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.

- Although MIDD has been defined in slightly different ways across industry groups, academia and regulatory agencies, the central concepts of these definitions include:
  i) Integrating data from multiple sources in the form of mathematical and statistical models based on the understanding of physiology, pharmacology, and disease processes;
  ii) Applying these models to inform drug development decision making and registration interactions, especially with respect to optimization of the design of future clinical studies, dose regimen optimisation and individualization.
- Many regulatory agencies expect to receive, and currently accept model-based analyses as part of dossier submissions. However, the level of integration of MIDD into regulatory decision making can vary between regulatory agencies, from application to application, and within agencies for similar submissions.
- The lack of common documentation standards, consistency in model assessment expectations and understanding of terminology hinders efficient assessment of model-based submissions, including quality of the data used, the robustness of the analysis, vis-à-vis the modelling impact and credibility with respect to its intended applications.
- 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 optimise designs, enhance the interpretation of subsequent confirmatory studies, and reduce reliance on traditional approaches to answering drug development questions.
- The topic proposal for the MIDD General Principles Guideline was approved by the ICH Assembly on the 17th to 18th of Nov 2021 (Press Release) and has been distributed to ICH parties. As a result of this approval, an informal Working Group (WG) will be formed in the June 2022 timeframe to finalize a Concept Paper and business plan which will be subsequently published on the ICH website. Per ICH procedures, the group will then transition into a formal Expert Working Group (EWG) to initiate development of the guideline. Development of the guideline is anticipated to require a 3-4 year timeline from initiation to completion of the guideline.

POTENTIAL VALUE OF OTHER MIDD RELATED GUIDELINES

The potential of additional value from **further MIDD related guidelines in addition** to the General Principles MIDD Guideline described above was aligned on with respect to two dimensions:

1. Provision of more specific guidance with respect to common MIDD approaches, including: Population PK (Pop PK), Exposure-Response (ER), PBPK, Quantitative Systems Pharmacology and Toxicology (QSP & T), Model Based Meta-Analysis (MBMA) and models characterising disease progression. It should be noted that the term "exposure-response" should be interpreted in its most general sense and is intended to represent characterizations of the relationship between measures of drug exposure (which could be based on dose or concentration) and response (which could be pharmacodynamic or clinical efficacy/safety responses).

   Recommendations include:

   - Further **specific technical details** on the planning, conduct, and assessment of MIDD work (including its credibility for its intended use) conducted using these approaches.

- Additional **specific reporting and documentation guidance** regarding data sources, analysis methods and assessment, and regulatory submission (including its credibility for its intended use).

2. Additional guidance with respect to the application of MIDD to specific technical questions that arise across research and development. For example:
    - Specifics with respect to the use of exposure-response to optimize dose finding/selection trial design, optimize dose/dose regimen selection and facilitation of extrapolation with respect to different regimens or routes of administration. This relates to considerations with respect to updates to ICH E4.
    - Specifics with respect to assessment of drug-drug interaction, ethnic sensitivity, and biopharmaceutical waivers for new formulation and formulation modifications. This relates to considerations with respect to updates to ICH M9, M12, E5, E17.
    - Greater specification with respect to use of approaches in the assessment of the impact of organ impairment including potential for interpolation and extrapolation in determining impact on PK, efficacy and safety.
    - Greater specification of situations where disease progression modelling could be of greater utility in enabling trial design, dose selection and extrapolation.

CONSIDERATIONS

The ICH MIDD DG aligned on this document as providing high-level **non-binding considerations** with respect to provision of further guidance for MIDD approaches and application, subsequent to the ICH MIDD General Principles Guideline reaching Step 2a ("ICH Parties consensus on Technical Document") in the ICH). At this point, the proposed scope from this technical document may highlight the need for this document to be refined or indeed for the additional guidance as outlined below to be formally proposed and considered by ICH. The ICH MIDD DG recommends that a review is conducted at that point in time.

Time frame & need for additional topic proposals

- Given regulatory resource limitations with respect to parallel development of guidelines and the evolving nature of MIDD the following considerations relate to development of ICH MIDD related guidance that would be subsequent to completion of the ICH MIDD General Principles guideline (3-4 years) and could be considered for development starting in approximately 3 years with the upper time bound of 10 years for completion**.**
- It is recognized that specific related appendices or Q&A supporting elements could be developed and released at the same time as part of the MIDD general principles guideline. However, new guidelines, revisions or updates of existing guidelines would require additional topic proposals to be endorsed by the ICH Assembly and prioritized by the ICH Management Committee. Accordingly, these considerations will depend on progress with the MIDD general principles guideline to Step 2a, the development of new topic proposals and ultimately ICH MC prioritization.

