is usually the current extend of dose individualization, and that greater precision based on superior understanding of each patient is rare. Precision dosing was compared to selecting shoes. It is unreasonable for everyone to wear the same type and size of shoe, so why is "one-size-fits-all" accepted with pharmacotherapy? The potential of PBPK for MIPD was discussed. This form of M&S is best recognized for "bottom-up" predictions of PK based on *in vitro-in vivo* extrapolation (IVIVE) of key ADME properties, but it can also incorporate model parameter optimization following clinical PK studies ("top-down"). This "middle-out" M&S technique brings together the advantages of both PBPK and population PK/PD (38,39). The PBPK approach is increasingly supported by regulatory agencies (guidance documents from the FDA and the EMA are available (40,41)). In addition to confidence around CYP-mediated DDIs, prediction of PK in several special populations continues to improve, including in pediatrics (21,42), in patients with renal impairment (43), and in pregnant women (44).

Professor Jae-Gook Shin (Inje University College of Medicine) summarized the status of PGx and the categories of barriers to clinical implementation. Although many drugs have PGx information (>130 drug-gene pairs in FDA-approved PI), and practical advice for prescribers is available via the Clinical Pharmacogenomics Implementation Consortium (CPIC) (45) (44 guidelines) and the Dutch Pharmacogenomics Working Group (46), uptake into routine clinical practice remains slow (47). A reason for this is the consideration of PGx alone within the broader complexity of patient care. For example, genetic sources only account for 30–40% of the variability in warfarin response (*CYP2C9*, *VKORC1*, *CYP4F2*, and rs12777823 genotypes). Preemptive dose estimation can be improved when non-genetic factors (gender, age, body weight, drug-drug interactions, vitamin K rich food) are also included in prediction algorithms (7). However, with the exception of warfarin, well-developed and valid dose predictions based on genetic and non-genetic sources of BPV are limited. This is mainly because the population approach requires the collection of big data on drug response phenotypes, genetic and non-genetic covariates, and PK parameters, covering huge diverse subsets of patients. To minimize this research burden, MIPD using IVIVE with PBPK is an attractive alternative. Categories of barriers for PGx have been identified: (i) scientific; (ii) educational; (iii) ethical, legal, and social issues; (iv) information technology; and (v) reimbursement for implementation (47). The relative importance of these barriers varies between countries and clinical centers. Importantly, MIPD faces the same categories of barriers as PGx, since both are novel disruptive technologies that impact prescribing and clinical workflow. While PGx sources of PK variability are extensively studied, less is known about the genetic drivers of PD, such as molecular target and disease heterogeneity (2,48,49).

Dr. Jae Kyoung Kim (Korea Advanced Institute of Science and Technology) explained that thorough understanding of physiology/pathophysiology is essential for mechanistic approaches to MIPD. The phase, period, and amplitude of the mammalian circadian clock are dependent on the core clock kinase (CK1d/e) (50). Selective CK1d/e inhibitors can delay the circadian phase and reset the circadian clock, thus treating circadian rhythm sleep disorders (CRSD). However, the effect of CK1d/e inhibition changes more than 3-fold with dosing time and is attenuated by light exposure. Therefore, the environment of the patient is important, *e.g.*, the time of season and whether they work indoors or outdoors. To investigate such complex drug effects, a QSP model was constructed based on an accurate and detailed mathematical model of the mammalian circadian clock (51). It was possible to predict how the effect of chronic dosing with a CK1d/e inhibitor (PF 670462) dramatically changes depending on dosing time and environmental light

conditions. Such large variations in response show that MIPD may need to consider dose time and dose size for some conditions such as CSRD (52) .

Session 2: The Role of Modeling and Simulation as Decision Support Tools

A common theme for the second session was the importance of providing clinicians with quality-assured user-friendly decision support tools for MIPD. These tools are often referred to as "dashboard systems," and may be web-based, available in application form for personal mobile devices, integrated into electronic health records (EHR) and prescribing software, or any combination of the three. Although simple dosing calculators have long been available, there is increasing clinical experience with dashboard systems as the clinical interface for pop PK/PD models linked to TDM (53–55).

