CERTARA

Key Decisions Informed:

Trial Design

Go/No Go Decisions

Regulatory Strategy

Special Populations

Drug Safety Profile

Label Optimization

Dosing Regimens

Cardiac Safety

Comparative Effectiveness

Treatment Approach

Drug-drug Interactions

Portfolio Management

Bridging Studies

Formulation

Pediatric Dosing

The Benefits of Modeling and Simulation in Drug Development

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Modeling and simulation (M&S), also known as model-informed drug discovery and development, has already had a profound impact on drug development, yet its full impact is just now coming to light.

M&S has the ability to influence every phase of the drug development process, including the commercial decisions around the benefits of even bringing a specific drug to market. One of the most important elements of M&S is that it allows carry-over of knowledge and wisdom from one phase to the next, and from one indication to the next, both in terms of successes and failures. M&S transforms data into information and information into knowledge.

Welcome to the M&S Revolution

Acknowledging the increasingly high costs and inefficiencies in the drug development process, the US Food and Drug Administration (FDA) launched the Critical Path Initiative (CPI) in 2004 to drive innovation in the scientific processes through which medical products are developed, evaluated, and manufactured. Specifically, the CPI called for an aggressive and collaborative effort to create a new generation of predictive tools, such as M&S, for informing crucial drug development decisions. Issues that the FDA wanted to address included first-in-human (FIH) dosing, better understanding of safety and efficacy, linking biomarkers to outcomes, optimizing trial design, and addressing special populations such as pediatrics.

M&S integrates two transformative technologies: computer-aided mathematical simulation and biological sciences. It uses pre-clinical and clinical data, along with published industry data to elucidate the relationships between drug exposure, drug response, and patient outcomes. Models quantify a host of crucial development decisions related to the right pathway, target, molecule, dose, and commercial performance. For example, a paper by Pfizer scientists evaluated failures in 68 clinical trials to identify root causes that could be addressed by M&S. Pfizer recognized the following causes:

- Insufficient characterization of the exposure-response relationship
- Inadequate knowledge of the treatment approach in the target population
- Incomplete knowledge of the drug, mechanistically related drugs, and the therapeutic indication
- Lack of experience with primary endpoints

Benefits

- Make data-driven decisions at all stages of drug development through a quantitative framework
- Leverage all available data on the drug in development, as well as public data on competitors, to achieve the target product profile
- Design safer, targeted, and more efficient trials
- In some cases, eliminate the need for clinical trials
- Select the right dose for the right patients, the first time
- Simulate virtual patients in hard to recruit or test patient populations, such as pediatric, pregnant women, elderly and/or organ-impaired
- Maximize the probability of commercial success

Since the CPI was published, the use of modeling and simulation has been steadily increasing, both by sponsors for R&D and by global regulators as a review tool. In a 2015 survey conducted by the International Consortium for Innovation and Quality in Pharmaceutical Development (IQ Consortium), more than 95 percent of the leading pharmaceutical companies participating used M&S in either all or key therapeutic areas. They used M&S to inform key safety and efficacy decisions, including dosing, trial design, target validation, compound triaging, comparison with competitor compounds, and mechanistic drug performance.

Regulators Now Expect Sponsors to Use M&S

In March 2015, FDA scientists published a 10-year review of the CPI's impact. Their paper provided an unquestionable endorsement of M&S as a valuable tool in drug development. The paper states, "modeling and simulation has served as a useful predictive tool in dose selection for pivotal trials, dosing in select populations such as pediatrics, optimization of dose and dosing regimen in a subset patient population, prediction of efficacy and dosing in an unstudied patient population in clinical trials, characterizing exposure and dose-related QT interval prolongation, and using physiological-ly-based pharmacokinetic (PBPK) modeling in predicting drug-drug interactions [DDIs]."

During this 10-year period, FDA has built a sizeable pharmacometric organization with staff that work in regulatory review, research, and policy development. As reviewers, FDA pharmacometricians support drug approval, labeling, and trial design decisions. They also focus on dose selection based on quantitative benefit-risk assessments.

