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.

It is envisioned that the General Principles Guideline would cover the following topics:

- Outline general scope and principles with respect to MIDD, and provide 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;
- 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 (though specific procedural recommendations are out of scope).

Background to the Proposal

As background, MIDD can be viewed as an umbrella term that encompasses:

- Both separate and integrated application of QSP, PBPK, Empirical & semi-mechanistic PK & PK/PD, dose/exposure-response and disease progression approaches.
- Future approaches which combine these areas and/or integrate them with data driven learning approaches such as machine learning and artificial intelligence.
- Both separate and integrated analysis of subject and summary level data with the latter including Model based Meta-analysis (MBMA) approaches; and extend from experimental non clinical and clinical trial data to real world data.
- Application and integration of pharmacometric and statistical analyses in support of clinical trial design and quantitative decision making.

MIDD can help to conserve resources for industry, aid regulators in limiting human exposure and enhancing regulatory review, and potentially reduce time for approval and availability of new medicines globally as well informing their better use.

ICH has previously reviewed: an MIDD topic proposal (December 2017), the associated initial reflection paper (December 2018), revised reflection paper (June 2019) and updated topic proposal (December 2019). It has also reviewed a separate ICH E4 Guideline revision proposal (June 2019). The ICH Management Committee agreed (June 2020) to launch a MIDD discussion group. The objective for this group was to finalise the scope for the MIDD General Principles Guideline, position this proposal with respect to revision of ICH E4 Guideline, and develop a plan to cover integration with existing guidelines and potential future guidelines.

The MIDD discussion group, which formed in January 2020 with a 1-year term, has reached consensus that there is significant value in the MIDD General Principles Guideline as the first guideline in this sequence and should be developed prior to any update of ICH E4 Guideline or any new MIDD-related specific application or methodology guideline. The primary rationale

is that this MIDD general principles guideline would most efficiently enable greater and wider adoption of MIDD within drug development and regulatory decision making.

Type of Expert Working Group and Resources

The composition of the MIDD Expert Working Group is expected to be diverse and should include representatives with expertise in the areas of general clinical pharmacology and general pharmacometrics, and colleagues with particular expertise which spans the MIDD scope outlined above.

Timing

It is anticipated that this guideline will take 3 years for completion.

1) Considerations with respect to future MIDD related guidelines output from ICH Model-Informed Drug Development (MIDD) discussion group (DG ICH MIDD DG 2021) https://database.ich.org/sites/default/files/ICH_MIDD_Roadmap_2022_0503.pdf