Abstract
Modeling and simulation is poised to transform drug development across the entire lifecycle from discovery to commercialization. For the biopharmaceutical industry, this transformation will enable knowledge-based decision making and foster new collaborative ways of working that will translate into more high-value treatments and increased development efficiencies. In the healthcare arena where value for money is paramount, modeling and simulation will inform future healthcare planning and practice.

This three-part series explores the potential of modeling and simulation practice throughout the drug development process. Part 1 discusses the concept of lifecycle modeling and simulation and its current applications in early drug development. Part 2 will consider expanding applications in Phases I-III, including portfolio management. Part 3 will examine modeling and simulation practice and potential in the post-approval arena, including applications aimed at improving healthcare planning and delivery.
Table of Contents

Abstract                      01
Introduction                  03
Transformative Power Across Industries 03
Biopharma Modeling and Simulation: Barriers and Progress 04
Deeper Knowledge:
Role of Modeling and Simulation in Understanding Relationships in Biology 06
Broader Knowledge:
Role of Modeling and Simulation in Understanding Outcomes 07
State of the Art: PK/PD Modeling 09
Regulatory Expectations; Biopharma’s Growing Practice 10
Realizing the Potential of Modeling and Simulation 11
References                    12
About the Authors             14
Introduction

Innovation depends on imagination and experience. It also depends on asking “what if” and evaluating possible outcomes. With exponential growth in data volume and advances in computational power, an increasing number of biomedicine’s complex what-if questions are being evaluated using computer-based modeling and simulation. For example:

- A multiple sclerosis genetics study recently used sophisticated modeling and simulation to identify 29 new genetic variants linked to the disease—a potential guide for drug target identification.¹
- In the midst of the 2008 influenza epidemic, the U.S. Food and Drug Administration (FDA) used modeling and simulation to identify and approve a safe pediatric dose of the experimental drug peramivir, which had never been studied in children.²
- When the American Diabetes Association needed to compare the effectiveness of current diabetes management approaches, Archimedes Inc. simulated a 30-year clinical trial to predict outcomes in a modeled patient population.³

Although modeling and simulation is still in its infancy in biopharmaceutical development and healthcare management, applications like these demonstrate its potential to expand knowledge at the molecular level, to increase efficiencies in clinical research, and to inform healthcare policy and decision making.

At present, the biopharmaceutical industry’s most mature application is pharmacokinetic modeling for dose determination. Now new applications are growing up quickly and the opportunities are enormous. They are based on an explosion of health data, the rapid growth of computational power, and increasingly sophisticated analytic tools that are allowing researchers to ask medicine’s toughest what-if questions.

Driven by biopharma’s need to increase productivity and healthcare’s need to improve outcomes and reduce costs, modeling and simulation is now poised to transform drug development across the entire lifecycle of therapeutic innovation, from discovery to commercialization.

Transformative Power Across Industries

Natural systems can be extremely complex and difficult to understand. Models are created to explain the behavior observed within systems. Models are based on historical observations but are commonly used to look forward to predict a future outcome or state. Models can be either deterministic or probabilistic (stochastic). Simulation is a method that takes a model and uses it to test how variability within a system can impact outcomes. In particular, simulations can use more extreme model inputs than have been previously observed to help understand the range of future potential outcomes. In this way, simulation can be used to better characterize risk and identify opportunities to optimize outcomes.
Modeling and simulation practice evolved to solve problems that could not be addressed using direct observation and measurement. The classic example comes from atomic physics. In 1946, Los Alamos Scientific Laboratory researchers needed to determine the distance neutrons would be likely to travel through various materials. Stanislaw Ulam solved the problem using a mathematical model and simulating a succession of movements by millions of particles in what he called the Monte Carlo method. Today, computer-based mathematical models and simulations are advancing such diverse fields as physics, chemistry, engineering, economics, meteorology, and even musical composition.

Enabled by supercomputing, modeling and simulation has become a transformative tool for innovation in industries like aeronautics. To reduce development costs for their 1903 flyer, the Wright brothers modeled and tested wing shapes in a wind tunnel. A century later, 800,000 simulation hours on the Cray Supercomputer replaced most physical prototypes in the design of the 2003 Boeing 787 Dreamliner. Computer-based modeling and simulation reduced the number of prototype wings tested from 77 for the earlier Boeing 767, to only 11 for the Dreamliner, which is acknowledged as an important advance in aircraft design.

