CERTARA

Best Practices in Drug Development Modeling and Simulation

Edmundo Muniz

# Best Practices in Pharmacological Modeling and Simulation

The use of modeling and simulation (M&S) in drug development has evolved from being a research nicety to a regulatory necessity. Today, modeling and simulation is leveraged to some extent, across most development programs to understand and optimize key decisions related to safety, efficacy, dosing, special populations, and others. Further, the use of M&S as a percentage of an entire drug development program is growing, as the advances in both computing power and our understanding of biological sciences increases, thus propelling both the need and value of the technology.

This paper provides a compilation of best practices to systematically leverage the many benefits of M&S across a drug development program.

The regulators are using an M&S quantitative toolbox—so should you

More than 90 percent of all 2015 drug approvals leveraged one or more technologies in the M&S toolbox. These methods were used by companies to inform key drug development decisions, and by regulators as a key component of clinical pharmacology and medical reviews. For companies, these tools support dose justification for general populations, specific covariates, and special populations; amplify efficacy trends; explain rare toxicities; and provide comparative efficacy information. From the regulators seat, these tools provide key answers to development gap questions, allow for a better understanding of risk: benefit, identify issues for further characterization (including the potential minimization of post-marketing requirements), and inform the drug label.

These methods in the quantitative M&S toolbox support critical decisions made in drug development and regulatory approval. Leveraging these tools allows for a better understanding of benefit:risk and helps fill development gaps.
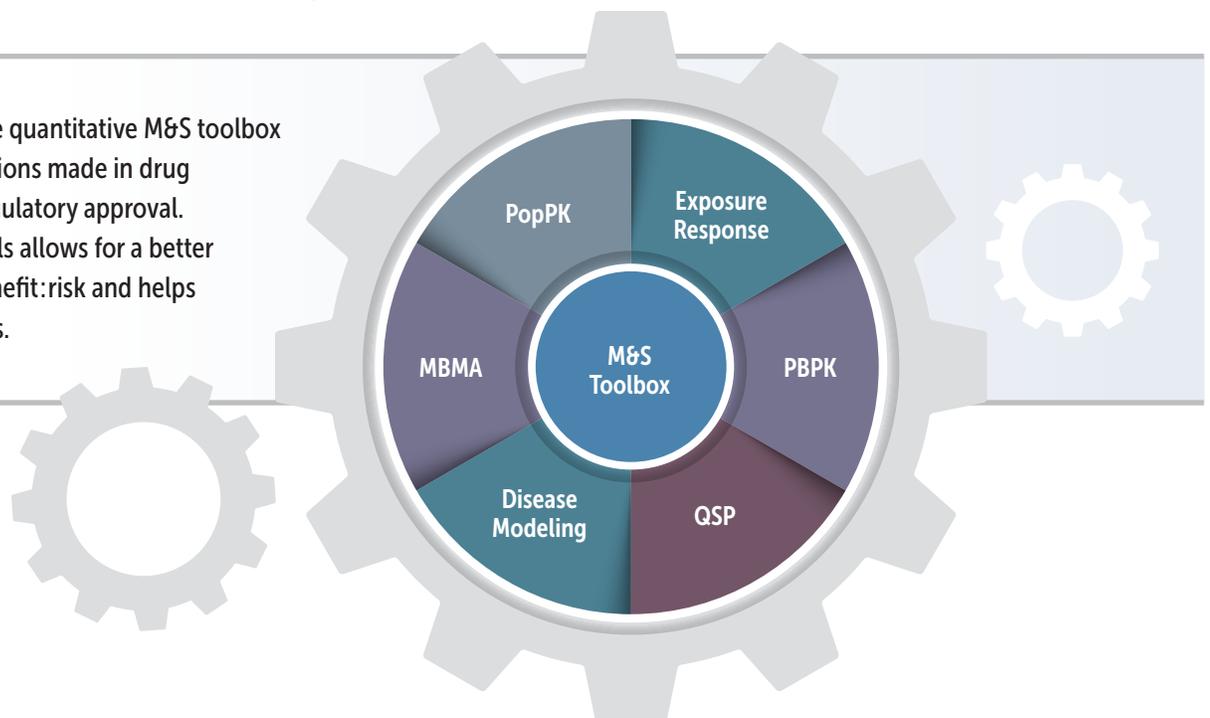
Best Practice #1:
Go beyond the chemical entity to unlock the full therapeutic value

As shared in Jonathan Kimmelman and Alex John London's paper, "The Structure of Clinical Translations,"[1] drug substances—the chemical or biological entities themselves—are not therapeutic agents. They're merely the "hardware." And much like a computer by itself without software or information populated by those using the computer, a drug by itself has limited value.

