ICH M15 - Model Informed Drug Development (MIDD): Steps Toward Harmonized Guideline

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Disclaimer

The views expressed in this presentation are those of the author and do not necessarily reflect the official policy or position of the author's corporate affiliation or the ICH M15 Expert Working Group.

Model Informed Drug Development (MIDD)

- **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 MID3 Workgroup et al. *CPT: PSP* vol. 5,3 (2016): 93-122.

Umbrella term that encompasses:

- **PK/PD, PBPK, QSP, dose-response, disease progression models,**
- **Integration of emerging methods like machine learning and AI,**
- **Combination of subject-level and summary-level data, including MBMA,**
- **Application across non-clinical, clinical, and real-world data,**
- **Support for clinical trial design and quantitative decision-making.**

MIDD Concept Paper, ICH Website, 2022

ICH: International Council for Harmonisation
of Technical Requirements for Pharmaceuticals for Human Use (1990)

- **Global initiative that brings together regulatory authorities and the pharmaceutical industry to harmonize scientific and technical standards for drug development and registration,**
- **Aims to reduce duplication of clinical trials, ensure more efficient processes, and improve drug safety and efficacy through the development of international guidelines.**

ICH Members

23 Members:

- Founding Regulatory:
  - EC, Europe; MHLW/PMDA, Japan; FDA, United States
- Founding Industry:
  - EFPIA; JPMA; PhRMA
- Standing Regulatory:
  - Swissmedic, Switzerland; Health Canada, Canada
- Regulatory:
  - ANMAT, Argentina; ANVISA, Brazil; COFEPRIS, Mexico; EDA, Egypt; HSA, Singapore; JFDA, Jordan; MFDS, Republic of Korea; MHRA, UK; NMPA, China; SFDA, Saudi Arabia; TFDA, Chinese Taipei; TITCK, Turkey
- Industry:
  - BIO; Global Self-Care Federation; IGBA

ICH Products

- **75 Guidelines on Technical Requirements on:**
  - Quality - 26 Guidelines
  - Safety – 16 Guidelines
  - Efficacy – 22 Guidelines
  - Multidisciplinary - 11 Guidelines

- **Creation of the Common Technical Document (CTD) and Global Adoption of Electronic Submissions (eCTD)**
- **MedDRA: Medical Dictionary for Regulatory Activities**
  - Particularly used in the reporting of adverse events and clinical safety data.

MIDD Related ICH Guidelines

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

MIDD: Steps Towards Harmonized Guidance. *Clin Pharmacol Ther*. Vol. 114, 5 (2023) :954-959.

MIDD Multidisciplinary Guideline Proposal (2020)

Problem Statements

- **Despite the increasing use of MIDD, there remains a lack of common understanding regarding its appropriate use, both within and between regulatory agencies and the industry.**

- **The absence of standardized documentation, model validation/assessment frameworks, and a uniform understanding of key terminology has limited the broader adoption and application of MIDD approaches.**

  - **Consequently, this has led to an over-reliance on empirical methods, resulting in less efficient drug development strategies and study designs.**

M15 Expert Working Group (Nov 2022)
27 persons - 15 parties

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Many thanks to former M15 EWG members Mohammad Alharbi, Chieng-Lung Tu, and former M15 Discussion Group Members: Rubina Bose. Issam Zineh, Takayo Ueno, Ja-young Kim, Ming Zhao, Yaning Wang, Amit Roy, and Omar Almazroo.

Expected Values of ICH M15 MIDD Guideline

PERSPECTIVES

Model-Informed Drug Development: Steps Toward Harmonized Guidance

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Objectives of ICH M15 MIDD Guideline

- **Introduces a harmonized framework for assessing MIDD evidence to support decision-making,**
- **Provides high-level guidance on interactions between sponsors and regulators regarding planning, conduct, submission, and assessment of MIDD applications,**
- **Provides general recommendations on model evaluation expectations to ensure consistency and quality in MIDD applications,**
- **Creates common documentation standards.**

Defining a Harmonized Framework to Assess MIDD Evidence

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

Colleen Kuemmel[1,*], Yuching Yang[1], Xinyuan Zhang[1], Jeffry Florian[1], Hao Zhu[1], Million Tegenge[2], Shiew-Mei Huang[1], Yaning Wang[1], Tina Morrison[3] and Issam Zineh[1]

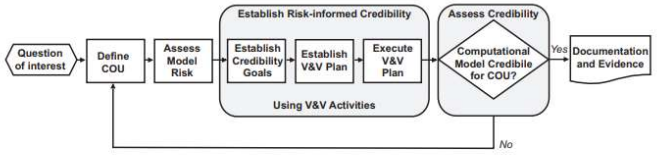
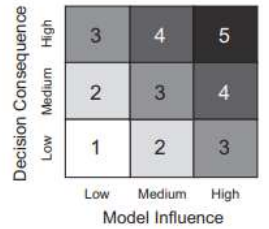


Figure 1 Overview of the ASME V&V 40 risk-informed credibility assessment framework. Modified from ASME V&V 40-2018, by permission of the ASME.[13] All rights reserved. ASME, American Society of Mechanical Engineers; COU, context of use; V&V, verification and validation.

