ICH M15 Model-Informed Drug Development General Principles Guideline

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BioBridges 2024, Prague, CZ - September 27, 2024

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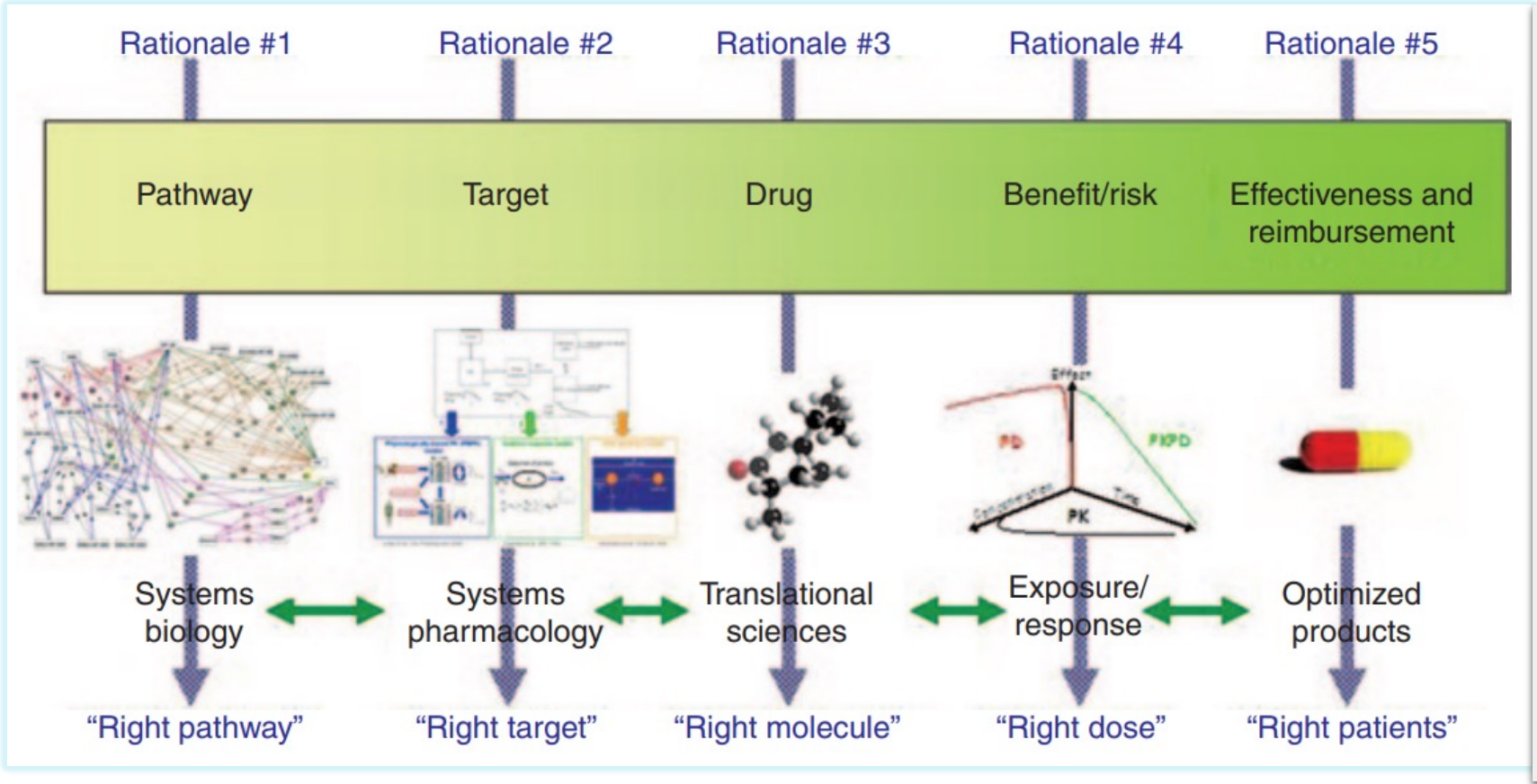
In accordance with ICH policy, the discussions and materials generated during the ICH M15 discussions are confidential prior to public consultation.