In addition, pharmacometric reviews are conducted during major submittal milestones. FDA now expects sponsors to perform these analyses and include them in the information package for End of Phase 2a meetings. FDA may also perform its own analyses to address particular problems or form an independent perspective. EMA, PMDA and other key regulatory agencies have also incorporated M&S in their review.

> "
> The US FDA has communicated the need for innovation in clinical evaluation to enhance medical-product development as part of its strategic plan for regulatory science. Modeling and simulation are among the enabling approaches to accomplish the envisioned efficiency and effectiveness in drug development.
> "
> — FDA Report, 2015

MODELING AND SIMULATION is a proven scientific approach used to inform crucial drug development decisions. Accepted by regulators and used across the development cycle, it integrates knowledge and relationships between the disease, drug characteristics, patient populations and clinical trial parameters.
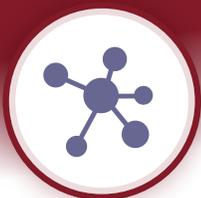
- Potency
- Solubility
- Binding
- IND Support

- Human PK Parameters
- FIH Dosing
- Pediatric Dosing
- Cardiac Safety Risk
- Toxicity

- PK Parameters
- Dose/Exposure
- Safety Profile
- DDI
- Special Populations

- Safety/Efficacy Model
- Exposure-Response
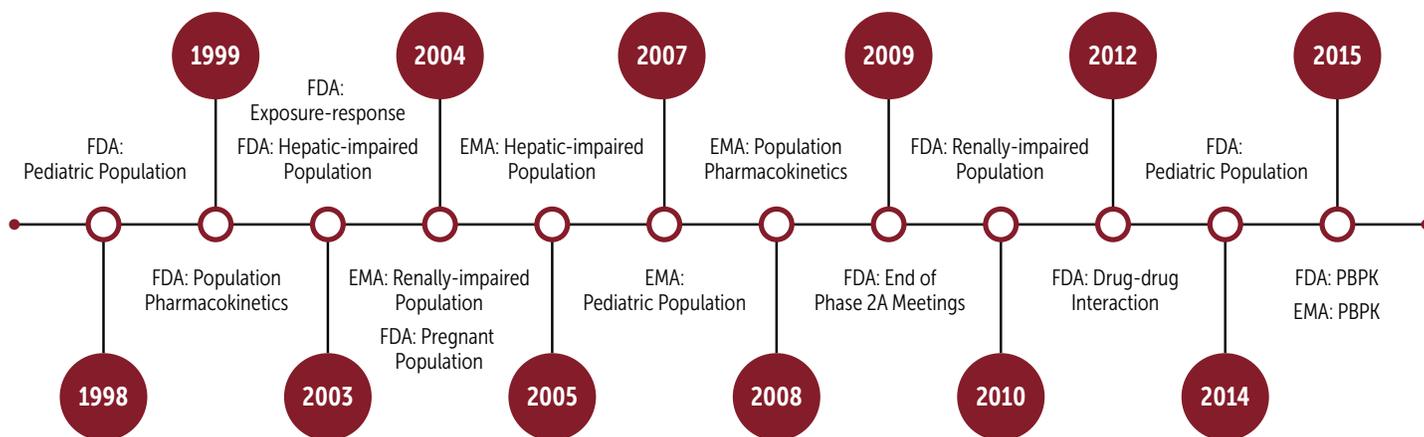- Trial Simulation
- Phase 2a Meeting Support

- Exposure-Response
- Comparative Effectiveness
- Regulatory Advisory Committee
- Post-marketing AE

KEY RESULTS
range from estimating drug safety and efficacy, to first-in-human dosing, through to clinical trial design.

Regulatory Guidance Documents Point to Benefit of Modeling and Simulation

Regulators' increased expectations for the use of modeling and simulation in drug development, as outlined in more than a dozen guidance documents.

Introducing QSP

Quantitative Systems Pharmacology (QSP) is a relatively new discipline that combines computational modeling and experimental methods to examine the relationships between a drug, the biological system, and the disease process. QSP takes M&S from our knowledge around target exposure to an understanding of target binding and target expression. A mechanistic modeling approach, QSP has the potential to have a significant impact on R&D productivity, especially on Phase 2 attrition.