The first presentation was by Professor Dong-Seok Yim (The Catholic University of Korea) and was titled, "Developing user-friendly dose individualization tools from user-hostile models." There are > 400 population PK studies in hospitalized patients (Pubmed search, December 2017). Most are investigator-initiated studies on marketed drugs that generate models that are never used outside the local institution. Commercially available TDM software attempts to scale these models, but users are prevented from modifying population PK parameters or model structures to suit local conditions. Two attempts to improve MIPD via pop PK/PD M&S in Korea were introduced. The first case was a web-based system for recommending initial antibiotic dose in burn patients ("ATOP-burn" provides dose recommendations for fluconazole, meropenem, and colistin and is available at http://pipet.or.kr/). The dashboard predicts the probability of therapeutic success after inputting antibiotic name, patient characteristics, initial dose, and microbial *in vitro* minimum inhibitory concentration (MIC). When the MIC is unknown, a mean MIC value is used from previous Korean reports. The second case was an open-access R Shiny TDM tool for vancomycin (https://pipet.shinyapps.io/vancomycin/) which also uses a pop PK model built using data from Korean patients. By entering dose history, observed vancomycin concentrations and patient characteristics, the user may obtain the individual PK parameters and predict concentration curves at any dose via sliding bars of dose and dose interval. Both tools have a user-friendly, flexible and easily accessible web-based interface that was designed by collaboration between clinical pharmacologists, pharmacometricians, and clinicians.

An attractive option for MIPD is to re-purpose established modeling software. Maintaining the quality of such a product would be essential. Dr. Masoud Jamei (Simcyp) described the lessons learned about quality assurance from updating the Simcyp® simulator. Since the year 2000, this has involved > 400 person years of work. During the course of each version development, the simulator is continuously tested against a subset of workspaces (~ 50) and periodically tested against a full set of workspaces (~ 1000) for verification and regression against previous versions to identify deviations. The results of testing are available to members of the Simcyp® consortium. Quality assurance is only possible because end-users are unable to adjust the "inner workings" of the software. However, transparency regarding the science and applications of the simulator is a core philosophy at Simcyp®. There are > 150 publications by the Simcyp® R&D team and > 250 publications by independent investigators reporting successes and failures of the software. Thus, the simulator is considered a "glass box" rather than a "black box." This approach to quality assurance and transparency will be required if PBPK M&S is to evolve into a universal MIPD tool.

Dr. Holly Kimko (Janssen Research and Development) reminded the audience that MIDD has been actively advocated by the pharmaceutical industry for more than two decades (56). Paradoxically, prediction of dose in special populations during drug development has fueled a one-dose-fits-all culture. This is because pharmaceutical companies at go/no-go decision points intentionally select compounds with a wide TI that will treat most patients at the same dose. Fewer dosage strengths (*e.g.*, pills, vial sizes) can then be manufactured for a market that requires less manufacturing batch quality/supply controls and less prescribing effort. In addition, to achieve statistical significance with fewer subjects and higher power, BPV in PK/PD is controlled by applying strict subject enrollment criteria, which results in the exclusion of many subpopulations. Therefore, these practical considerations from pharmaceutical companies have resulted in limited access to potentially effective and safe drugs in all types of patients. To make drugs with a narrow TI more widely available, the development of MIPD companion tools is encouraged (19). However, the development strategy should be decided early by consulting with the commercial group/s responsible for reimbursement, and with the regulatory agencies for justification of statistical operating characteristics for drug approval (from frequentist view) and/or the information that can be borrowed from other studies with relevant assumptions (from Bayesian view). The roles and responsibility for handling legal problems that may arise from MIPD companion tools should be established. With appropriate commercial incentives and regulatory support, the pharmaceutical industry could provide drugs with companion MIPD tools that give information on optimal doses for specific patients. The relationship between treatment and clinical response could be refined further in clinical settings by utilizing comprehensive databases of "real-world evidence".

Session 3: Facilitators to Clinical Implementation—Focus on PBPK-Based MIPD

The final session highlighted recent advances in the science of PBPK. This form of M&S requires three sections of data. (1) A *drug file* based on physicochemical characteristics and the *in vitro* kinetics of interactions with DMETs. (2) A *population file* (the "system") based on demographic information and known values of physiological parameters and the activities of DMETs. (3) The *study design*, which describes how the drug is given to patients, including dose, route and frequency of administration, and the timing of any concomitant drugs and food (18). Unique clinical scenarios are simulated with various permutations of *drug*, *population*, and *study design* (57). While this form of M&S holds promise for MIPD, considerable work is required to increase the number and quality of drug files and population files.

Professor Howard Lee (Soul National University Hospital and College of Medicine) started the session by discussing

how a coordinated effort is required to increase the number of population files in PBPK platforms. These files are traditionally developed for industry, so limited numbers are suitable currently for predicting PK in clinical practice. To advance MIPD in Korea, a Korean population file was built in Simcyp® and its predictive performance was evaluated using six substrate drugs of seven major DMETs. Forty-three parameters, including the proportion of phenotypes in DMETs, were incorporated. The simulated concentration-time profiles overlapped most of the observed data, with < 2-fold difference in clearance. The Korean population file can be used to evaluate the impact of this ethnicity on PK, and to support PBPK-guided MIPD in Korean patients.