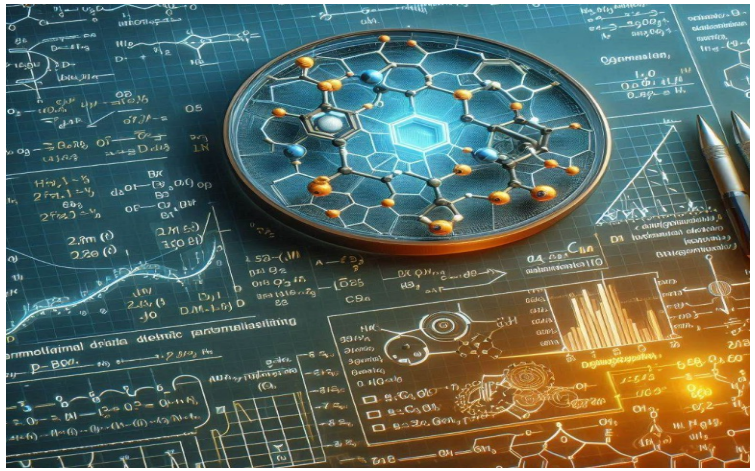
Model-Informed Drug Discovery & Development



"A quantitative **framework** for prediction and extrapolation centered on knowledge and inference, generated from **integrated models** of compound, mechanism and disease level data aimed at **improving the quality, efficiency and cost effectiveness of decision making**"

EFPIA CPT PSP. 5, 93–122 (2016)

Definition of MIDD



Model-Informed Drug Development is an approach that utilizes **mathematical models** and **simulations** to support key decisions in drug development.

Key Components:

- **Data Integration**: Combines diverse data sources to inform decision-making.
- **Predictive Modeling**: Uses exposure-based, biological, and statistical models to forecast clinical outcomes.
- **Risk Mitigation**: Aims to reduce uncertainty and improve the probability of success in drug development.

Applications of MIDD

Clinical Trial Design	Optimizes trial parameters and patient selection
Dosing Strategies	Supports the development of effective dosing regimens
Safety Evaluation	Predicts potential adverse effects and enhances product safety

The growing value of MIDD

- Driven by the need for greater efficiency in drug development
- Enabling of the optimal **dose**, appropriate **population** and informative **endpoint selection** in design of **more efficient trials**, as well as providing the **framework to enable extrapolation** to alternative **treatment paradigms** and different **populations**.
- Expanding in situations :
  - when other types of evidence generation are challenging due to the disease under study
  - where there are ethical and/or practical aspects in studying the drug development question in the target population of interest
  - due to the complexity of the modality being investigated

Concept of Risk Based Assessment
Credibility Assessment Framework : EMA/FDA

Challenge: Sufficient use cases and global acceptance

Potential Solution: Extract requirements in to more general risk based framework

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DOI: 10.1002/psp4.12669

WHITE PAPER

Scientific and regulatory evaluation of mechanistic *in silico* drug and disease models in drug development: Building model credibility

Flora T. Musuamba[1,2,3] | Ine Skottheim Rusten[1,4] | Raphaëlle Lesage[5,6] | Giulia Russo[7] | Roberta Bursi[8] | Luca Emili[8] | Gaby Wangorsch[1,9] | Efthymios Manolis[1,10] | Kristin E. Karlsson[1,11] | Alexander Kulesza[12] | Eulalie Courcelles[12] | Jean-Pierre Boissel[12] | Cécile F. Rousseau[13] | Emmanuelle M. Voisin[13] | Rossana Alessandrello[14] | Nuno Curado[15] | Enrico Dall'ara[16] | Blanca Rodriguez[17] | Francesco Pappalardo[7] | Liesbet Geris[5,6,18]

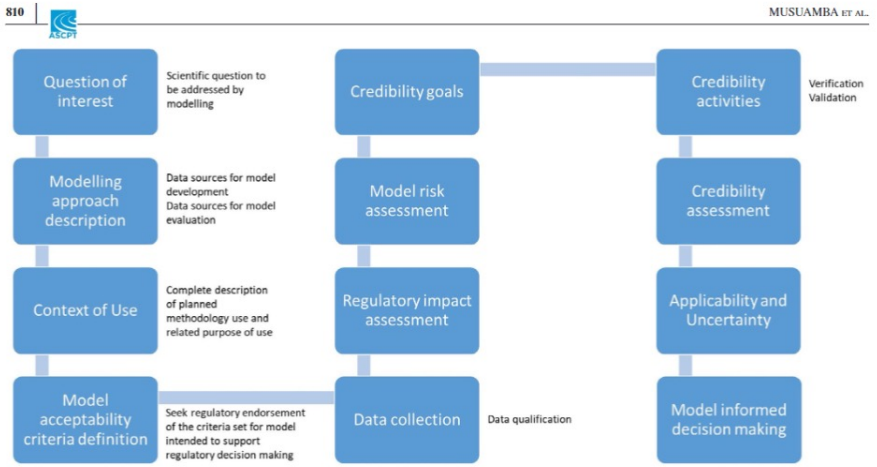
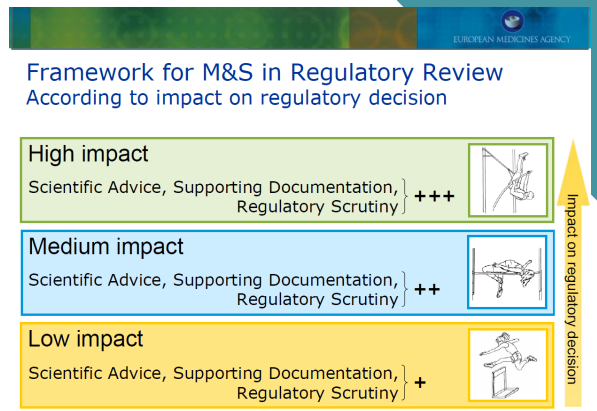