Both FDA and the European Medicines Agency (EMA) have already issued more than a dozen M&S-related guidance documents, addressing population pharmacokinetics (PopPK), drug-drug interactions (DDI), pediatric, hepatic- and renally-impaired, and pregnancy populations. In fact, top down PK/PD M&S studies, using clinical data and iterated throughout the phases, are now expected by the regulatory bodies. With regard to PBPK, multiple agencies which include the Food and Drug Administration (FDA), European Medicines Agency (EMA), Medicines and Healthcare Products Regulatory Agency (MHRA), and the Pharmaceuticals and Medical Devices Agency (PMDA), have clearly articulated the many advantages of M&S in dose selection, clinical trial design, understanding special populations, DDIs, gene-drug interactions, and overall labeling.

Value Across Drug Development Phases

These quantitative methods are powerful tools for building a comprehensive knowledge-base of drug discovery, pre-clinical, early-phase clinical, literature, and competitor data, which can be used to optimize decisions in later development, including the "go/no go" that will lead to commercial activities. These analyses can also inform post-approval study decisions.

One of the most important elements of M&S is that it allows knowledge and wisdom, both in terms of successes and failures, to be carried over from one phase of the drug development process to the next. The companies that benefit most from these methods systematically integrate the technology across all drug development phases and tap into what has been known about a drug or drug candidate in order to optimize a model and certainly prior to enrolling patients in trials. As stated in the 2015 European Federation of Pharmaceutical Industries report on this subject, "Only fully integrated plans can serve to highlight the interdependence between experimental conditions, data generation, evidence base generation, and model informed drug discovery and development."

M&S can deliver the most value when started in the discovery phase to identify molecules that can deliver the highest efficacy with the least amount of toxicity. During the pre-clinical stage, it provides the foundation for scientific rather than intuitive dose selection, identifying the optimal dose and achieving the best therapeutic window. It helps to ascertain the right drug dose and the right safety profiles. It can also characterize patient sub-populations that respond differently in terms of efficacy and safety. This is important because a significant number of the doses (some estimate as high as 40 percent) selected in already approved drugs are actually suboptimal and create unnecessary toxicity and unnecessarily lower levels of efficacy.

M&S can guide numerous pivotal decsions. Using *in vitro* or *in vivo* data, it can help inform the following:

- First-in-human dose selection and dosing regimen

- Phase 1 clinical design

- Toxicology profile

- Data description by providing a mechanistic perspective

- Risk mitigation by offering an early view on drug-drug interactions

- Go/no go and portfolio management decisions

- Comparison to competitor compounds

Virtual Drug Development

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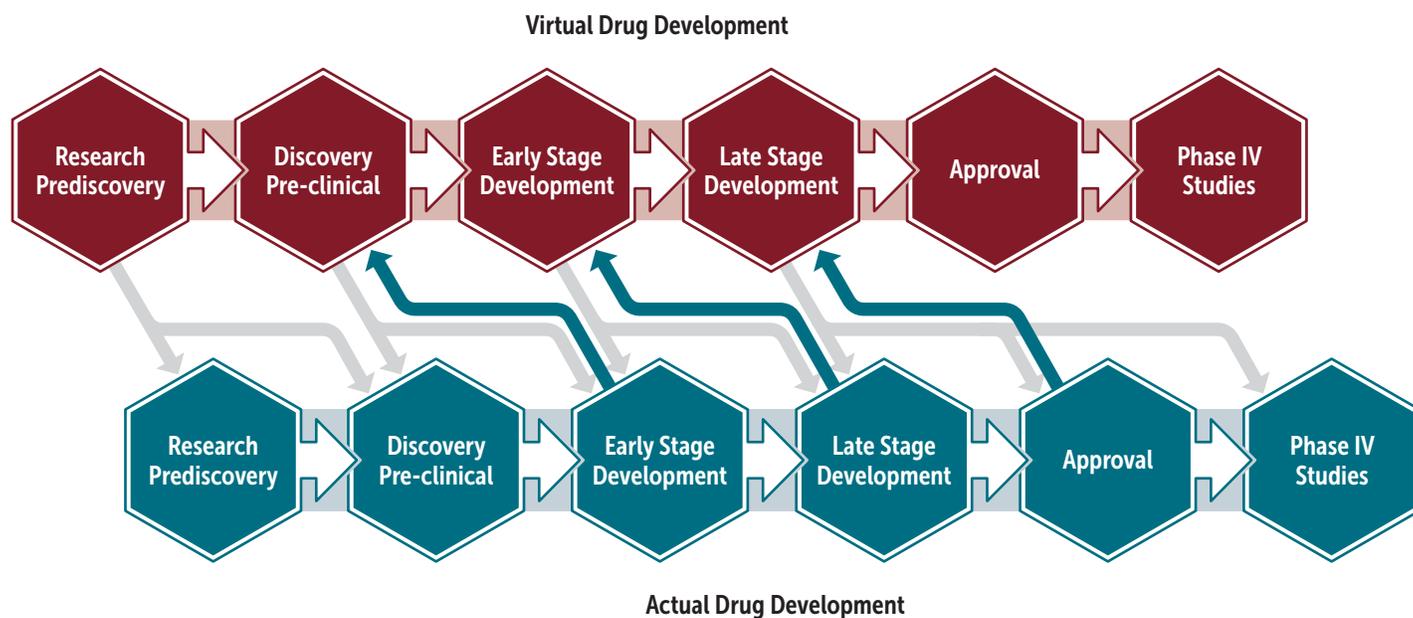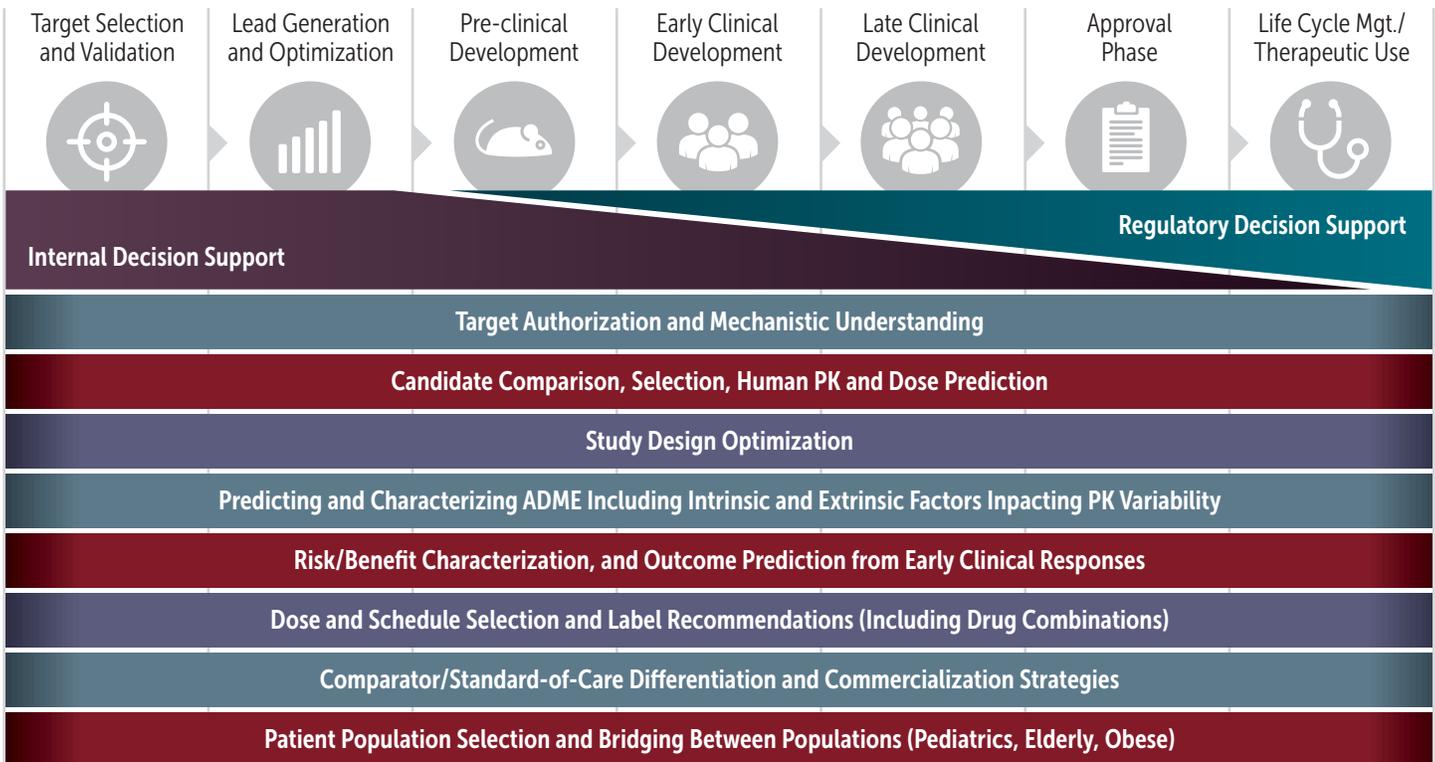
We recommend building parallel, but connected, *in vivo* and *in silico* development paths. The virtual drug development program is always ahead in each "time zone" to the *in vivo* drug development program. This paradigm confers a self-learning process that guides *in vivo* drug development. Thus, the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

