



**Regulatory
Writing**

**Model-informed
Drug Development**

Integrating Regulatory Writing and Modeling and Simulation into the Drug Development Process

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The use of model-informed drug development to bridge traditional studies with robust modeling that integrates prior knowledge has led to improved predictions, rationale, and justification for formulation, dosing, and study design decisions.

As the adoption of modeling and simulation for drug development expands, so too does the need to integrate it into the documentation submitted to regulatory agencies. Model-informed drug development (MIDD) includes physiologically-based pharmacokinetic (PBPK) and pharmacokinetic/pharmacodynamic modeling. This methodology is emerging as not just an internal decision-making aid to reduce expenses and time, but also as an ethical imperative to optimize the number of subjects exposed to newly tested therapies.

The use of MIDD to bridge traditional studies with robust modeling that integrates prior knowledge has led to improved predictions, rationale, and justification for formulation, dosing, and study design decisions. There are also recent examples of regulatory agencies accepting it in place of clinical trials for some drug-drug interactions¹ and thorough QT studies,² thus reducing the number of subjects exposed to investigational treatments. Indeed, using MIDD to avoid performing a clinical study can easily save six months to a year and \$500K to \$1M. There is growing confidence among health authorities that MIDD strengthens traditional approaches by enabling more comprehensive evaluation, minimizing the need for certain studies and, ultimately, lower risks to patients. This trend has been confirmed through numerous regulatory guidance documents³ and publications.⁴

Programs such as the FDA's Critical Path Initiatives are increasing pharmaceutical innovation and speed-to-market.⁵ For example, almost half of the recently approved New Molecular Entities (NMEs) that used PBPK in lieu of clinical studies participated in FDA's breakthrough, fast track, accelerated and/or priority review programs.⁶ These programs by definition involve more frequent sponsor-regulator meetings, requiring the sponsor to crisply articulate the scientific rationale behind the request for accelerated approval.

Presenting a sponsor's drug program in the best possible light to regulatory authorities has long been the standard for strategic regulatory writing. Successful use of MIDD requires crafting regulatory documents that clearly and powerfully present the models and their results to health authorities in order to obtain their buy-in. As the science of MIDD is still relatively new, sponsors must instill confidence in the discipline and allow the health authorities to validate the results with traditional data.

There are significant challenges in communicating the value of MIDD to communities outside the field of mathematics and engineering.⁷ While predictive modeling adds a tremendous value from discovery through pre-clinical development, communication with regulatory agencies really begins with the decision to go into the clinic. The best strategy for leveraging modeling and simulation should be communicated starting with the pre-IND meeting request. For instance, the request could propose using PBPK models to aid dose selection for first-time-in-man studies. By using modeling and simulation to increase predictability, sponsors will reduce the overall study burden and potentially decrease the number of subjects needed to achieve study objectives.

Model-informed Drug Development

- Translational medicine
- Dosing and dose regimens
- Bridging studies – age, race, gender, special populations
- Pediatrics, geriatrics
- QT prolongation
- Comparative effectiveness

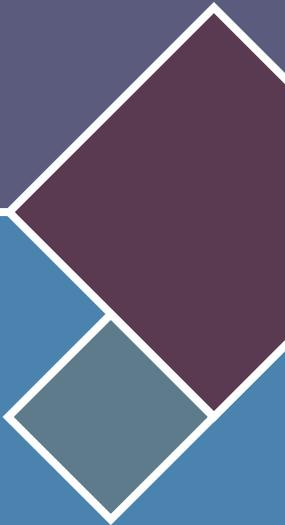
Regulatory Communications

- Clinical pharmacology roadmap
- Use of MIDD for decision-support
- Label optimization
- Dose justification
- Drug-drug and drug-food interactions
- Regulatory agency meetings

Justifying an MIDD approach to the agency is both an art and a science. It starts with asking the right questions, creating the justification based on pre-clinical data and the strength of the model, and ends with getting health authority approval. In addition, successfully employing MIDD requires addressing specific challenges in each therapeutic area while satisfying the sponsor's overall business objectives and constraints. Meeting these challenges requires strategic regulatory writing, a thorough understanding of modeling and simulation, as well as traditional clinical operations, and an understanding of the global health authorities' positions. The first step is to develop pre-IND or CTA meeting questions and briefing packages that describe a path forward that benefits all stakeholders. Realizing the value of integrated MIDD and regulatory writing requires the right group of people who can deliver this vision. Certara's scientific and regulatory writing consultancy, Synchrogenix, has successfully helped dozens of clients obtain drug approvals using this approach. Having technology-enabled pharmacometricians and strategic medical writers as part of a sponsor's team will improve their chances of success. By harnessing the power of MIDD and superior regulatory writing, Certara is reshaping the pharmaceutical industry's approach to drug development.

References

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About Certara

Certara is a leading provider of decision support technology and consulting services for optimizing drug development and improving health outcomes. Certara's solutions, which span the drug development and patient care lifecycle, help increase the probability of regulatory and commercial success by using the most scientifically advanced modeling and simulation technologies and regulatory strategies. Its clients include hundreds of global biopharmaceutical companies, leading academic institutions and key regulatory agencies.

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