Scope of consideration

- The ICH MIDD discussion group has assessed the scientific and regulatory landscape related to existing ICH MIDD guidance and potential future ICH MIDD related guidance.

Potential options for additional guidance (See table 1)

- The following options were considered: Guideline revision, Annex (Q&A) to existing guidance or the proposed MIDD General Principles Guideline or the development of new standalone guidelines.
- Specific discussions with respect to approaches to update E4 guidance were held (See next section)
- Appendices to ICH MIDD general principles guideline should only cover "additional specific guidance" for more common MIDD approaches (e.g. popPK, ER, PBPK, QSP&T, PBBM, MBMA & Disease progression models) considered to fall under this guideline. This could include specifics with respect to technical aspects or reporting/documentation
- Specific applications of MIDD may be better covered in standalone guidance rather than added to existing guidelines. This is proposed as a consideration as it would allow domain science experts to participate in the development of a more general guidance

SPECIFIC CONSIDERATIONS WITH RESPECT TO REVISION OF ICH E4

There is a need for an updated E4 guideline (Dose Response Information to support Drug Registration) aimed at re-aligned practices and expectations from regulators and industry on the value and acceptability of methods and designs for DER characterization and the value of DER to support registration. In this respect, DER is considered critical for dose/regimen selection in the course of the development and final posology recommendations including also special populations. Furthermore, DER provides a scientific solid basis for (paediatric) extrapolation, DDI recommendations, personalized medicine, and characterization of relative effectiveness.
The following important aspects for DER should be considered during the ICH E4 GL revision:

- Study design optimization for dose finding trials (methodological aspects including adaptive/seamless designs, model informed adaptations, and Fisher Information Matrix based methods, etc.)
- Methods for characterizing the DER relationship (e.g., pharmacometrics, quantitative systems approaches (QSP & T), regression methods, Bayesian approaches, model based meta-analysis, etc.)
- Decision criteria for dose selection for the confirmatory trial Special Cases: small populations (paediatrics, rare/orphan diseases), Narrow Therapeutic Index (NTI) drugs, targeted biotherapeutics, Advanced Therapy Medicinal Products (ATMP) such as cell and gene therapies, etc.
- Labelling claims on the basis of DER
- A future E4 revision topic proposal should be prepared in collaboration with other stakeholders, such as clinical and biostatistical experts.

POTENTIAL PRIORITIES WITH RESPECT TO ADDITIONAL GUIDANCE (SEE TABLE 1)

- The following nonbinding priority order is proposed:
    - Given the importance of MIDD to many aspects of the ICH E4, this was prioritized to be the next guidance for update or replacement after the MIDD general principles guideline. While there is recognized dependency on the MIDD general principles guideline, the staggering of the development is mostly related to predetermined limitation with respect to regulatory resources.
    - It was agreed that additional guidance related to Pop PK, exposure-response, PBPK should be prioritized before MBMA and disease progression modelling. This was based on the general view that the first set of approaches are mature enough to be subject to additional harmonized regulatory recommendations if required post the development of the MIDD general principles guideline. It was recognized that guidance on use of MBMA would have significant overlap with other meta-analysis and evidence synthesis approaches and may require more general meta-analysis guidance to be proposed and developed. Similarly, it was recognized that further guidance related to disease progression modelling could be limited by ICH remit with respect to technical rather than disease specific guidelines.
    - QSP & T application in regulatory submission is an emerging area and further discussion is required before deciding how this should be placed within the priority ranking.
    - In terms of other existing guidelines which could have a linked or specific section related to MIDD e.g., E11A, E20, E14/S7B, E5, E17, the DG was aligned that this should occur on an opportunistic basis following the MIDD general principles guideline reaching Step 2a. The opportunity would be when the guideline was under revision or related Annex's were being revised or added. Given the wide range of possibilities, these opportunities are not covered in table 1.
    - The newly formed ICH MIDD EWG should look to consult with other EWGs developing MIDD related guidelines (e.g., E11A (Paediatric Extrapolation), M13 (Bioequivalence) & M12 (DDI)) to identify potential opportunities to provide corresponding or specific additional guidance.
    - New topic proposal in areas that could benefit from sections related to MIDD e.g., Biopharmaceutic assessment and Bio-waivers should be driven by proposals from the domain scientists but it is recommended that such proposals are aligned with emerging MIDD guidance and assessed by any established MIDD EWG. The potential application of PBPK in biopharmaceutical assessment or Physiologically Based Biopharmaceutical Modelling (PBBM) is covered in table 1.
    - Artificial Intelligence (AI)/deep learning), non-GCP data/qualification and validation (e.g., related to use of Real World Data) were highlighted as related topic areas of interest but are currently out of the core scope for the MIDD DG.
    - While the integration of different MIDD approaches to enable decision-making within "learning", "confirming" phases of development, as well as within regulatory submissions is often effectively utilized, it was not possible to identify the need for specific additional recommendations prior to development of the ICH MIDD general principles guideline.