Dr. Thomas Polasek (Certara and Monash University) presented data from the first study to predict drug exposure in patients following individualization of a population file in Simcyp®. Updated *in vitro* data describing the kinetics of olanzapine metabolism (58) was used to generate a drug file that was validated against previously reported single-dose PK studies in health volunteers, Chinese and geriatric North European Caucasians. The variability of olanzapine exposure in a TDM database of patient samples was also predicted. The olanzapine PBPK model was then individualized based on ethnicity, gender, height, weight, liver and kidney functions, CYP1A2 phenotype, and CYP2C8 genotype. This was used to predict steady-state olanzapine concentration in individual patients (observed concentrations *versus* predicted concentrations gave R^2 values of 0.833 or 0.884 dependent on whether patients were genotyped for CYP2C8). Importantly, a hypothetical decrease in the BPV of olanzapine exposure was demonstrated after dose adjustment based on M&S (36). Thus, re-purposing the Simcyp® platform could be an important facilitator of MIPD.

Professor Jae-Gook Shin (Inje University College of Medicine) closed the session by presenting work to support MIPD of anti-tuberculosis (TB) drugs. Tuberculosis is an ongoing public health crisis with > 1 million deaths annually worldwide. Various anti-TB drug regimens are recommended based on patterns of TB resistance. However, these drugs have large BPV in PK, are victims and perpetrators of PK-DDIs that are difficult to predict, and may cause severe toxicities, *e.g.*, nephrotoxicity, drug-induced liver injury, neurotoxicity etc. The use of TDM is advocated to estimate how close previous dosing is to PK/PD targets, but TDM assays are often unavailable in many countries with the highest TB prevalence (59). Population PK/PD models linked to TDM have been tried for several anti-TB drugs, including linezolid, isoniazid, amoxicillin, para amino-salicylic acid (PAS), rifampin, isoniazid, pyrazinamide, and ethambutol (60). Unfortunately, many of these models are built on limited datasets and their utility is restricted in patients dissimilar to those in the base model, *e.g.*, different ethnicities. An alternative is the use of PBPK for MIPD (61). Uptake of this approach has been slow, however, because quality *in vitro* data for IVIVE are unavailable for many anti-TB drugs. To address this need, a comprehensive program of *in vitro* studies is underway to characterize systematically the inhibitory interaction and substrate potentials of most available anti-TB drugs with SLC and ABC transporters (62,63). As a result, these data may improve the predictive performance of IVIVE within a PBPK framework. By leveraging both opportunistic and in-house *in vitro* data, new PBPK models for ethambutol (64), PAS, and ethionamide (unpublished data) were developed to investigate factors affecting BPV in their PK. These models may allow preemptive dosing and/or dose adjustment based on predicted anti-TB drug concentrations in the lung and epithelial linings and exposure to toxic metabolites in off-target organs (61).

TAKE HOME POINTS FROM THE PANEL DISCUSSION

All speakers participated in a panel discussion prior to taking questions from the audience. The consensus was that the science of MIPD is maturing rapidly but that clinical implementation had been difficult and unscalable beyond academic-hospital centers. Clinicians doing MIPD urgently need to communicate their experiences to colleagues outside the field who are generally less familiar with the application of clinical pharmacology principles. Medical disciplines identified as priorities were pediatrics, infectious diseases, oncology and hematology, transplant medicine, nephrology, hepatology, and gastroenterology. Regarding the underlying models for MIPD, there were polarized views regarding preference for either population-based methods or the PBPK approach. Others were agnostic about the models for MIPD, taking a more pragmatic view. Despite pockets of excellence, particularly in pediatrics (23,55,65–67) and infectious diseases (26), a long-term plan is required to generate the clinical evidence and experience necessary to make MIPD common clinical practice.

The following points summarize the main questions from the audience and the responses of the panel.

1. Which models are the best for MIPD? It is important to progress beyond the debate of which M&S technique is "the best" for MIPD. The evidence of improved clinical outcomes with MIPD is largely for drugs requiring TDM. No studies have used PBPK M&S outside of clinical trials for dose selection, although several studies are underway with protein kinase inhibitors, antipsychotics, anticoagulants, atomoxetine, anti-TB drugs, and opioids. For MIPD to succeed, thought leaders from both the population PK/PD and PBPK fields must collaborate to find the best models for many diverse clinical scenarios.
2. What does the pharmaceutical industry think about MIPD? Despite the widespread use of models in drug development, there is currently no serious support from industry to translate these models into dosing tools for clinical practice. The focus is on *p* values from clinical trial results rather than individual patient outcomes. A shift in mind-set to greater individualization of dose during drug development will occur only when the financial incentives are in place, *e.g.*, outcome-based pricing.
3. What is the best way to scale MIPD? The most important first step is to continue generating clinical evidence to support MIPD. Then, this evidence must be communicated broadly outside the discipline of clinical pharmacology in a fashion that resonates with everyday clinicians, *i.e.*, the language of "evidence-based medicine." Seamless integration into workflow is essential. Using established EHRs on a site-by-site basis is too slow due to local IT hurdles, whereas complete integration with EHRs available via applications for mobile devices accelerates site initiation and allows for easier ongoing support.