In meteorology, computer-based atmospheric models and simulations now predict events from localized tornadoes to global atmospheric movements. In 2011, the modeled path of Hurricane Irene was constantly adjusted until landfall, after which Irene followed the modeling-and-simulation-predicted track up the East Coast. IBM’s “Deep Thunder” simulation delivers not only precise forecasts up to three days ahead of time, but also predicts possible storm damage to municipal or business infrastructure to provide “personalized” forecasting.

In financial modeling, behavioral models use simulation to quantify the tradeoffs between quantifiable risks and returns. Models take into account financial and business variables, then simulations present a range of possible outcomes used to make business decisions.

Biopharma Modeling and Simulation: Barriers and Progress
Biopharma lags other industries in its application of modeling and simulation. Despite important advances in clinical trial designs and technologies, today’s drug development remains an inefficient, high-risk enterprise with poor predictability. The biopharmaceutical industry cannot sustain its present business model of high development costs and low product yield. New tools and approaches are urgently needed to make research more informative and efficient.

Inefficiencies in drug development are due in large measure to the fact that the scientific underpinnings of so many aspects of therapeutics, the nature of disease, and the biological systems in which they act are still unknown. One of the objectives of clinical research is to “discharge risk” through the controlled study of investigational medications using rigorously designed experiments.
that yield insight into the true effect of medicines on individuals and populations. Modeling and simulation can help developers better plan and design these experiments by exploring and quantifying risks prior to clinical trials.

Modeling and simulation can help to optimize the clinical development process—and improvements cannot come too soon. The FDA confirms that clinical trials are growing in size and duration, trending toward databases of 5,000 subjects.\textsuperscript{5} Longer-term safety evaluations are pushing clinical development timelines beyond seven years.\textsuperscript{6} Cost averages $1.3 billion per new drug approval,\textsuperscript{7} and as few as eight percent of compounds entering Phase I reach the marketplace.\textsuperscript{8} Despite the genetics revolution and computer-assisted discovery technologies, the production rate of novel drug therapies has not increased for the past 60 years.\textsuperscript{9} In the broader healthcare arena, U.S. health expenditures are projected to climb to 17.6 percent of GDP in 2012, testament to the critical need for more efficient health policy and delivery.\textsuperscript{10}

Solutions through computer-based drug discovery and development have been a dream for decades. What if we could screen potential drugs in virtual biosystems? What if we could learn more about therapies via virtual patients? What if we could accurately predict health outcomes and costs in real-world medical practice? Three barriers have limited progress toward these goals: the vast complexity of biological systems; the lack of data on a population level; and the reluctance of drug developers to invest in approaches with uncertain regulatory outcomes. Now these barriers are beginning to fall.

\textbf{Supercomputers are Mastering Complexity}

In the past 60 years, computational speed has accelerated from one floating point operation per second to more than 250 \textit{trillion} per second.\textsuperscript{11} Computational power is growing rapidly and becoming more economically affordable with cloud-based systems. Sophisticated analytical tools and open-source software consortiums, such as R Project\textsuperscript{12} and OpenBUGS,\textsuperscript{13} also are emerging to enable investigation of medicine's most complex questions. In biomedical research, this translates into the ability to model vastly complex systems. In 2005, researchers created a 2.64-million-atom model of a ribosome, the producer of proteins in all organisms.\textsuperscript{14} The Blue Brain Project is now building a simulation of the human brain at the molecular level.\textsuperscript{11}

\textbf{Data, Data Everywhere}

An explosion of data—from gene banks to electronic health records—is facilitating the construction of models. Evaluation of real-world drug effects and health outcomes has been hampered by the lack of population-level data. This deficiency is now being overcome by data from large observational databases and surveillance systems such as FDA's Sentinel System. Sentinel expects to access data from 100 million patients by 2012.\textsuperscript{15} Health transaction data, like the Kaiser
Permanent medical database of health records for more than 28 million members, are available for research. In the UK, researchers have access to anonymized patient information databases including the General Practice Research Database (GPRD) and The Health Improvement Network (THIN).

Regulatory Support
In the 2004 report that launched the Critical Path Initiative, the FDA cited modeling and simulation as an important opportunity to improve drug development. In 2009, the agency issued its Guidance for Industry End of Phase 2A Meetings that encourages use of “trial simulation and quantitative modeling of prior knowledge to design trials for better dose response estimation and selection.” The United Kingdom’s National Institute for Health and Clinical Excellence (NICE) advises drug sponsors that “probabilistic analyses are preferred.” In November 2011, U.S. and EU regulators met with industry representatives to share ideas about how best to use modeling and simulation in drug development.

