Model-Informed Drug Development

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PERSPECTIVE

Model-Informed Drug Development: Steps Toward Harmonized Guidance

Scott Marshall[1,*], Malidi Ahamadi[2,24], Jenny Chien[3], Daisuke Iwata[4], Pavel Farkas[5], Augusto Filipe[6], Nicolas Frey[7], Erin Greene[8], Norisuke Kawai[9], Jian Li[10], Jörg Lippert[11], Flora Musuamba Tshinanu[12], Efthymios Manolis[13], Mark C. Peterson[14], Sarem Sarem[15], Mohamad Shebley[16], Million Tegenge[17], Chia-Hsun Tsai[18], Chien-Lung Tu[19], Yasuto Otsubo[4], Jiawei Wei[20], Lucia Zhang[21], Hao Zhu[22] and Kristin E. Karlsson[23]

Global alignment of expectations is required to achieve consistency in the planning, conduct, reporting, and regulatory review of model-informed drug development (MIDD) applications. An International Council for Harmonization (ICH) MIDD general principles guideline has been positioned to provide a common standard of practice including a framework for risk-based assessment of MIDD-derived evidence within the context of global regulatory decision-making. This perspective provides the background, our viewpoints, and the next steps in the development of this guideline.

THE CURRENT VALUE OF MODEL-INFORMED DRUG DEVELOPMENT

The relevance of model-informed approaches to drug development and regulatory review continues to grow in line with the need for greater efficiency in drug development.[1] Appropriate utilization of model-informed drug development (MIDD) can enable selection of optimal doses, provide justification for the study population, and identify informative end points in design of more efficient trials. MIDD can further provide a framework enabling extrapolation to alternative treatment paradigms and different populations. The role of MIDD is also expanding in situations where other types of evidence generation are challenging due to the disease being studied,[2,3] and where there are ethical and/or practical aspects in studying the drug development question in the target population of interest[4] or due to the complexity of the modality being investigated.[5]

MIDD GENERAL PRINCIPLES GUIDELINE PROPOSAL

Over the past 10 years, there has been significant growth in regional regulatory and industry interactions on topics related to MIDD. In particular, under the Prescription Drug User Fee Act (PDUFA) VI, the US Food and Drug Administration (FDA) hosted a series of MIDD-oriented workshops and after a pilot phase have introduced paired project meetings dedicated to MIDD planning and application.[6] The FDA has also revised MIDD-related guidance and established the first review standard operating procedure for MIDD-related submissions. There has been similar growth in interest via industry regulatory workshops and development of regional regulatory

[1]Clinical Pharmacology Modelling and Simulation, GSK, Stevenage, UK; [2]Clinical Pharmacology Modeling and Simulation, AMGEN, Thousand Oaks, California, USA; [3]Global PK/PD & Pharmacometrics, Eli Lilly and Company, Indianapolis, Indiana, USA; [4]Pharmaceuticals and Medical Devices Agency, Tokyo, Japan; [5]Global Clinical Operations, Teva, Zagreb, Croatia; [6]Nonclinical and Clinical R&D, Tecnimede SA, Lisbon, Portugal; [7]Roche Pharma Research and Exploratory Development, Pharmaceutical Science, Roche Innovation Center, Basel, Switzerland; [8]International Regulatory Sciences & Policy, Pfizer, New York, New York, USA; [9]Clinical Research, Pfizer R&D Japan, Tokyo, Japan; [10]National Medical Products Administration, Beijing, China; [11]Pharmacometrics, Bayer, Berlin, Germany; [12]Federal Agency for Medicines and Health Products, Brussels, Belgium and University of Namur, Namur, Belgium; [13]European Medicines Agency, Amsterdam, The Netherlands; [14]Clinical & Quantitative Pharmacology, Vertex Pharmaceuticals, Boston, Massachusetts, USA; [15]Health Canada/Pharmaceutical Drugs Directorate, Ottawa, Ontario, Canada; [16]Clinical Pharmacology, AbbVie, North Chicago, Illinois, USA; [17]U.S. Food and Drug Administration, Center for Biologics Evaluation and Research, Silver Spring, Maryland, USA; [18]Center for Drug Evaluation (CDE), Taipei, Taiwan; [19]Center for Drug Evaluation, Taipei, Taiwan; [20]Novartis Institutes for Biomedical Research Co., Shanghai, China; [21]Health Canada, Biologic and Radiopharmaceutical Drugs Directorate, Ottawa, Ontario, Canada; [22]US Food and Drug Administration, Center for Drug Evaluation and Research, Silver Spring, Maryland, USA; [23]Swedish Medical Products Agency, Uppsala, Sweden; [24]Present address: Modeling and Simulation, Pharmacokinetics, Dynamics & Metabolism, Sanofi, Bridgewater, New Jersey, USA. *Correspondence: Scott Marshall (scott.f.marshall@gsk.com)