FIGURE 1 In silico Model Process flowchart



Citation: CPT Pharmacometrics Syst. Pharmacol. (2020) 9, 21–28; doi:10.1002/psp4.12479

WHITE PAPER

Consideration of a Credibility Assessment Framework in Model-Informed Drug Development: Potential Application to Physiologically-Based Pharmacokinetic Modeling and Simulation

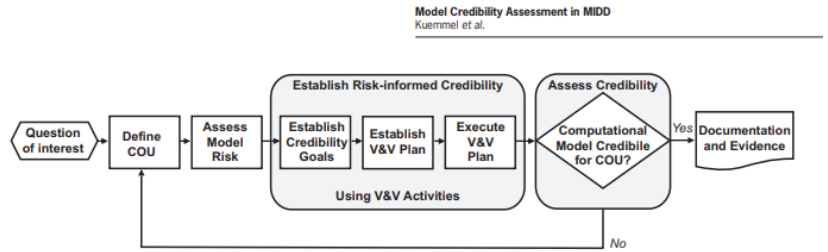
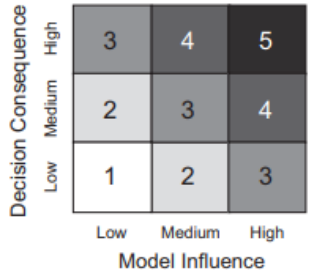


Figure 1 Overview of the ASME V&V 40 risk-informed credibility assessment framework. Modified from ASME V&V 40-2018, by permission of the ASME.[13] All rights reserved. ASME, American Society of Mechanical Engineers; COU, context of use; V&V, verification and validation.

Concept 4: Establishing credibility

The model risk levels can then be used to select V&V activities and define outcomes that will provide evidence to demonstrate credibility for a COU. The V&V activities proposed should be described according to the model's COU. Potential activities can be graded on a scale from least to most rigorous to align with level of credibility needed. More rigorous activities may be selected for models that have



High Level Guidance with respect to interactions between sponsors & regulators

Challenge: One Sponsor – Multiple Regulatory Bodies

Potential Solution: Extracted Principles rather than Procedures

The US Food and Drug Administration's Model-Informed Drug Development Paired Meeting Pilot Program: Early Experience and Impact

Rajanikanth Madabushi[1], Jessica M. Benjamin[1], Renmeet Grewal[1], Michael A. Pacanowski[1], David G. Strauss[1], Yaning Wang[1], Hao Zhu[1] and Issam Zineh[1,*]

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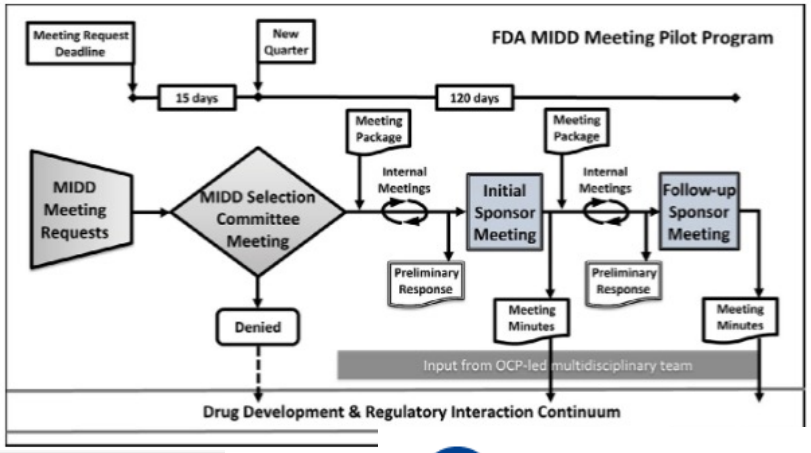
Received March 11, 2019; accepted April 4, 2019. doi:10.1002/cpt.1457



FDA Announces Continuation of the MIDD Paired Meeting Program Under PDUFA VII

On September 30, 2022

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Questions during scientific advice can relate to:

