Model-informed drug development in rare diseases

An introduction for medical writers

Natalie Brine, Claire Dyer, Kelly Smith
Certara
Oxford, UK

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Correspondence to:
Natalie Brine
natalie.brine@certara.com

Abstract

Model-informed drug development (MIDD) approaches maximise and connect information obtained on a drug during development, allowing better characterisation of its risk: benefit profile. MIDD is especially useful for rare diseases with few patients to study. Children represent more than half of patients affected by rare diseases, most of which are genetic. In recent years, submissions for rare diseases have come to rely on modelling and simulation, and regulators now expect their inclusion in dossiers. All types of regulatory documents are impacted by MIDD, from protocols to product labels. The ability to translate complicated scientific information into comprehensive text is particularly vital in MIDD due to its complex nomenclature and multifaceted data outputs.

Model-informed drug development (MIDD) is defined as the strategic use of computational modelling and simulation methods that integrate non-clinical and clinical data, prior information, and knowledge (e.g., drug and disease characteristics) to generate evidence to guide decision making during drug development and regulatory evaluation.[1] MIDD approaches provide a quantitative framework to maximise and connect all the information obtained on a drug during development, enabling extrapolation of that data to unstudied situations and populations.

By building models of drug concentrations and/or drug responses over a time course (pharmacokinetics [PK]), we can understand how the amount, frequency, and duration of dose affect drug concentration and demonstrate the relationship between the drug concentration and pharmacodynamic (PD) responses. These models also help to characterise the PK/PD variability of drugs and the clinically relevant factors contributing to variability. Ultimately, MIDD aims to expedite drug development, enhance regulatory science, and produce benefits for patients.[2] While MIDD can be applied to all therapeutic areas, rare diseases have a greater need for MIDD because of the smaller number of patients available for study.

> The requirement for experienced medical writers to support regulatory and medical communications in rare disease will grow in the future.

MIDD in drug development and assessment

MIDD is not new, with MIDD first contextualised by the International Council for Harmonisation (ICH) in Guideline E4.[3] In the 1990s, it was largely used experimentally to support drug development programmes, but was not pivotal to decision making. However, it is now at the cornerstone of 21st century pharmacological research,[4] with the use of "Population PK", "PK/PD" and "Exposure-Response" embedded in drug development and a critical part of many international regulatory guidance documents and frameworks.[5]

Global regulatory agencies, such as the EMA and the US FDA , recognise the value MIDD provides during drug development and assessment and have been collaborating with the ICH and focused working parties to develop a harmonised guidance to optimise its use. The new overarching ICH M15 "General Principles for Model-Informed Drug Development (MIDD)" has very recently been endorsed by the ICH assembly for public consultation.[1] This guideline aims to facilitate greater and wider adoption of MIDD principles in drug development and regulatory decision making across the major ICH regions (Europe, Japan, and the US), and among the standing worldwide regulatory and industry members, as well as ICH observers (e.g., the WHO).

During the past decade, the EMA has published papers on MIDD, drafted guidelines that discuss modelling and simulation approaches, created a working party, and hosted MIDD-centric workshops that promote the use of MIDD in dose-finding. The EMA has produced guidance documents on the use of MIDD approaches in: paediatric drug development, which has significant overlap with the rare disease space (approximately 50% to 70% of rare diseases affecting children[6] are genetic in nature); drug-drug interaction risk assessment; renal and hepatic impairment; obesity; and pharmacogenetics.

The FDA has incorporated MIDD into regulatory guidance and review processes, with the MIDD Paired Meeting Programme as part of the Prescription Drug User Fee Act (PDUFA) VII commitment. Designed to promote early interactions between drug developers and the FDA on the use of modelling approaches to support a drug's development, the MIDD Paired Meeting Programme will undoubtably further facilitate and increase the use of MIDD in rare disease research.[7]

In recent years and particularly since 2021, submissions for rare diseases have come to rely heavily on the modelling and simulation provided as part of MIDD. While it used to be a supplemental part of the dossier, regulators now expect the inclusion of modelling in the dossier.