CHALLENGES IN REACHING CONSENSUS ON OPTIONS AND PRIORITISATON

There was consensus that development of the future **MIDD General Principles Guideline is considered a key step** in the harmonisation of the practice and application of MIDD. Beyond the revision of ICH E4 guideline released in March 1994, it was challenging to determine the underlying need, options, and priority of further MIDD guidelines including updates to existing guidelines until the general principles guideline reaches Step 2a.

RECOMMENDATIONS

- The discussion on the document helped to emphasise that the MIDD general principles guideline is the essential next step for this field with respect to ICH. Specific needs beyond the MIDD general principles guideline and ICH E4 guideline were hard to determine without this important guideline having reached at least Step 2a key milestone in its development and harmonization.
- Therefore, it is recommended that this document be reconsidered after the MIDD general principles guideline has reached Step 2a in the ICH Process.

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TABLE 1 LIST OF EXISTING AND PROPOSED GUIDELINES

AND SPECIFIC CONSIDERATIONS AND NONBINDING RECCOMMENDATIONS

DG RANKING CATEGORIES	DEFINITION
HIGH	Next guideline: Earliest opportunity only limited by resource availability
MEDIUM	Priority dependent on further evaluation post Step 2a completion of the MIDD general principle guideline
LOW	No immediate priority post completion of MIDD general principle guideline.
UNKNOWN	Area is under significant development. Further evaluation post Step 2a completion of the MIDD general principle guideline. This may coincide with increased examples of application in regulatory submissions.

ICH GUIDELINE/TOPIC	DG RECOMMENDED RANKING/PROPOSED ORDER OF TOPICS	Considerations regarding development or update of guidance	Non-binding recommendations
E4 Dose-response	High	There is a need for an updated E4 guideline (Dose Response Information to support Drug Registration) aimed at re-aligned practices and expectations from regulators and industry on the value and acceptability of methods and designs for Dose-Exposure-Response (DER) characterization and the value of DER to support registration. In this respect DER is considered critical for dose/regimen selection in the course of the development and final posology recommendations including also special populations. Furthermore, DER provides a scientific solid basis for (paediatric) extrapolation, DDI recommendations, personalized medicine, and	Full revision suggested. A proposal should be prepared in collaboration with other stakeholders **The DG could reach a recommendation**

		characterization of relative effectiveness.	
Pop PK & ER	Medium	The DG considered that technical and documentation aspects of these approaches are adequately captured in current regional guidance. However, in order to promote utilization and acceptance of applications using these approaches globally additional specifics over and above the MIDD general principles guideline may be merited. Medium priority is assigned due to the range of regional guidelines currently available and incremental value from additional harmonized guideline at this time over and above the intended MIDD general principles guideline	Options considered: Approach specific guideline Annex to MIDD general principles guideline **The DG <u>reached a</u> recommendation on this being the best option**
PBPK	Medium	Further methodology focused guidance could be required in order to give more specifics with respect to both technical and documentation aspects associated with PBPK. An appendix to MIDD guideline could be possible. This could provide additional specifics with respect to verification & qualification of platform (system) and specific application, recommendations regarding provision of source for and biological plausibility of parameters. Recommendations with respect to presentation of	Options considered included a standalone application orientated guideline and /or an annex to M12 guideline under development or provision of additional technical guidance as an annex to the MIDD general principles guideline **The DG <u>could not</u> reach a recommendation at this time**