Therapeutic agents arise from the totality of three elements. The first one is obviously the chemical and/or biological entity. The second element is the practices surrounding that entity. These include the drug dose, schedules of administration, and associated clinical tests. The third element is the constraints on prescribing practices—special populations, co-morbidities, contraindications. How do we move from thinking that a therapeutic is a chemical entity to the notion that therapeutic agents are a multiplicity of information surrounding that chemical entity?

The chemical entity is the most visible element of a therapeutic intervention.[2] Yet, what is ultimately validated and what the drug label reflects is not only the substance, but a set of coordinated building blocks which allow drug development organizations to unlock the clinical value of that substance. The value of modeling and simulation is to increase the reliability and predictability of this information, to improve R&D productivity, impact clarity of the drug label and better translate the value of the chemical entity into therapeutic innovation.

Best Practice #2:
Use M&S to resolve the tension between R&D exploration and confirmation

Exploration
How much?
How long?
How predictably?

Confirmation
How much?
How long?
How reliably?

The work of drug development has an epistemic—"knowledge-related"—division of labor. Some of us explore; some of us confirm. Trying to balance exploration and confirmation causes either epistemic errors or excessive costs.[3]

A common question in drug development is: how much, for how long, and how predictably do we explore this chemical entity that we want to get approved in an indication? On the other hand, product teams, drug development teams and senior management ask the question: how much do we confirm, for how long, and how reliably can we do that?

This division of labor was created to try to optimize drug development. But in reality, the exploration-confirmation dichotomy is an abstraction. You don't start exploring drug development and then finish with 100 percent confidence that your hypothesis is ready for confirmation. Likewise, you can't perform a clinical trial that absolutely confirms your research hypothesis.

The cost, speed, predictability, and reliability of drug development are casualties of this tension. Commonly, we explore too much and lose valuable time related to the drug's intellectual property. Then, when we move to confirmation, the value of the drug has declined significantly. Likewise, when moving from pre-clinical to Phase 2 trials, and most notably, from open-label Phase 2 trials to Phase 3 pivotal trials, exploration often has not been consummated. So, coupling information and knowledge using modeling and simulation will mitigate relief and inform the resolution of that tension.