The importance of MIDD in rare disease

High costs and long timelines due to limited patient populations and the lack of validated endpoints are associated with rare disease drug development, along with a multitude of other unique challenges for clinical trial design and completion. Rare diseases represent a significant unmet medical need. While 7,000 to 10,000 rare

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diseases affecting over 350 million people worldwide[8] have been identified and described, it is estimated that only around 5% of rare diseases have an FDA-approved drug.[9] The majority (~80%) of rare diseases are genetic,[10–12] with children representing more than half of all patients affected by rare diseases. Staggeringly, approximately 30% of children with these debilitating diseases will not live to their fifth birthday.[8] Traditionally, treatment strategies for genetic disorders were not generally aimed at targeting the underlying genetic mutation, but were designed to treat or manage the associated signs and symptoms of the disease. However, today, disease-modifying drugs, such as nucleic acid-based therapies, are now under development.

From a medical writing perspective, there has been a significant increase in publications pertaining to rare or orphan diseases in the last two decades – from less than 2,000 in 1996 to around 6,000 in 2012 to 2014.[13] Furthermore, in 2023, 28 of 55 (51%) of FDA novel drug approvals received orphan drug designation

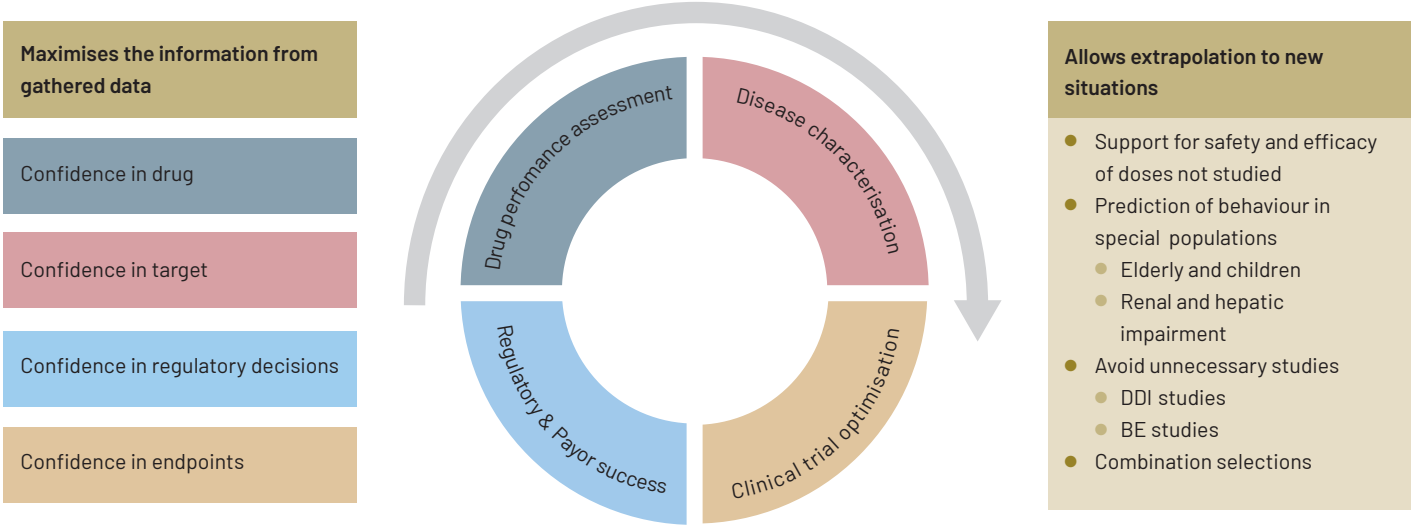

Figure 1. Why is MIDD so powerful?

Abbreviations: BE, bioequivalence; DDI, drug-drug interaction; MIDD, model-informed drug development.