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guidelines, including an MIDD guideline from the National Medical Products Administration (NMPA; **Table 1**).

Discussions on the potential need for an overarching MIDD general principles guideline were initiated following publication of the European Federation of Pharmaceutical Industries and Associations (EFPIA) good practice paper.[7] This paper was a response to a European Medicines Agency (EMA) request for industry to provide a set of good practices to increase the consistency and quality of MIDD with regulatory submissions (https://bit.ly/3Pwj3Cn).

Several International Conference on Harmonization (ICH) guidelines directly or indirectly relate to certain aspects of MIDD (**Table 1**). However, these guidelines focus on specific applications, and do not provide guidance on the conduct of the referenced modeling and simulation, pharmacokinetic (PK)/pharmacodynamic (PD), or exposure-response approaches. The initial ICH topic proposal was developed by Pharmaceutical Research and Manufacturers of America (PhRMA) via its MIDD workgroup formed in response to an FDA MIDD-specific PDUFA VI commitment and for future expectation of joint industry-FDA interactions.

This topic proposal had to be aligned with other proposals with respect to the ongoing update or *de novo* development of other ICH guidelines in the areas of MIDD or where MIDD would have been a major component. Consideration with respect to an update to the ICH E4 Dose–Response Guideline was also required. In June 2020, the ICH Management Committee agreed to launch an MIDD Discussion Group (DG; formed January 2021 with a 1 year term) to evaluate the proposal and recommend a path forward to the ICH Assembly.

The DG aligned on the development of an MIDD general principles guideline as the next step and revision of the E4 Dose–response guideline as the highest priority subsequent step. Importantly, the DG recognized that an overarching guideline would not provide specifics with respect to a particular MIDD approach (e.g., population PK (PopPK)(/PD), exposure response, Quantitative Systems Pharmacology (QSP), Model Based Meta-Analysis (MBMA), and Physiologically-Based Pharmacokinetics (PBPK)). However, it would be inefficient to develop aligned individual ICH guidances for each approach as well as to try to cover all potential applications. The DG also believed the E4 Dose–Response revision would benefit from the MIDD general principles guideline. Similarly, the potential for future interplay of these approaches with other important areas, such as application to real-world evidence and integration with artificial intelligence/machine learning (AI/ML), was considered better covered at a higher level.

A subsequent topic proposal for the MIDD general principles guideline was approved by the ICH Assembly in November 2021 https://bit.ly/443ntFd) and was distributed to ICH parties. The ICH MIDD DG in parallel also developed a roadmap (https://bit.ly/46uh6g6) outlining ICH MIDD-related guidelines in order to help prioritize their development.

Following the approval of the topic proposal, an ICH M15 Informal Working Group (IWG) was endorsed in June 2022, with initial discussions starting in September 2022. Under ICH processes, the IWG became an Expert Working Group (EWG) upon finalization and approval of the Concept Paper and Business Plan (https://bit.ly/3PD0nRx, https://bit.ly/3PAYZPp; November 2022).