		assumptions and associated sensitivity analysis to drive confidence in the model. It could utilise existing regional guidelines (1,2,3) & workshop proceeding & Tutorials and good practices (4) EWG would require specific experts from PBPK community	
QSP&T	Unknown	Additional benefit from ICH guidance in this area is expected given the expected increase in global applications in support of regulatory decision making. A methodology focused guideline as an appendix to MIDD general principles guideline may be possible. A standalone guideline may be merited in order to more fully cover generic application types. There are no current regulatory guidelines but this was prioritized due to expected increase in applications containing QSP&T approaches and the increased complexity of this approach vs other MIDD approaches. Emerging good practices from recent regulatory (FDA, United States) (5) workshops and industry consortia whitepapers (6,7,8 etc)	Options considered: Methodology focused guideline Annex to MIDD guideline, or standalone guideline **The DG <u>could not</u> reach a recommendation at this time**
Disease progression modeling	Low	An increase in global applications including support for regulatory decision making is expected.	Options considered: Methodology focused guideline Annex to

		The MIDD general principle guideline should be able to capture generic aspects related to the important topic of disease progression modelling. Benefit of additional ICH guideline is considered limited by the ICH remit being related to technical guidelines only. However, additional technical and documentation aspects as an appendix to MIDD general principles guideline may be of value. However, a standalone guideline which would provide more scope to include design and application considerations may also be merited. Examples of disease progression qualification exist (9) and FDA, United States workshop Nov 2021 (10) There are limited good practice papers (11) and overlap with mechanistic ER models and QSP&T is recognized. Nonetheless, this is an area will many applications now and into the future.	MIDD guideline, or standalone guideline **The DG <u>could not</u> reach a recommendation but Annex to MIDD guideline may be more likely in the context of ICH**
MBMA	Low	The MIDD general principle guideline should be able to capture generic aspects related to use of Model based meta-analysis within MIDD. Additional methodological guidance here would likely relate to the wider general	Options considered: Methodology focused guideline Annex to MIDD guideline, or standalone guideline **The DG <u>could not</u> reach a recommendation at this time**

		meta-analysis methods and systematic review procedures. Therefore further guidance in this area would involve cross-functional engagement with statistical colleagues and evidence synthesis colleagues to see if this was required. National Institute of Clinical Excellence (NICE) and International Society of Pharmacoeconomics and Outcomes Research (ISPOR) have guidelines for evidence synthesis that are pertinent and there is overlap with HTA assessment approach standards	
PBBM modelling	Low	An application focused cross disciplinary guideline which cross references to other existing regulatory guidelines in quality, bioequivalence and IVIVr fields but also covers emerging use of PBPK It could cover: -Mechanistic in vivo in vitro relationship (IVIVr) -Virtual bioequivalence for waiving clinical trials -Bridge between formulations -Development of clinically relevant in vitro specifications	Options considered: Large addendum to M9 or as an application focused standalone guideline driven by rapid rise in regulatory submissions in this area. May cross reference to PBPK guidance **The DG could not reach a recommendation at this time**

References from table

1) European Medicines Agency Guideline on the reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation 1st July 2019

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3) MHLW/PMDA, Japan Guidelines for Analysis Reports Involving Physiologically based Pharmacokinetic Models December 21, 2020 https://www.pmda.go.jp/files/000240811.pdf

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5) Bai JPF etal FDA-Industry Scientific Exchange on assessing quantitative systems pharmacology models in clinical drug development: a meeting report, summary of challenges/gaps, and future perspective - PubMed (nih.gov) AAPS .J Apr 30;23(3):60**.** doi: 10.1208/s12248-021-00585-x

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7) Azer, K etal History and Future Perspectives on the Discipline of Quantitative Systems Pharmacology Modeling and Its Applications - PubMed (nih.gov) Front Physiol. 2021 Mar 25;12:637999. doi: 10.3389/fphys.2021.637999. eCollection 2021.

8) Bradshaw EL etal Applications of Quantitative Systems Pharmacology in Model-Informed Drug Discovery: Perspective on Impact and Opportunities - PubMed (nih.gov) CPT Pharmacometrics Syst Pharmacol

9) Qualification opinion of a novel data driven model of disease progression and trial evaluation in mild and moderate Alzheimer's disease EMA 2013 www.ema.europa.eu/en/documents/regulatory-procedural-guideline/qualification-opinion-novel-data-driven-model-disease-progression-trial-evaluation-mild-moderate_en.pdf

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Appendix: Members of ICH MIDD Discussion Group January 2021 to March 2022

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