- quality aspects (e.g. manufacturing, chemical, pharmaceutical and biological testing of the medicine);
- non-clinical aspects (e.g. toxicological and pharmacological tests designed to show the activity of the medicine in the laboratory);
- clinical aspects (e.g. appropriateness of studies in patients or healthy volunteers, selection of endpoints, i.e. how best to measure effects in a study, post-authorisation activities including risk management plans);
- methodological issues (e.g. statistical tests to use, data analysis, modelling and simulation);
- overall development strategy (e.g., conditional marketing authorisation, bridging strategy for generics, safety database), significant benefit for maintaining orphan designation, and paediatric developments.

pmda 独立行政法人 医薬品医療機器総合機構
Pharmaceuticals and Medical Devices Agency

Consultations

Consultations

PMDA offers consultations to give guidance and advice on clinical trials of drugs, medical devices, and cellular and tissue-based products as well as on data for regulatory submissions. In clinical trial consultations for new drugs, PMDA checks whether a proposed clinical trial complies with the requirements for regulatory submission, taking into consideration the ethical and scientific aspects and reliability of the clinical trial as well as the safety of trial subjects, and also gives advice to facilitate the improvement of the clinical trial. Starting in FY 2009, PMDA provides prior assessment consultations, in which its reviewers evaluate data on the quality, efficacy, and safety of a product in the pre-submission stage and
the consultation process constitutes part of the review of the product once the application is submitted.

ICH M15 -Background

- Still no common understanding on the appropriate use of MIDD within and between regulatory agencies and industry, despite the increasing use of MIDD analyses
  - **Outline general principles with respect to MIDD**

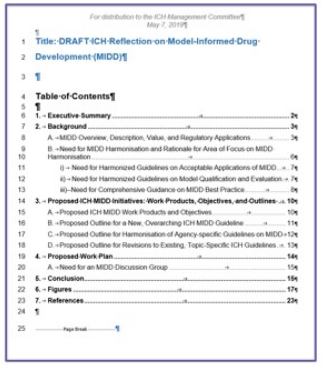
- The lack of documentation standards and model assessment, hinders the assessment of the modelling impact and credibility with respect to its intended applications
  - Guidance on standardization of reporting and documentation
  - **Introduce the concept of a risk-based assessment**

ICH M15 –Background - continued

- The absence resulting in over reliance on empirical approaches, inefficient drug development strategies and study designs
  - **Strengthen the interaction and dialogue between disciplines involved in drug development decision-making with respect to the role of MIDD**
  - Recommendations with respect to interactions between sponsor and regulator regarding the planning, conduct, submission, and assessment of MIDD application

Path to the PhRMA ICH Topic Proposal 2020

PhRMA MIDD ICH Topic Proposal (2019)


For distribution to the ICH Management Committee
May 7, 2019

Title: DRAFT ICH Reflection on Model-Informed Drug Development (MIDD)

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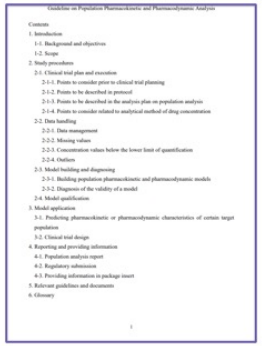
PMDA – Population PK/PD 2019


Guideline on Population Pharmacokinetic and Pharmacodynamic Analysis

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NMPA – Population PK 2020

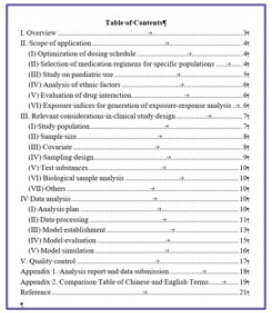
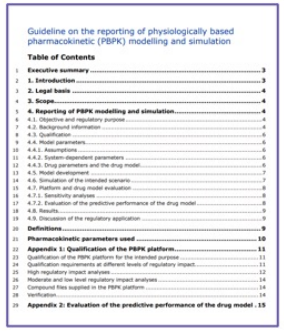


Table of Content

EMA – PBPK 2019


Guideline on the reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation

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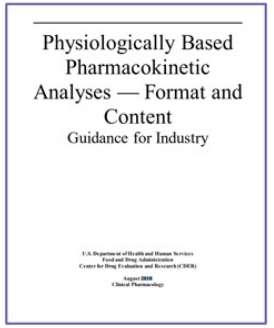
FDA – PBPK 2018


Physiologically Based Pharmacokinetic Analyses — Format and Content

Guidance for Industry

EFPIA MIDD White paper(2016)


WHITE PAPER

Good Practices in Model-Informed Drug Discovery and Development: Practice, Application, and Documentation