Development of the guideline is anticipated to require 3 years from initiation to completion.

OUTLINED SCOPE OF MIDD GENERAL PRINCIPLES GUIDELINE

The EWG anticipates the MIDD general principles guideline will cover the following topics:

(i) An outline of the general scope and principles with respect to MIDD, providing some generalized examples of the appropriate use of MIDD throughout the course of drug development.
(ii) General recommendations on high-level strategic planning, data quality and relevance, planning and implementation of analysis, interpretation of results, reporting, and documentation, with the objective to improve communication of MIDD throughout the drug lifecycle.
(iii) The concept of a risk-based assessment, such that the rigor of the MIDD application is commensurate with the impact or risk of the regulatory decision based on the results of the analysis.
(iv) A framework for multidisciplinary teams, to strengthen the interaction and dialogue involved in drug development and decision making with respect to the role of MIDD.
(v) High-level general recommendations with respect to interactions between a sponsor and regulator regarding the planning, conduct, submission, and assessment of MIDD application (although specific procedural recommendations are out of scope).

The scope includes the key focus on the concept of a risk-based assessment, the value of multidisciplinary team alignment with respect to MIDD strategy, and provision of high-level guidance on the need for early alignment with global regulators when the application of MIDD has higher impact on regulatory decision making.

Although the application of risk-based assessment and consideration with respect to degree of impact of MIDD output has been a discussion point between industry and regulatory authorities for some time,[6–8] the concept has been more recently formalized in the credibility framework within regulatory interactions in both the European Union[9] and the FDA.[10] Alignment of this approach has enabled successful interaction both with respect to the EMA Scientific Advice/Qualification and the FDA MIDD Paired Meeting Program. Based on the FDA's initial review experience, this framework is being explored for emerging modeling approaches, such as mechanistic modeling[11] and AI/ML modeling. The need for closer alignment between MIDD practitioners and other decision makers has been a common theme across industry and regulatory agencies. More generally, there is a need to ensure multidisciplinary team alignment of the strategic planning of MIDD activities with the underlying clinical development questions, so that the activities can appropriately inform and be informed by the associated clinical studies.

Table 1 MIDD related regional and ICH guidelines or policy statements

Region	Related guideline
Canada	Policy statement: Use of pharmacometrics in drug submissions and clinical trial applications
China	2020 guideline on MIDD
	2020 guideline on population PK analysis
Europe	2008 EMA guideline on reporting of the results of population PK analysis
	2013 EMA qualification opinion of a novel data driven model of disease progression and trial evaluation in mild and moderate Alzheimer's disease
	2014 EMA qualification opinion of MCP-Mod as statistical methodology for model-based design and analysis of dose finding studies
	2015 EMA guideline on the use of PKs and PDs in the development of antibacterial medicinal products
	2016 EMA guideline on the qualification and reporting of PBPK modeling and simulation
	2018 EMA reflection paper on the use of extrapolation in the development of medicines for pediatrics
	2022 EMA qualification opinion of islet autoantibodies as enrichment biomarkers for type 1 diabetes prevention clinical trials
Japan	2019 MHLW guideline on population PK and PD analysis
	2020 MHLW guideline for exposure-response analysis of drugs
	2020 MHLW guidelines for analysis reports involving PBPK models
United States	2003 FDA exposure-response relationships–study design, data analysis, and regulatory applications guidance for industry
	2003 FDA PK in patients with impaired hepatic function–study design, data analysis, and impact on dosing and labeling guidance for industry
	2013 FDA Drug Development Tools: Fit-for-Purpose Initiative
	2013 FDA Acute Bacterial Skin and Skin Structure Infections: Developing Drugs for Treatment guidance for industry
	2014 FDA general clinical pharmacology considerations for pediatric studies for drugs and biological products guidance for industry
	2015 FDA Product Development Under the Animal Rule Guidance for Industry
	2015 FDA Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment Guidance for Industry
	2016 FDA Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product Guidance for Industry
	2017 FDA Antibacterial Therapies for Patients With an Unmet Medical Need for the Treatment of Serious Bacterial Diseases Guidance for Industry
	2017 FDA Pediatric Rare Diseases — A Collaborative Approach for Drug Development Using Gaucher Disease as a Model Guidance for Industry
	2018 FDA MIDD pilot program
	2018 FDA PBPK analyses–format and content guidance for industry
	2019 FDA Drugs for Treatment of Partial Onset Seizures: Full Extrapolation of Efficacy from Adults to Pediatric Patients 2 Years of Age and Older Guidance for Industry
	2019 FDA Attention Deficit Hyperactivity Disorder: Developing Stimulant Drugs for Treatment Guidance for Industry
	2020 FDA PKs in patients with impaired renal function–study design, data analysis, and impact on dosing and labeling
	2020 FDA Drug–Drug Interaction Assessment for Therapeutic Proteins Guidance for Industry
	2020 FDA Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions Guidance for Industry
	2020 FDA *In Vitro* Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions Guidance for Industry
	2020 FDA The Use of Physiologically Based Pharmacokinetic Analyses — Biopharmaceutics Applications for Oral Drug Product Development, Manufacturing Changes, and Controls Guidance for Industry