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



Received: 8 February 2021 | Revised: 27 May 2021 | Accepted: 27 May 2021
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

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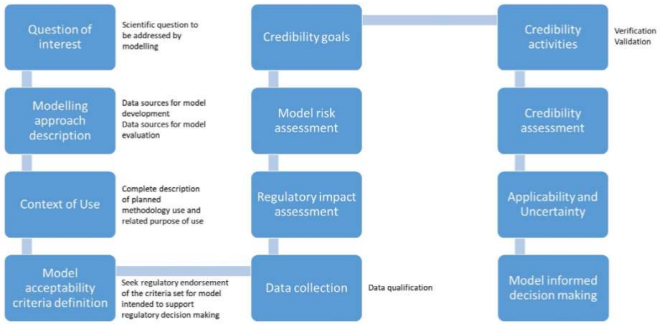
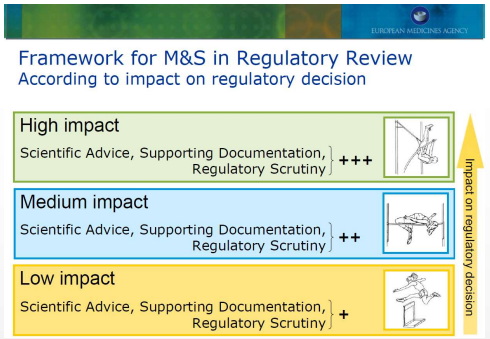
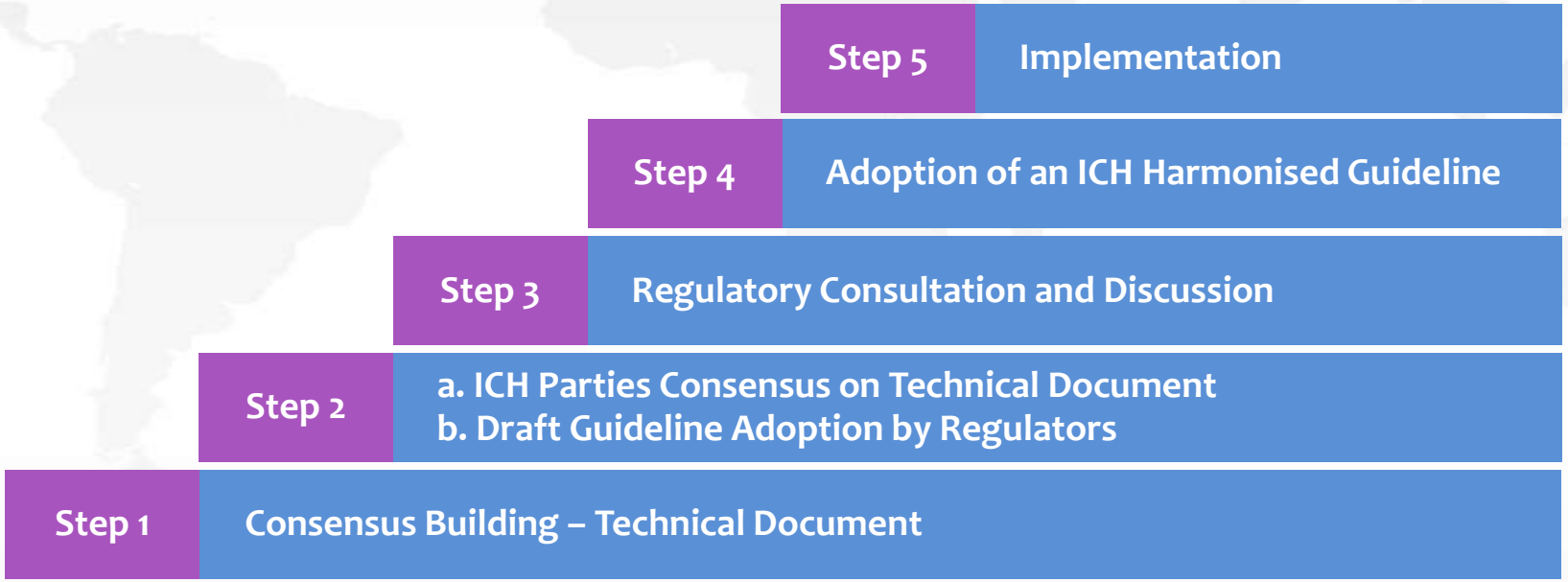


FIGURE 1 In silico Model Process flowchart



https://www.ema.europa.eu/en/documentspresentation/presentation-role-modelling-simulation-regulatory-decision-making-europe_en.pdf

Steps in the ICH Process



https://www.ich.org/page/formal-ich-procedure

ICH M15 Next Step

- Q4 2024 – Step 3 Regulatory Consulation and Discussion (Including Public Consultation)

- We are looking forward to your comments ☺

Backup

Considerations for Future MIDD Related Guidelines

ICH GUIDELINE /TOPIC	PRIORITY	CONSIDERATIONS
E4 Dose-response	High	Need 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)

ICH MIDD roadmap (ICH_MIDD_Roadmap_2022_0503.pdf)