Exposure Response 2020


Guideline for Exposure-Response Analysis of Drugs

Contents

MIDD 2020


Technical Guideline on Model-Informed Drug Development

Content

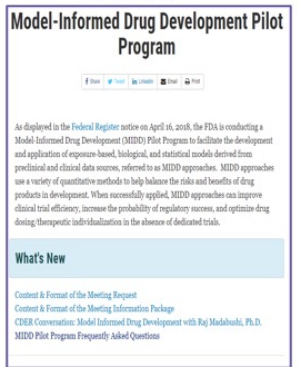
Extrapolation 2018


EUROPEAN MEDICINES AGENCY

Reflection paper on the use of extrapolation in the development of medicines for paediatrics

Final

MIDD Pilot 2018


Model-Informed Drug Development Pilot Program

What's New

Content & Format of the Meeting Request

Content & Format of the Meeting Information Package

CDER Conversation: Model Informed Drug Development with Raj Madabushi, Ph.D.

MIDD Pilot Program Frequently Asked Questions

Updated PhRMA ICH Topic Proposals 2020

ICH Timelines

June 2020

ICH Management Committee agreed to launch an MIDD Discussion Group (DG)

January 2021

MIDD Discussion Group evaluated the proposal and recommended a path forward to the Assembly

June 2022

ICH M15 Informal Working Group (IWG) was endorsed, with initial discussions starting in September 2022.

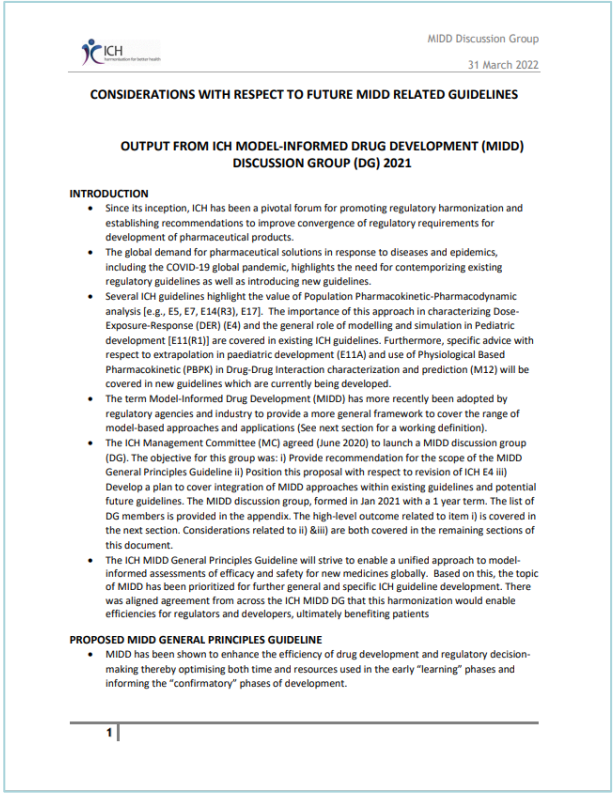
November 2022

The IWG became an Expert Working Group (EWG) upon finalization and approval of the Concept Paper and Business Plan