(Continued)

Table 1 (Continued)

Region	Related guideline
	2022 FDA population PKs guidance for industry
	2022 FDA Pharmacokinetic-Based Criteria for Supporting Alternative Dosing Regimens of Programmed Cell Death Receptor-1 (PD-1) or Programmed Cell Death-Ligand 1 (PD-L1) Blocking Antibodies for Treatment of Patients with Cancer Guidance for Industry
	2022 FDA Pulmonary Tuberculosis: Developing Drugs for Treatment Guidance for Industry
	2023 FDA Evaluation of Gastric pH-Dependent Drug Interactions With Acid-Reducing Agents: Study Design, Data Analysis, and Clinical Implications
ICH	ICH E4 Guideline: Dose–response information to support drug registration
	ICH E5(R1) Guideline: Ethnic factors in the acceptability of foreign clinical data
	ICH E7 Guideline: Studies in support of special populations: Geriatrics
	ICH E11(R1) Guideline: Addendum: Clinical investigation of medicinal products in the pediatric population
	ICH E11A Guideline: Pediatric extrapolation
	ICH E14 Guideline: The clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs
	ICH E17 Guideline: General principles for planning and design of multi-regional clinical trials
	ICH E20 Guideline: Adaptive clinical trials
	ICH S7B Guideline: Nonclinical evaluation of potential for delayed ventricular repolarization (QT interval prolongation) by human pharmaceuticals
	ICH M12 Guideline: Drug interaction studies

EMA, European Medicines Agency; FDA, US Food and Drug Administration; ICH, International Council for Harmonization; MHLW, Ministry of Health, Labour, and Welfare; MIDD, model-informed drug development; PBPK, physiologically-based pharmacokinetics; PD, pharmacodynamic; PK, pharmacokinetic.

Globally, each region has separate procedures regarding how industry may engage with regulators in seeking advice on potential MIDD applications, alignment on how the work will be ultimately evaluated, and the extent to which it may guide regulatory decision making. However, it is important that the general need and considerations around the nature of the interactions are commonly shared. Achieving consistency of key aspects covered in the application process and subsequent sponsor-regulator discussions, together with a common view on the expected level of detail recommended by regulators, would help to ensure efficiency with respect to interactions as part of global drug development programs.