Regulatory support is having a significant impact. At FDA, the number of new drug applications using modeling and simulation has increased six-fold in 10 years. A 2011 review of 198 submissions between 2000 and 2008 reported that modeling and simulation is not only influencing regulatory decisions, but also that FDA is using modeling and simulation internally to extend clinical findings and guide additional clinical testing. Dramatic regulatory endorsements of modeling and simulation include FDA’s initiatives to develop open-use models for drug and medical device developers: one is aimed at predicting species-specific variations in liver toxicity as a means to improve dosing decisions; another will enable device developers to pre-evaluate devices such as hip and knee joints.

This changing landscape sets the stage for lifecycle modeling and simulation to play a major role in revolutionizing therapeutics and healthcare delivery. Twenty-first century medicine is advancing on two frontiers of knowledge: deeper understanding of causality and broader understanding of real-world outcomes. Modeling and simulation is an essential tool in both arenas and can increase connectivity between drug development insights and drug impact in real-world medical practice.

Deeper Knowledge:
Role of Modeling and Simulation in Understanding Relationships in Biology
Expanding knowledge at the molecular level is increasing understanding of biology and disease processes. Resources are growing in massive genetics databases such as the U.S National Institutes of Health’s GenBank, which currently holds more than 680,000 nucleotides and 606 gene sequences. Research surrounding genetic linkages, proteomics, and cellular lineages and environments is generating a new definition of disease as a constellation of changes in an individual’s network of genes, proteins and biochemical pathways.

This is giving rise to new therapeutic approaches that focus on more individualized intervention at the molecular level. Targeted therapeutics rely on biomarkers to identify specific patient populations that experience increased safety and effectiveness. One example is the breast cancer drug Herceptin which targets the HER2 gene variant found in about 25 percent of breast cancer patients. Biomarkers and pharmacogenomics strategies make it possible to develop drugs like Herceptin whose therapeutic effects are masked in the broad population but seen clearly when targeted to specific subpopulations.
Gene therapy, stem cell therapy, regenerative medicine and tissue engineering are no longer futuristic ideas but clinical realities. In just one 2011 example, virologists used zinc finger nucleases—which act as molecular scissors to snip out bits of DNA—to create human stem cells that lack the CCR5 receptor necessary for HIV to invade CD4 immune cells. In mice, the engineered stem cells are giving rise to HIV-resistant immune cells, suggesting a strategy toward a functional cure for AIDS.24

In discovery and early stage development, computer-based modeling and simulation is playing an ever greater role in advancing and using knowledge at the molecular level in lines of research ranging from systems biology to drug screening.

Systems Biology
Computational modeling is a core discipline in the emerging field of systems biology, which has the potential to produce a new paradigm in drug discovery. Systems biology integrates huge volumes of molecular and genetic information with large-population clinical datasets to create predictive models of disease and biological systems. Simulations can then bring to life the what-if questions posed by researchers and used to assess potential results based on a range of assumptions. The resources required for these models are so large that some are being created by consortia for open use in a “pre-competitive” research space. One example is the $6.7 million partnership between Sage Bionetworks and the National Cancer Institute to build computational models to predict breast, colon, liver and pancreatic cancer.23

Genetics
Computer-based modeling is helping to identify potential drug targets. In one example—the largest multiple sclerosis genetics (MS) study ever attempted—a research consortium compared DNA from more than 9,700 MS patients to that of 17,300 healthy controls and identified 29 new genetic variants that are associated with susceptibility to the disease. Modeling principles pointed researchers to genes related to the immune system, including two involved in vitamin D metabolism.1

Drug Screening
Increasingly sophisticated computer models are identifying better development candidates faster. The Cresset Group, for example, has developed multi-dimensional modeling software that models compound interactions. In a recent project, a Cresset model screened a virtual database of 3.8 million compounds to generate 500 “hits” for candidates that inhibit an enzyme targeted for obesity therapy.25

Broader Knowledge: Role of Modeling and Simulation in Understanding Outcomes
Spanning drug discovery, evaluation and real-world drug use, lifecycle modeling and simulation applications will increase with the availability of health data. Observational and health-transaction databases will collect and quantify real-world health and treatment experience, generating data that can be used to model everything from disease screening programs to medication adherence. Sophisticated analytics will be used to ask what-if questions at the population level. Simulations will test-run interventions and treatment options to predict outcomes and guide health policy, not only to address therapeutics, but also to understand and increase positive health behaviors.
Simulating Trials
The beginnings of modeling and simulation-informed trial design, therapeutic evaluation, and healthcare policy can be seen in current applications of simulated clinical trials aimed at predicting health outcomes and comparing alternative interventions. Researchers now are modeling clinical trial populations by matching subject characteristics and inclusion/exclusion criteria. One advantage is that simulated trials can model and incorporate clinical trial subject’s adherence to study drug—a factor that has major impact on results but often is not sufficiently considered—to achieve better predictions of likely outcomes.26