ICH M15 Topic Proposal & Business Plan

General ICH M15 link

ICH MIDD DG Road Map



MIDD Discussion Group

31 March 2022

CONSIDERATIONS WITH RESPECT TO FUTURE MIDD RELATED GUIDELINES

OUTPUT FROM ICH MODEL-INFORMED DRUG DEVELOPMENT (MIDD) DISCUSSION GROUP (DG) 2021

INTRODUCTION

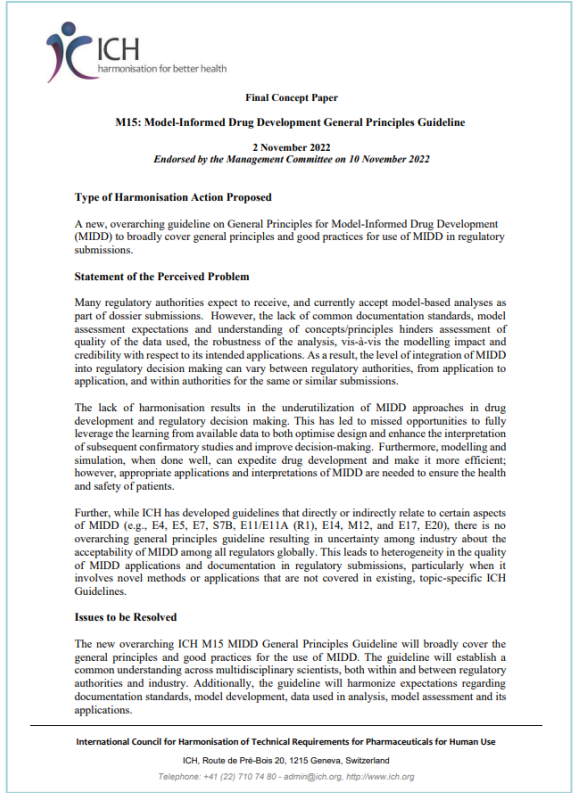
- Since its inception, ICH has been a pivotal forum for promoting regulatory harmonization and establishing recommendations to improve convergence of regulatory requirements for development of pharmaceutical products.
- The global demand for pharmaceutical solutions in response to diseases and epidemics, including the COVID-19 global pandemic, highlights the need for contemporizing existing regulatory guidelines as well as introducing new guidelines.
- Several ICH guidelines highlight the value of Population Pharmacokinetic-Pharmacodynamic analysis [e.g., E5, E7, E14(R3), E17]. The importance of this approach in characterizing Dose-Exposure-Response (DER) (E4) and the general role of modelling and simulation in Pediatric development [E11(R1)] are covered in existing ICH guidelines. Furthermore, specific advice with respect to extrapolation in paediatric development (E11A) and use of Physiological Based Pharmacokinetic (PBPK) in Drug-Drug Interaction characterization and prediction (M12) will be covered in new guidelines which are currently being developed.
- The term Model-Informed Drug Development (MIDD) has more recently been adopted by regulatory agencies and industry to provide a more general framework to cover the range of model-based approaches and applications (See next section for a working definition).
- The ICH Management Committee (MC) agreed (June 2020) to launch a MIDD discussion group (DG). The objective for this group was: i) Provide recommendation for the scope of the MIDD General Principles Guideline ii) Position this proposal with respect to revision of ICH E4 iii) Develop a plan to cover integration of MIDD approaches within existing guidelines and potential future guidelines. The MIDD discussion group, formed in Jan 2021 with a 1 year term. The list of DG members is provided in the appendix. The high-level outcome related to item i) is covered in the next section. Considerations related to ii) &iii) are both covered in the remaining sections of this document.
- The ICH MIDD General Principles Guideline will strive to enable a unified approach to model-informed assessments of efficacy and safety for new medicines globally. Based on this, the topic of MIDD has been prioritized for further general and specific ICH guideline development. There was aligned agreement from across the ICH MIDD DG that this harmonization would enable efficiencies for regulators and developers, ultimately benefiting patients

PROPOSED MIDD GENERAL PRINCIPLES GUIDELINE

- MIDD has been shown to enhance the efficiency of drug development and regulatory decision-making thereby optimising both time and resources used in the early "learning" phases and informing the "confirmatory" phases of development.

1

ICH M15 Concept Paper



ICH harmonisation for better health

Final Concept Paper

M15: Model-Informed Drug Development General Principles Guideline

2 November 2022

Endorsed by the Management Committee on 10 November 2022

Type of Harmonisation Action Proposed

A new, overarching guideline on General Principles for Model-Informed Drug Development (MIDD) to broadly cover general principles and good practices for use of MIDD in regulatory submissions.

Statement of the Perceived Problem

Many regulatory authorities expect to receive, and currently accept model-based analyses as part of dossier submissions. However, the lack of common documentation standards, model assessment expectations and understanding of concepts/principles hinders assessment of quality of the data used, the robustness of the analysis, vis-à-vis the modelling impact and credibility with respect to its intended applications. As a result, the level of integration of MIDD into regulatory decision making can vary between regulatory authorities, from application to application, and within authorities for the same or similar submissions.

The lack of harmonisation results in the underutilization of MIDD approaches in drug development and regulatory decision making. This has led to missed opportunities to fully leverage the learning from available data to both optimise design and enhance the interpretation of subsequent confirmatory studies and improve decision-making. Furthermore, modelling and simulation, when done well, can expedite drug development and make it more efficient; however, appropriate applications and interpretations of MIDD are needed to ensure the health and safety of patients.

Further, while ICH has developed guidelines that directly or indirectly relate to certain aspects of MIDD (e.g., E4, E5, E7, S7B, E11/E11A (R1), E14, M12, and E17, E20), there is no overarching general principles guideline resulting in uncertainty among industry about the acceptability of MIDD among all regulators globally. This leads to heterogeneity in the quality of MIDD applications and documentation in regulatory submissions, particularly when it involves novel methods or applications that are not covered in existing, topic-specific ICH Guidelines.

Issues to be Resolved

The new overarching ICH M15 MIDD General Principles Guideline will broadly cover the general principles and good practices for the use of MIDD. The guideline will establish a common understanding across multidisciplinary scientists, both within and between regulatory authorities and industry. Additionally, the guideline will harmonize expectations regarding documentation standards, model development, data used in analysis, model assessment and its applications.