VALUE OF A FUTURE MIDD ICH GUIDELINE

At a practical level, the M15 guideline will provide an overarching framework that covers a wide range of MIDD approaches and applications. Its adoption should prevent the need for the construct of similar guidelines for each type of MIDD approach at the ICH level or indeed multiple regional guidelines. However, the guideline would not preclude the provision of specific additional guidelines with respect to individual approaches and applications, but rather capture the common features across approaches.

The guideline should serve as a signpost, marking the evolution of MIDD from being a niche component in research and development (R&D) to being a key source for evidence generation. In this regard, the strategic planning of MIDD as an integrated part of drug development planning is considered an important recommendation.

From a regulatory assessment perspective, adoption of a harmonized approach for decision making and transparency on the decision criteria, should improve consistency in outcomes and communication within and between organizations.

The adoption of the final guideline and subsequent training and implementation opens the potential for a further global adoption of MIDD as a concept with wider understanding across the R&D community.

In this regard, and as highlighted in **Figure 1**, achieving harmonization of

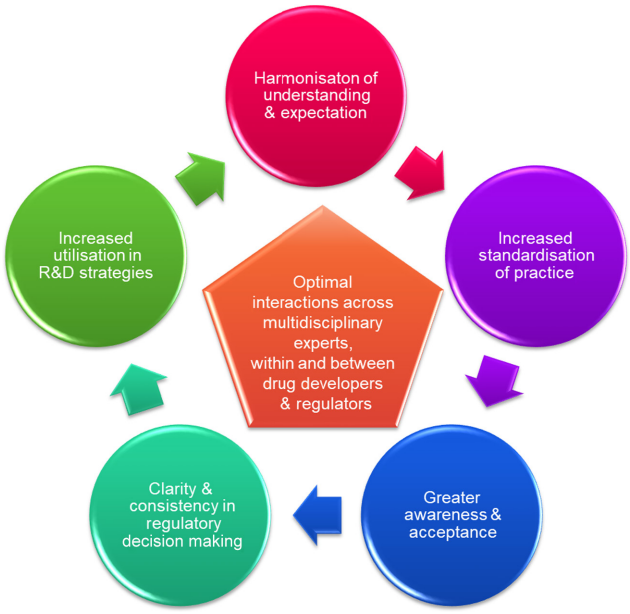

Figure 1 Expected value of International Council for Harmonization (ICH) M15 general principles guideline to future practice of model-informed drug development (MIDD). R&D, research and development.

understanding and expectations in the planning, conduct, reporting, and regulatory review of MIDD applications is part of a virtuous circle which should drive an increased standardization of practice, greater awareness and acceptance, further clarity of its role in regulatory decision making, and focused utilization within R&D strategies.

Central in this interplay is the interaction between regulators and industry, both at the level of MIDD practitioners as well as multidisciplinary teams who need to understand and jointly align on the credibility of the application within the planned context of use. A significant aim going forward will be to increase the level of understanding and to align expectations among all stakeholders. In this regard, it is envisioned that this guideline will allow for more effective positioning and evaluation of evidence derived by MIDD approaches within the global multidisciplinary regulatory review process and associated regulatory decision making. Specifically, it is expected to provide guidance on the risk-based assessment of MIDD as supportive of, or primary evidence in, regulatory decision making.

SUMMARY AND NEXT STEPS

In accordance with ICH policy, the discussions and materials generated during the ICH M15 discussions are confidential prior to public consultation, which is planned for 2024. EWG members are looking forward to engaging with the MIDD community via our recognized regional scientific meetings, where we will present the Concept Paper, capture feedback, and engage in associated scientific discussions. As part of this process, we are pleased to offer this perspective on the steps to reach this point and our collective viewpoint on the scope as outlined in the Concept Paper.

We are highly motivated by the significant milestone that an ICH MIDD guideline would represent in terms of enabling future practice in the context of global drug development and regulatory decision making.

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CONFLICT OF INTEREST

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DISCLAIMER

This perspective represents the perspectives of the individual authors and does not represent the views of their institution or the ICH M15 EWG.

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