Best Practice #3:
Institute systematic and broad adoption of modeling and simulation across the drug development cycle
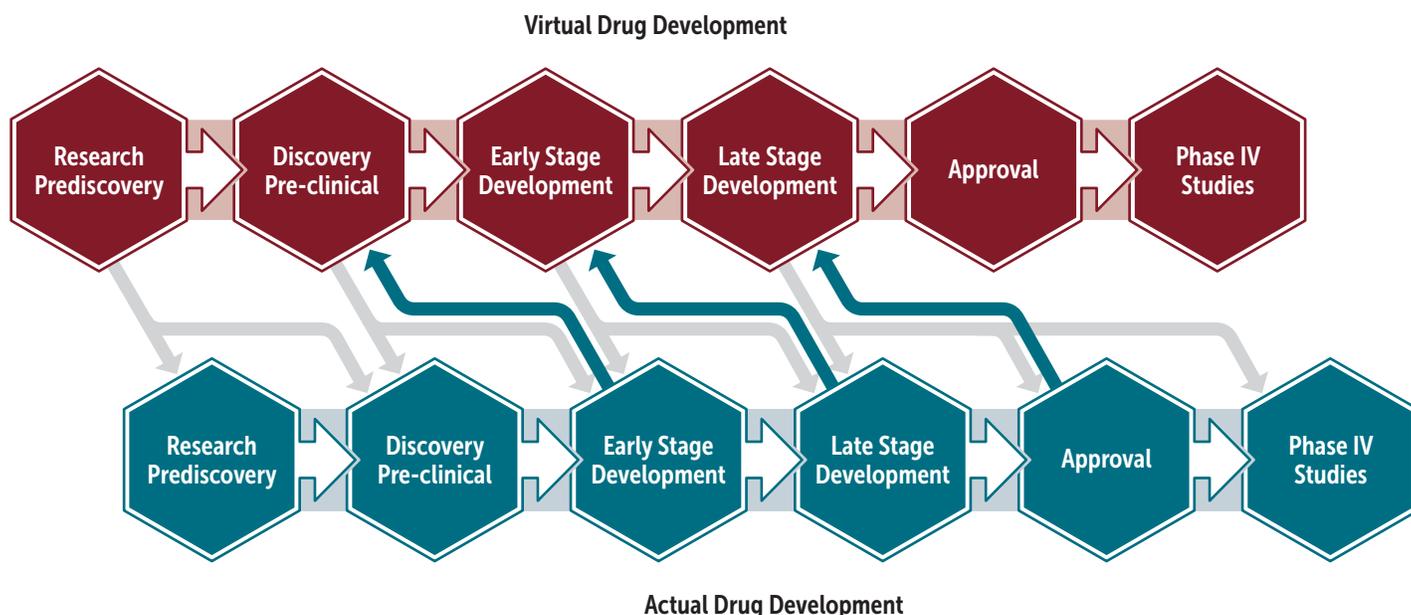
Today, we have access to significant computer processing power and sophisticated technology platforms. These technological advances support treating drug development as a circular process as opposed to the linear paradigm of drug development. Modeling and simulation can link one phase of development to a phase that was implemented traditionally much later in the process. Using M&S relieves the *in vivo* constraints of sequentially answering core questions.

So, you could use post-marketing data to inform discovery and pre-clinical decisions. You can also use *in vitro* data to enhance the label of an already-approved drug. And, you can use *in silico* technology to help make *in vivo* development faster, better, and cheaper. In some cases, *in silico* modeling is the only path to answer questions regarding "untestable" patient populations, such as pregnant women, pediatrics, and patients with organ impairment.

Modeling and simulation should be a prerequisite of any and every human *in vivo* study. Due to its ability to increase the reliability and predictability of drug development, modeling and simulation has become an instrumental asset in our armamentarium. M&S also supports practical decision-making. Companies use this tool to articulate their decision-making process to regulatory agencies and internal constituencies.
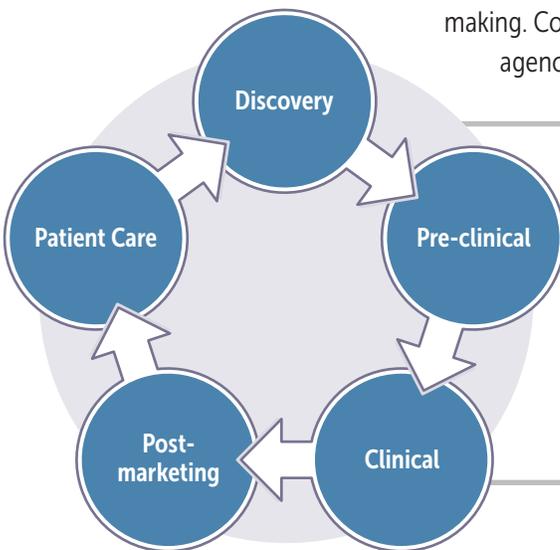
Drug development is often depicted as being linear, but we must abandon that thinking. In reality, the information flow is circular. For example, you can perform modeling and simulation of patient data when you are looking at a discovery model, or you can use post-marketing data to build new clinical models. In short, employing modeling and simulation will mitigate, relieve, and resolve the exploration-confirmation tension by providing a common language from our quantitative toolbox.

Virtual Drug Development

| Research Prediscovery | Discovery Pre-clinical | Early Stage Development | Late Stage Development | Approval | Phase IV Studies |

Actual Drug Development

We recommend building parallel, but connected, *in vivo* and *in silico* development paths. The virtual drug development program is always ahead in each "time zone" to the *in vivo* drug development program. This paradigm confers a self-learning process that guides *in vivo* drug development. Thus, the clinical program gains the ability to move faster, more predictably, and more reliably.