International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

ICH, Route de Pré-Bois 20, 1215 Geneva, Switzerland

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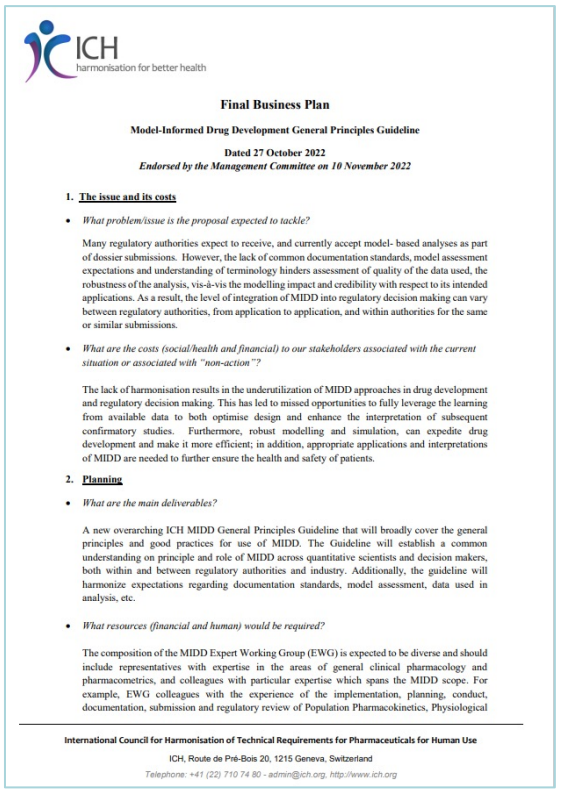
ICH M15 Business Plan



ICH harmonisation for better health

Final Business Plan

Model-Informed Drug Development General Principles Guideline

Dated 27 October 2022

Endorsed by the Management Committee on 10 November 2022

1. **The issue and its costs**

- *What problem/issue is the proposal expected to tackle?*

Many regulatory authorities expect to receive, and currently accept model- based analyses as part of dossier submissions. However, the lack of common documentation standards, model assessment expectations and understanding of terminology hinders assessment of quality of the data used, the robustness of the analysis, vis-à-vis the modelling impact and credibility with respect to its intended applications. As a result, the level of integration of MIDD into regulatory decision making can vary between regulatory authorities, from application to application, and within authorities for the same or similar submissions.

- *What are the costs (social/health and financial) to our stakeholders associated with the current situation or associated with "non-action"?*

The lack of harmonisation results in the underutilization of MIDD approaches in drug development and regulatory decision making. This has led to missed opportunities to fully leverage the learning from available data to both optimise design and enhance the interpretation of subsequent confirmatory studies. Furthermore, robust modelling and simulation, can expedite drug development and make it more efficient; in addition, appropriate applications and interpretations of MIDD are needed to further ensure the health and safety of patients.

2. **Planning**

- *What are the main deliverables?*

A new overarching ICH MIDD General Principles Guideline that will broadly cover the general principles and good practices for use of MIDD. The Guideline will establish a common understanding on principle and role of MIDD across quantitative scientists and decision makers, both within and between regulatory authorities and industry. Additionally, the guideline will harmonize expectations regarding documentation standards, model assessment, data used in analysis, etc.

- *What resources (financial and human) would be required?*

The composition of the MIDD Expert Working Group (EWG) is expected to be diverse and should include representatives with expertise in the areas of general clinical pharmacology and pharmacometrics, and colleagues with particular expertise which spans the MIDD scope. For example, EWG colleagues with the experience of the implementation, planning, conduct, documentation, submission and regulatory review of Population Pharmacokinetics, Physiological

International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

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Current EWG members (27 persons - 15 parties)

ICH harmonisation for better health

FIRST NAME	LAST NAME	PARTY
Mark	Peterson	BIO-Topic Leader
Malidi	Ahamadi	BIO- Deputy Topic Leader
Kristin	Karlsson	EC, Europe-Regulatory Chair
Efthymios	Manolis	EC, Europe -Deputy Topic Leader
Flora	Musuamba Tshinanu	EC, Europe -Topic Leader
Rania	Shousha	EDA, Egypt – Observer Expert
Nicolas	Frey	EFPIA-Topic Leader
Jörg	Lippert	EFPIA-Deputy Topic Leader
Million	Tegenge	FDA, United States--Deputy Topic Leader
Hao	Zhu	FDA, United States-Topic Leader
Sarem	Sarem	Health Canada, Canada-Topic Leader
Lucia	Zhang	Health Canada, Canada-Alternate Expert
Jiawei	Wei	IFPMA-Topic Leader
Liying (Leon)	Sun	IFPMA-Alternate Expert