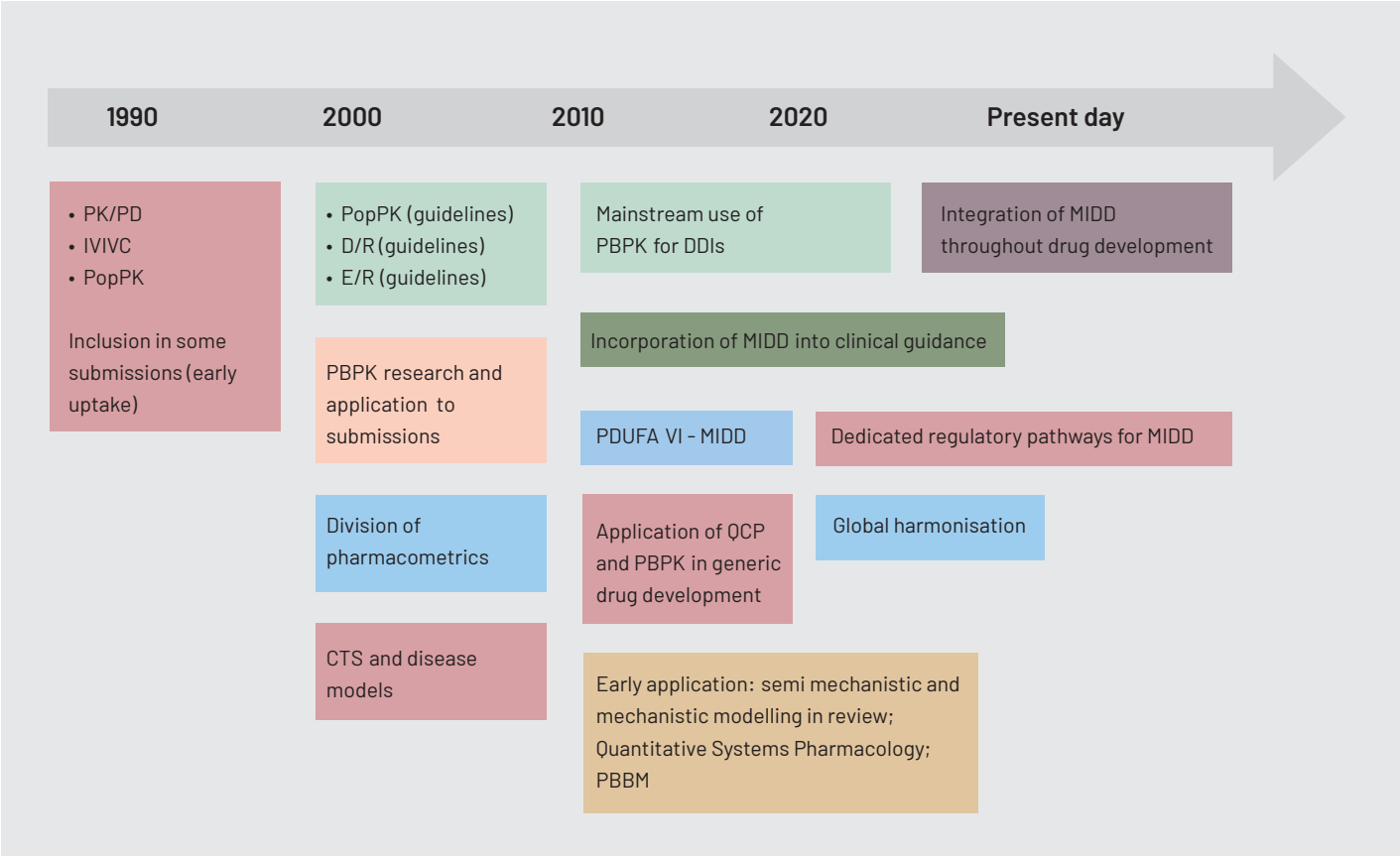

Figure 2. Evolution of MIDD

Abbreviations: CTS, clinical trial simulations; DDI, drug-drug interaction; D/R, dose-response; E/R, exposure-response; IVIVC, in vitro-in vivo correlation; MIDD, model-informed drug development; PBBM, physiologically based biopharmaceutics models; PBPK, physiologically based pharmacokinetics; PDUFA, Prescription Drug User Fee Act; PK/PD, pharmacokinetics/pharmacodynamics; PopPK, population pharmacokinetics; QCP, quantitative clinical pharmacology.

because they target rare diseases.[14] Among the 77 medicines recommended for marketing authorisation by the EMA in 2023, 17 (22%) had a confirmed orphan drug designation.[15] The number of known rare diseases is also increasing, with five new rare diseases described in the literature each month.[8] Therefore, the requirement for experienced medical writers to support regulatory and medical communications in rare disease will grow in the future.