Best Practice #4:
Create a pan-R&D integration repository of data analytics, models, and workflow

The amount of data and the ability to generate data of every type has increased exponentially. Thus, resolving how to capture data and transform it into practical insights is a key practice of drug development.
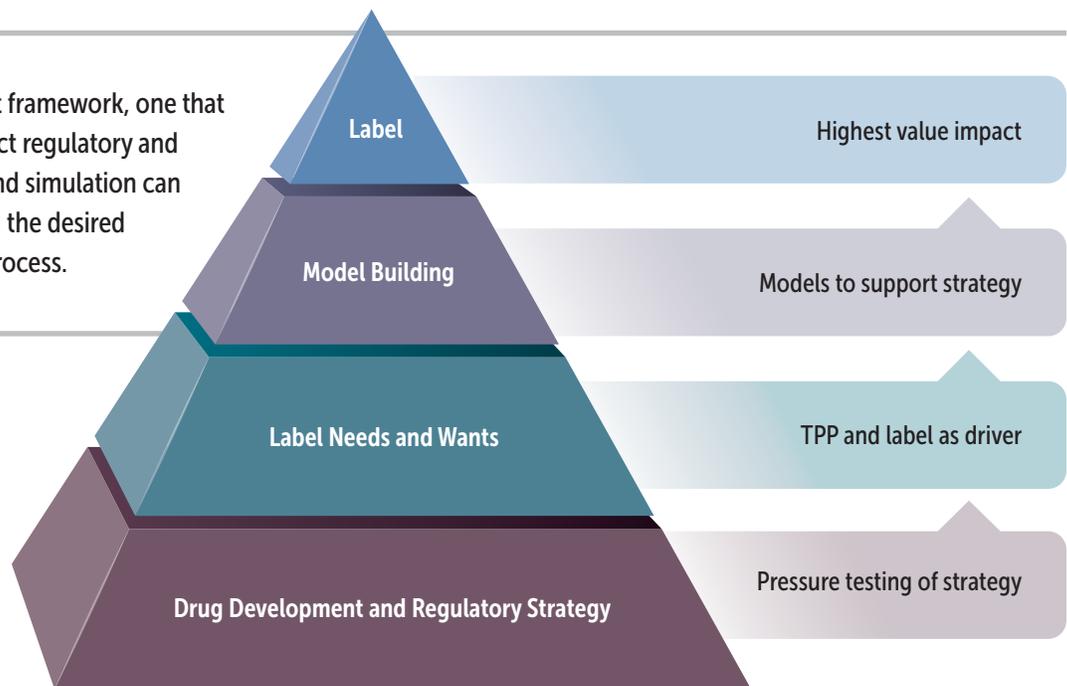
Creating a pan-R&D integration of data and workflow allows sponsors to retain information from previous phases of development, families of compounds, and trials and put it to work on new innovations. By leveraging this type of platform, development teams can take the data, information and learnings from the previous stages of development, families of compounds, trials and real-world evidence to be used at the moment where they are assessing a clinical decision. As a consequence, data is transformed into actionable information and knowledge.

Best Practice #5:
Seamlessly integrate drug development with modeling and simulation strategies

High- and low-performing teams are differentiated by their ability to integrate M&S, data analytics, and drug development R&D into regulatory strategies. Teams that remain isolated from the big picture of the strategy, or that place too much emphasis on only the details while ignoring data and predictive analytics, can make significant mistakes. In short, the most valuable applications of M&S are in the context of a pressure-tested drug development and regulatory strategy. By the same token, a strong drug development and regulatory strategy is suboptimal unless M&S informs its core decisions.

Within the right drug development framework, one that is focused on label goals that reflect regulatory and commercial priorities, modeling and simulation can inform the gaps that exist between the desired label and the drug development process.