In the early clinical stages, when models can be further refined with clinical data, it's decision-making powers expand with an eye toward the future drug label. In this stage, M&S can provide guidance regarding:

- Final dosing and alternate dosing approaches

- Optimal and alternate drug formulations

- Drug-drug interactions and other safety concerns

- Drug absorption

- Phase 3 clinical study design, including optimizing sampling schemes

- Institutional Review Board (IRB) justification

- Special populations and disease states, such as hepatic- or renally-impaired populations

- Additional go/no go and comparative effectiveness decisions

Range of Applications for M&S

Target Selection and Validation	Lead Generation and Optimization	Pre-clinical Development	Early Clinical Development	Late Clinical Development	Approval Phase	Life Cycle Mgt./ Therapeutic Use

Regulatory Decision Support

Internal Decision Support

Target Authorization and Mechanistic Understanding

Candidate Comparison, Selection, Human PK and Dose Prediction

Study Design Optimization

Predicting and Characterizing ADME Including Intrinsic and Extrinsic Factors Inpacting PK Variability

Risk/Benefit Characterization, and Outcome Prediction from Early Clinical Responses

Dose and Schedule Selection and Label Recommendations (Including Drug Combinations)

Comparator/Standard-of-Care Differentiation and Commercialization Strategies

Patient Population Selection and Bridging Between Populations (Pediatrics, Elderly, Obese)

Courtesy of EFPIA MID3 Workgroup

In late stage clinical trials, modeling is now designed to strengthen regulatory filings and commercial potential. At this stage, M&S can then provide guidance regarding:

- Scale from biomarker to clinical endpoints

- Dose adjustments based on patient-specific characteristics, such as age, gender, ethnicity, concomitant disease, or medication

- Expand molecule viability to additional new indications

- Confirm drug-food and drug-drug interactions

- Bridging studies

- Post-marketing study analyses

M&S: From 'Nice to Have' to 'Must Have'

Taken together, the advances in M&S and its increasing use in regulatory approvals have delivered unquestionable results; they have helped bring safer therapies to patients faster. M&S allows sponsors to make data-driven decisions at all stages of drug development by leveraging all available data in a proven quantitative framework. It systematically takes risk out of the drug development process. It reduces time and cost, facilitating earlier approvals. It serves as valuable currency with regulators, who use these technologies themselves for review and are helping to lead the M&S revolution. Furthermore, by designing safer, targeted and more efficient trials, the industry is responding to the ethical imperative to minimize potential harm to patients.

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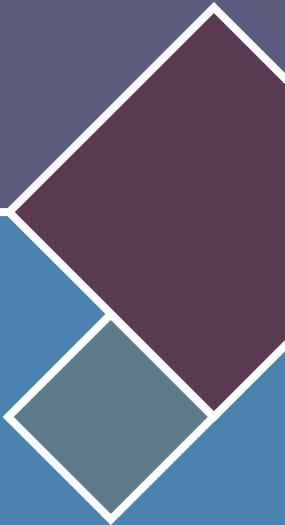
About Certara

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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