Trial simulations are being used to support team decisions regarding study design. Traditional approaches can be sufficient to guide the design of a trial when a treatment’s safety and efficacy profile is well known. However, if there is uncertainty—as is often the case—the team can simulate a likely range of safety and efficacy profiles and run trials in silico to explore advantages and disadvantages of possible trial designs. Simulation results then can be evaluated by the whole clinical development team.

There are also modeling and simulation approaches, such as the simulated trials offered by the healthcare modeling company Archimedes Inc., that enable researchers to refine clinical trial strategy by elucidating the impact a drug is likely to have in real-world use—for example, the impact on long-term health outcomes and on health system utilization. This is becoming increasingly important within the clinical-commercial convergence arena to guide development decisions that maximize both the therapeutic and commercial value of biopharma company assets.

Predicting Health Outcomes
Modeling and simulation offers a promising tool to predict drug safety and to evaluate the impact of various interventions on health outcomes in real-world medical practice. For example, a recent simulated trial of a modeled Medicare population compared a variety of health interventions to learn which had the greatest impact on cardiovascular and diabetes outcomes at three time points—in 10, 20 and 30 years.27 Interest in such modeling and simulation applications is growing. For example, the U.S. Department of Health and Human Services (HHS) is expanding government use of healthcare modeling to forecast quality and cost outcomes. The HHS recently contracted with Archimedes to make modeling tools available to government agencies to conduct large-scale analyses of treatment effectiveness and healthcare spending.28

Informing Health Policy
Modeling and simulation can provide predictive evaluations of cost effectiveness necessary to guide health policy and improve healthcare value and delivery. The attraction of modeling and simulation for the payer is that it can provide estimates of cost that reflect the numerous uncertainties pertaining to real-life outcomes and costs. For example, researchers in Ireland conducted a health technology assessment (HTA) that modeled and simulated outcomes to evaluate the cost-effectiveness of various options for a colorectal cancer screening program.29

Development/Commercial Convergence
For the biopharma industry, modeling and simulation can help bridge the needs of drug development and commercialization. Better decisions are needed to guide the selection of drug candidates for development based on a host of factors surrounding potential benefit, long-term outcomes, risk, cost effectiveness, and the competitive environment. Modeling and simulation can evaluate tradeoffs and inform product portfolio decisions aimed at maximizing the commercial value of drug products.
State of the Art: PK/PD Modeling

In drug development, the most advanced modeling and simulation application is the use of pharmacokinetic (PK) and pharmacodynamics (PD) data for dose modeling. PK/PD modeling has been streamlining clinical trials for a decade, has proved its value, and has won widespread industry and regulatory support.

Identifying the optimal exposure-response relationship for a drug is the single most important thing to get right in drug development: if the exposure is too high, the result is toxicity; if too low, the drug fails to achieve effectiveness. Suboptimal dosing is a major challenge in drug development. A 2002 study of 499 new molecular entities approved by the FDA between 1980 and 1999 found that one in five of those evaluable (354) required dosage changes after introduction; four out of five changes were reductions for safety.30

Traditionally, exposure (that is, the relationship between dose and concentration) is determined in a series of Phase I single- and multiple-ascending dose (SAD and MAD) trials conducted in stages over a period of nine to 12 months. The range of exposures determined in Phase I can then inform Phase II dose selection for patient testing to get an initial characterization of the exposure-response relationship.31

PK/PD dose modeling and simulation has dramatically improved the costly, time-consuming and often imprecise process of dose selection. PK/PD data from preclinical and Phase I research are used to build mathematical models of drug actions in the body. Simulations of drug effects at different dosage levels are used to select optimal doses for clinical testing. Models are iteratively adapted and improved as more data are acquired, beginning with preclinical data and advancing with data derived from first-in-human SAD and MAD studies continuing through Phase II/III.20 This is often referred to as the “learn-and-confirm” cycles of modeling and simulation.32

In traditional clinical development, clinical pharmacologists concerned with PK/PD analysis had limited input into designing trials and analyzing results. Recognizing the importance of PK/PD modeling, more drug developers are incorporating this discipline into their modeling and simulation teams to leverage early data and improve decision making downstream. In Phase II, modeling and simulation can test assumptions to gain insight into the potential impact of drug exposure on efficacy endpoints. In therapeutic categories such as oncology and CNS where correlations between exposure and endpoints are not well defined, PK/PD modeling can help to affirm or reject the suggested relationship.