FIRST NAME	LAST NAME	PARTY
Pavel	Farkas	IGBA-Topic Leader
Augusto	Filipe	IGBA-Deputy Topic Leader
Norisuke	Kawai	JPMA- Topic Leader
Daisuke	Iwata	MHLW/PMDA, Japan- Topic Leader
Yasuto	Otsubo	MHLW/PMDA, Japan- Deputy Topic Leader
Essam	Kerwash	MHRA, UK – Topic Leader
Jian	Li	NMPA, China- Topic Leader
Limin	Zou	NMPA, China- Alternate Expert
Erin	Greene	PhRMA- Rapporteur Supporter
Scott	Marshall	PhRMA- Rapporteur
Jenny	Chien	PhRMA- Topic Leader
Mohammed	AlHarbi	SFDA, Saudi Arabia- Topic Leader
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Jen	Moyers	Synchrogenix, Certara

4

Expected value of (ICH) M15 general principles guideline to future practice of model-informed drug development (MIDD)

PERSPECTIVES

(Concept paper)

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]

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Intended Scope and Content of M15 Guidance

- Outline of **general scope and principles** with respect to MIDD, provision of some genericized examples of the appropriate use of MIDD throughout the course of drug development;

- Guidance on **quantitative strategies, analysis and interpretation** of results, **standardization of reporting and documentation**, with respect to data sources and results with the objective to improve communication of MIDD throughout the drug lifecycle;

- Introduce 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;

Intended Scope and Content of M15 Guidance- continued

- 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;

- A high-level general guidance on recommendations with respect **to interactions between sponsor and regulator** regarding the planning, conduct, submission, and assessment of MIDD application
(*specific procedural recommendations are out of scope*);

Summary of a future MIDD ICH guideline

- Will represent an overarching framework that covers a wide range of MIDD approaches and applications, will capture the common features across approaches
- Will serve as a signpost with respect to the evolution of MIDD from being a niche component in R&D to being a key source for evidence generation
- Thanks to the risk-based analysis approach, should improve consistency in outcomes and communication within and between organizations
- Will result in achieving harmonization of understanding and expectations in the planning, conduct, reporting, and regulatory review of MIDD applications

Central in this interplay is the interaction between regulators and industry, both at the level of MIDD practitioners as well as multidisciplinary teams

Upcoming ICH M15 EWG Work Plan

Expected Completion date	Deliverable
October 2024	• Step 1 Technical document signed off by topic leaders Step 2a Parties consensus on technical document Step 2b Draft Guideline adoption by Regulators
4Q 2024	• Step3 Regulatory Consultation & Discussion (including public consultation)
4Q 2025	• Step 3 Signoff • Step 4 Adoption of M15 guideline

Considerations for Future MIDD Related Guidelines

ICH GUIDELINE /TOPIC	PRIORITY	CONSIDERATIONS
E4 Dose-response	High	Needs to be updated to re-aligned practices and expectations from regulators and industry on the value and acceptability of methods and designs for Dose-Exposure-Response characterization
Population PK & Exposure-Response	Medium	To further promote utilization and acceptance of applications using these approaches a global guideline may be merited (could be annexed to ICH MIDD guideline)
PBPK (Physiologically based PK modelling)	Medium	A methodology focused guidance could be required in order to give more specifics with respect to both technical and documentation aspects associated with PBPK (could be annexed to ICH MIDD guideline)

Utilization of Model-based BE (MBE) approach

- Allows pivotal information of clinical trials to be simulated to streamline drug development, optimize its costs and duration as well as facilitate a regulatory review
- **Enhances efficiency of drug development** and regulatory decision-making
- Optimizes both time and resources used in the early "learning" phases
- Informs the "confirmatory" phases of development

MBE can be beneficial or even the first line solution to the assessment of bioequivalence for:

- *Complex MR dosage forms*
- *Drugs with complex PKs that may violate assumptions of non-compartmental analyses*
- *Endogenous compounds*
- *Systemic drug exposure not relevant for efficacy*
- *Difficult study population*
- *Safety issues*
- *Sparse sampling*

Bringing about complex and costly drug therapies affordable to broader populations of patients worldwide

Challenges of Model-Informed Bioequivalence for Regulatory Decision Making

- Complex and more mechanistic models require a multi-disciplinary development teams as well as review teams
- Model evaluation should include technical and clinical validation of the model as well as assessment of its applicability
- Qualification of platforms and models intended to be used in multiple drug development programs
- Novel methodologies and approaches for generic drug development need to be consulted with regulators.

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