With an inherently small pool of people with a specific rare disease, few patients enrol in clinical trials. Often, it is not possible to run more than one pivotal phase 3 study, and that is usually of a small sample size. There are frequently insufficient data in the early phase studies to inform dose selection for later phase studies, and dose optimisation studies can be unfeasible.[16] Furthermore, the availability of natural disease history data and real-world data is often limited in rare diseases. Both play important roles in defining patient populations, characterising disease progression, and establishing novel biomarkers and clinical endpoints.[17] Maximising the use of all available data about a new product is thus paramount in rare disease drug development, and brings opportunities for MIDD.[18] MIDD approaches allow the integration of all available data, including preclinical studies, controlled clinical trial data, observational data, and aggregated literature data, thereby providing a totality of evidence to enable a more robust characterisation of the risk:benefit profile of the drug.

> Maximising the use of all available data about a new product is paramount in rare disease drug development.

Additional data sources, such as patients' electronic health records, genetic data, and patient registry information, can be leveraged in MIDD to further our understanding of the rare disease and the investigational treatment.[16,19] More importantly, the models allow prediction of responses and inform efficient clinical trial design in diseases with scarce patients.

What does MIDD mean for medical writers?

Development of new drugs for rare diseases is one of the pivotal areas in which quantitative modelling is used extensively. The challenge of generating adequate evidence under conditions of limited information content, such as in rare diseases, has gained visibility over the past two decades. Modelling and simulation are used in all phases of drug development in regions across the world and have historically been used most frequently to support the clinical pharmacology files and labelling for new drug applications. With the expectation of inclusion of modelling in the files from regulators to allow for scrutiny of all available data, marketing applications in the EU and US are rarely submitted without modelling being used to describe the PK of a new medicine, especially in settings in which there is a paucity of clinical data.

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Currently, medical writers are most likely to come across population pharmacokinetic (PopPK) and pharmacodynamic models, which are the most prominent class of pharmacometric models used in clinical drug development. Familiarity with the documents and outputs associated with this type of modelling, such as PopPK and exposure-response/exposure-safety (ER-ES) analysis reports and plans, is integral for working on rare disease submissions. It is highly likely that medical writers will encounter additional models and associated documents in the near future, so it's important to keep abreast of this rapidly evolving topic.

MIDD is a highly collaborative process, involving not only statisticians and pharmacometricians, but multidisciplinary teams. The role of regulatory medical writers cannot be underestimated given the importance of communicating the results of often complex modelling and simulation exercises to decision-makers and upper management in the pharmaceutical industry, as well as to multidisciplinary review teams within regulatory agencies.[2] MIDD impacts all types of documents that a medical writer may encounter, from protocols to clinical study reports and summary documents, and ultimately product labels.

The role of regulatory medical writers cannot be underestimated given the importance of communicating results of often complex modelling and simulation exercises to decision-makers and upper management.

In addition, the recent draft ICH M15 Guideline[1] refers to modelling analysis plans and reports, as well as MIDD assessment tables, for communication within and between drug developers and regulatory authorities.

Regulatory medical writing requires a style of writing that translates complex medical and scientific information into comprehensive, yet concise and consistent, text. This skill is particularly vital in MIDD, with its complex nomenclature and multifaceted data outputs. Often medical writers with a specific background or interest in PK are the only ones considered for writing the components of the submission involving the explanation of the MIDD and presentation of modelling and simulation data. Especially in light of the increased visibility and emphasis of modelling and simulation in all submissions, challenging yourself and gaining expertise in writing for MIDD could be an area of growth and learning for many regulatory writers, and an important skill set for companies to build within their medical writing groups.

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The opinions expressed in this article are the authors' own and not necessarily shared by their employer or EMWA.

Disclosures and conflicts of interest

All authors are full-time employees of Certara.

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Author information

Natalie Brine, PhD, **Claire Dyer**, PhD, and **Kelly Smith**, PhD, are Directors of Global Submissions at Certara with experience in clinical and non-clinical regulatory documents and submission leadership. They have over 60 years of cumulative experience within a range of therapeutic areas and across submissions for various regions