Simulations also can test assumptions regarding the impact biomarkers have on clinical outcomes. For example, if a cancer biomarker is assumed to be highly predictive, what is likely to be its relationship with tumor growth? Then in Phase III development, population PK/PD data can be modeled to predict dose adjustments for target populations, including obese patients, patients with impaired liver and renal function, children, the elderly, and ethnic groups using a population based approach.33

Population PK/PD models incorporate covariates that are often helpful in guiding dose adjustments in the package labeling. Population PK/PD models typically are used in cases where dosing needs to be adjusted for weight (for example, enoxaparin, heparin and fondaparinux), renal function (gentamicin and vancomycin) and cytochrome P450 genotype-related drug/drug interactions.
A powerful example is FDA’s use of existing PK/PD data from clinical evaluation of the influenza drug peramivir to model and simulate a safe, effective pediatric dose. Peramivir had never been tested in children. To make therapy available during the 2008 H1N1 flu epidemic, FDA approved the intravenous pediatric dose based solely on the simulation. Results from later pediatric trials confirmed the simulated outcomes.

The power of PK/PD modeling and simulation to predict safety is also evident in QT modeling and E14 analysis. FDA now expects to see concentration QT analysis as a part of any thorough evaluation of the cardiac safety of noncardiac drugs. Such analysis may also be required in the future for additional therapeutic areas, such as CNS drug evaluation.

Regulatory Expectations; Biopharma’s Growing Practice

The FDA and other regulatory agencies have embraced “model-based drug development”—the use of preclinical and available clinical data to create pharmaco-statistical models of efficacy and safety—as an important tool to improve development knowledge, processes, and decision making across the full spectrum of drug development. In the 2009 Guidance for Industry: End-of-Phase 2A Meetings, FDA encouraged sponsors to seek regulatory meetings to discuss clinical trial simulation and quantitative modeling as a means to make more informed decisions about trial design and dose selection.

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A report from the Pharmacometrics Division of FDA’s Center for Drug Evaluation Research Center (CDER) cites a dramatic increase in the number of NDA’s that include modeling and simulations, as well as an increase in the impact of modeling and simulation on FDA decisions. The agency uses increasingly sophisticated PK/PD models, together with patient characteristics, to guide decisions on safety and effectiveness for approval, labeling, and requirements for and design of additional studies.

FDA is developing its own models and simulations for open use to speed development and evaluation processes. “DILI-sim” (Computer Models for Human Drug-Induced Liver Injury) is an FDA-industry collaboration to build models that can predict species differences in liver toxicity. DILI-sim models will help distinguish between drugs that have the same toxic liver effects in humans and animal models such as mice, and drugs that may be safe in one or more nonhuman species but not in humans. Development of the agency’s Antiviral Information Management System (AIMS) will include an automated tool for modeling and trial simulation linked to a database of hepatitis C and HIV clinical trials.
Regulatory leadership is influencing the industry’s increasing use of modeling and simulation. A 2010 survey of 10 large and mid-size biopharma companies found that modeling and simulation is achieving broad applications in early and late phase development where it is significantly influencing corporate decisions. Responder companies expected to increase their applications of all types of modeling and simulation, especially in PK/PD exposure response, study design simulation, and disease progression.35

Realizing the Potential of Modeling and Simulation
With data resources, computational power, and regulatory positions now coming into alignment, lifecycle modeling and simulation is poised to enable the expansion of knowledge-based drug design and evaluation, and evidence-based health policy and delivery. Experts suggest that full realization and exploitation of computational models and simulations could reduce the overall cost of drug development by as much as 50 percent.19

This advance will require new ways of working—a breaking down of traditional silos and a transition to interdisciplinary operations. Within institutions, experts from diverse fields must come to the table with data and knowledge to frame questions and to quantify assumptions for testing. The practice of modeling and simulation requires experts to collaborate throughout the innovation lifecycle, from discovery to commercialization, rather than to contribute at a specific stage of the development process. Such collaboration will undoubtedly enrich drug development and lead to better, more informed decision making.

Discussion of lifecycle modeling and simulation will continue in Part 2 of this series, which explores applications in Phase I to Phase III development to improve trial design, clinical project design, and portfolio management. Part 3 will focus on the post-approval arena and the potential of modeling and simulation to improve healthcare planning and delivery.
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