Label	Highest value impact
Model Building	Models to support strategy
Label Needs and Wants	TPP and label as driver
Drug Development and Regulatory Strategy	Pressure testing of strategy

Communication is also critical to the drug development process. There are two essential types of communication: internal communication of the product teams and decision makers and communication of the results to regulatory agencies. High-performance teams will pressure test the drug development and regulatory strategy to establish the target profile of the label and its key drivers. Next, they lay the framework for a target product profile and label that reflects the priorities of the drug development and regulatory strategy. Finally, they identify the opportunities where M&S can bridge the gap between the desired label and the drug development process.

How do you strike the right balance for the label in terms of serving your patient population and meeting your commercial goals? Without the context of a sound drug development strategy, even quantitative experts are hamstrung. Similarly, without the enabling power of M&S, even otherwise well-planned drug development and regulatory strategies are incomplete.

Best Practice #6:
Create the right blend of *in vivo* and *in silico* R&D

The goals of a drug label can be achieved using *in silico* development, *in vivo* development, and by combining both approaches. The strategy for *in vivo* and *in silico* research tracks will determine the balance of *in vivo* decision making and *in silico* trials. The right blend of *in vivo* and *in silico* R&D always impacts speed, value, and quality.

While PopPK and exposure-response *in silico* methods have been leveraged in drug development for the past decade or so, the impact of physiologically-based pharmacokinetic (PBPK) models is now increasing exponentially. In certain cases, the regulators have accepted the results of these models in lieu of requiring a sponsor to conduct a clinical study. PBPK has influenced not only drug approvals, but the writing of labels, thus shaping target product profiles.

In fact, in the past two years, 100 label claims have been informed by PBPK. These label claims support predictions regarding drug-drug interactions (DDIs), drug absorption, ethnic bridging, and drug formulations. PBPK has also supported label claims for many therapeutic areas including oncology, pulmonary disease, infectious disease, and central nervous system diseases.

As shown in this regulatory document, M&S is a key lever used in NDA and BLA regulatory review. Optimizing the *in vivo* and *in silico* blend will not only increase speed and decrease cost, but is a valuable currency to demonstrate well-rounded decision-making processes to the regulators.

2.2.4.1   What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for *efficacy*? If relevant, indicate the time to the onset and offset of the desirable pharmacological response or clinical endpoint.

2.2.4.2   What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for *safety*? If relevant, indicate the time to the onset and offset of the desirable pharmacological response or clinical endpoint.

2.2.4.3   Does this drug prolong the QT or QTc interval? *(You must answer this question, unless this is addressed in the question above.)*

2.2.4.4   Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues? *(In some cases, it may be possible to combine this with 2.2.4.2 and 2.2.4.3.)*

2.3.1   What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

2.3.2   Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations (examples shown below), what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

Best Practice #7
Educate to influence

Successful drug development teams use modeling and simulation to inform key drug development decisions, including: go/no go choices; selecting first-in-human, final dose and dosing regimens; designing safer, more efficient trials; identifying drug-drug interactions and determining comparative efficacy. There are a number of important constituencies involved in developing a drug and making these pivotal decisions, many of whom do not understand the tremendous value and proof points of modeling and simulation. Decision makers in biopharm companies may include scientific, commercial, finance, contracts, procurement, and IT teams. Likewise, modeling and simulation teams can influence important external groups such as key opinion leaders (KOLs), regulatory agencies, payers, and healthcare professionals. Through education, and a shared language around the concepts of decision support, these teams can influence the productivity of drug development.

The revolution has arrived—modeling and simulation delivers unquestionable value

Our job as drug developers is moving to decision optimization. In this probability game, those possessing enablers of decision optimization will win. Science and technology help transform data into information, information into knowledge, and knowledge into wisdom. The wiser teams will win, and drug development and patient care will be transformed. Not in the distant future. This trend is happening now and is rapidly moving to patient care.

Further reading

Jonathan Kimmelman and Alex John London conceived of the notions of a drug as hardware vs. a multiplicity of information as well as the concept of the exploration-confirmation tension in drug development. You can read more about their ideas in the 2015 Hastings Center Report, "The Structure of Clinical Translation: Efficiency, Information, and Ethics." (1, 2, 3)

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.

For more information visit www.certara.com or email sales@certara.com.