4. Do clinicians understand the need for precision dosing? The answer to this question is dependent on the medical specialty. The specialties identified earlier in this section are the most knowledgeable about precision dosing because the "stakes are high," *e.g.*, transplant acceptance or rejection. However, many other clinicians underappreciate the extent of BPV in drug exposure and response, and accept that poor outcomes from pharmacotherapy are unavoidable "collateral damage" of doing the job. The decline in clinical pharmacology education in medical curricular over the last 20–30 years is an important gap in this regard. Overall, more clinical "champions" from all areas of medicine are needed to support MIPD.

VISION FOR THE IMMEDIATE FUTURE

Modeling and simulation is set to accelerate drug development further. Computational approaches will be applied more broadly at every stage of drug development from preclinical and clinical research through to market access strategy and post-marketing activities. Due to the problem of BPV in drug response, clinical academic groups will continue to build models based on the patients they treat and then apply these models at the bedside or in the clinic (25,26,54,55,60,65,68–71). However, for MIPD to become common rather than niche, a much higher level of activity is required—one with a business mind-set. A major boast for MIPD would be the re-purposing of models used in drug development for clinical application. Co-development of MIPD companion tools with new drugs is one strategy (19). However, this will occur only if drug developers are rewarded financially for demonstrating positive benefit: risk at the individual patient level rather than the traditional *p* value oriented approaches, *e.g.*, randomized controlled trials (RCTs). Clear regulatory pathways are required to incentivize greater translation of M&S to the clinic. Whether this occurs via the current medical device pathways or novel alternatives will depend on how the regulatory landscape evolves.

Demonstrating benefits to patients is the only way for disruptive healthcare technologies to succeed. In addition to the traditional ways of generating clinical evidence (pilot studies, RCTs etc.), novel approaches for studying MIPD are expected to include the use of real-world evidence and model-based meta-analysis of prior clinical trial data (72,73).

The ability to individualize dose based on PK/PD targets is now established with real-time MIPD assisted by TDM for several drugs (23,24,26,67,68), but successful methods that are independent of TDM are increasingly likely in the medium term. In this way, solving the problem of BPV in PK will progress rapidly in relatively simple patients with few medical problems and concomitant medications. Progress in predicting PK in more complex patients, such as the elderly with multiple comorbidities and polypharmacy (4), will be slower. Combining the benefits of PBPK and pop PK, the so-called middle-out approach, is expected to become increasingly common to address such challenges (38,39).

With the exception of infectious diseases, for which PD is guided by microbe sensitivities (MIC), understanding the PD sources of variability in drug response is poor (48). Genetic variability in the molecular sites of drug action (49) and disease heterogeneity (48) are two examples where considerable work is required before prediction of drug response in individual patients is improved. Modeling of drug interactions with complex biological systems by QSP and QST holds promise in this regard. Studies are already available that link PBPK and pop PK models with QSP/QST (13,35). More complex modeling techniques that are not addressed in this report may also be required, such as machine learning (48).

Any section on future vision is incomplete without recognizing the role of greater collaboration between the groups wishing to accelerate progress. The field of MIPD is no exception. Clinical, academic, industry, regulatory, funding, and patient groups will need to balance self-interest with the spirit of collaboration if MIPD is to become common clinical practice. In this regard, efforts are underway to form cross-society special interests groups on MIPD. The "Clinical Pharmacometrics Special Interest Group" is an initiative of the American College of Clinical Pharmacology and the International Society of Pharmacometrics that formed in 2017. An International Consortium or Society for MIPD that unites all interested parties would be ideal.

CONCLUSIONS

This paper describes the background and status of MIPD and the activities at the 1st Asian Symposium of Precision Dosing. The major advances in MIPD since the Manchester healthcare summit in 2016 include the creation of a wider range of clinically relevant drug profiles and population files for PBPK M&S, publication of the first virtual twin studies, growing evidence to support real-time MIPD in infectious diseases and pediatrics, regulatory approval of the first companion MIPD tool (for octocog alfa), and increased awareness of MIPD as a precision medicine technology with the potential to improve drug therapy. The meeting concluded with the commitment to continue efforts to expand research into the clinical implementation of MIPD, to educate healthcare professionals regarding MIPD, and to place improved patient care at the center of our efforts.

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COMPLIANCE WITH ETHICAL STANDARDS

Conflict of Interest Thomas M. Polasek, Amin Rostami-Hodjegan, and Masoud Jamei are employees of Certara. Certara makes modeling and simulation software, including one type of PBPK platform (Simcyp®), which is used by the pharmaceutical industry for drug development. All other authors declare that they have no conflicts of interest.

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