

The Future of Drug Development is Virtualized and Personalized

Today, drug development is carried out in human subjects and animals. However, as computing power and the number of sophisticated technology platforms grow exponentially, and our knowledge of human health and disease increases, the virtualization of clinical research and development will grow steadily.

The new blockbuster will target a well-defined patient population with clear and precise dosing instructions, with full understanding of the patient or subpopulation genetic polymorphism, and with full accountability of the patient-specific epidemiologic and epigenetic factors.

Biosimulation (also called modeling and simulation), which integrates computer-aided mathematical simulation and biological sciences, will continue to tap into synergy between those two trends.

We have already seen increased use of modeling and simulation to inform drug development and drug labels, which is positively impacting payors, patients, and drug developers.

Regulatory agencies have fully embraced modeling and simulation as part of the drug development process. In fact, in the Food and Drug Administration's (FDA's) paper on "Catalyzing the Critical Path Initiative: FDA's Progress in Drug Development Activities,"¹ Janet Woodcock, MD, director of the agency's Center for Drug Evaluation and Research (CDER), identified modeling and simulation as core disciplines that are likely to modernize drug development and clinical research.

"Fifteen years ago, 20% of drug candidate attrition was due to poor absorption, distribution, metabolism, and excretion (ADME) characteristics; now, the attrition rate due to ADME problems is down to 1 to 3%," says Lawrence Lesko, PhD, FCP, former director of the Office of Clinical Pharmacology for CDER and current clinical professor and director of the Center for Pharmacometrics and Systems Pharmacology in the University of Florida College of Pharmacy. "That's due to the use of modeling and simulation, because we can simulate not only structure-activity relationships, but also simulate realistic dissolution and pharmacokinetic profiles."

Lesko adds, "Physiologically based pharmacokinetic (PK) models now allow researchers to predict clinical drug-drug interactions and drug-gene interactions in untested scenarios. Biosimulation

approaches also enable those predictions to be made from a limited number of clinical trials. Such information is now almost routinely being included in the labels of FDA-approved drugs."

Biosimilar registration is a future opportunity for biosimulation, according to Lesko. Earlier this year, FDA approved the biosimilar of Remicade. Its sponsor conducted a three-way PK bridging study to justify the clinical relevance of comparative efficacy data using the European version of Remicade. That PK study could have been done by biosimulation if it was not the first biosimilar of Remicade.

Virtual Drug Development

Virtualization is going to become a dominant trend. When that occurs, pharmaceutical companies will develop parallel drug development paths. They will create a virtual drug development path, and a real-patient, real-life drug development path—each guiding the other and establishing a mutually positive feedback loop.

The virtual drug development program will, on an ongoing basis, inform each phase of development. It will receive data from the real world and use them to refine the models for the next phase. The virtual drug development program will then provide those data for the real-world drug development to start a new phase. In a very positive cycle, the virtual world and real-life patient drug development will become intimately intertwined.

Today, the percentage of virtualization in drug development is quite small. No more than 10% of the \$150 billion drug development market is thought to be virtualized. Therefore, this market has an extraordinary opportunity to grow.

Biosimulation and precision medicine will definitely move into patient care—first at the hospital level, to inform precise dosing for complicated patient populations; next for multiple in-hospital applications; then for outpatient treatment; and eventually inside patient homes (the ultimate point of care).

That trend is not unique to biology. In fact, this industry is late to that process. In 2007, the British government and the aerospace industry agreed to a three-year, £17.4 million modeling and simulation program to accelerate aircraft design.² The program goal was to reduce development time and create a more eco-friendly process.

The aerospace consortium (led by Airbus) developed the simulation software. The British Department of Trade and Industry predicted that by 2012, simulations would replace physical testing, cutting parts of the design process from 350 days to 36 days.² It decided to invest in that transformative technology.

The Next Scientific Horizon

For biosimulation to reach its full potential, there will need to be additional work done in the area of mechanistically based pharmacodynamics (PD) or response to exposure to drugs, says Malcolm Rowland, PhD, DSc, professor emeritus at the Manchester School of Pharmacy at the University of Manchester, U.K., and adjunct professor in the Department of Bioengineering and Therapeutic Sciences in the Schools of Pharmacy and Medicine at the University of California San Francisco (UCSF).

PK-related issues and epigenetic and epidemiological factors are well-represented in the current biosimulation models; however, PD-related issues are not as well understood.

Rowland adds, “Advances will need to be made in quantitative systems pharmacology (QSP) and therapeutics, so that researchers can understand the underlying pathophysiology of individual processes in the body and the network system that operates. Most drugs fail in Phase II clinical trials due to lack of efficacy. But if researchers can understand mechanistic PK/PD, and the networking structure better, they will be able to produce drugs that are efficacious and also have a better safety profile. They will be in a better position to predict more accurately which drugs are likely to produce adverse events, enabling their development to be stopped much earlier, before they are given to large groups of patients.”

QSP is a relatively new discipline, but it has the potential to dramatically improve pharmaceutical research and development productivity. By furthering their understanding of QSP and systems biology, researchers will be able to create a comprehensive modeling and simulation system that will improve prediction of the safety and efficacy profile of investigational drugs in virtual patients.

Biological Personalized Avatars

Precision medicine will become dominant in drug development, and it will become a core approach in patient care. “Precision medicine” refers to developing drugs and treating patients with a precise understanding of the subgroup or individual PK, PD, and epidemiologic or epigenetic factors that will impact their drug response.

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In two or three decades, when modeling and simulation and the virtualization of drug development and precision medicine have undergone their next evolution, we may be living in a virtual drug development and patient care world where biological computer-based avatars will guide drug development and point-of-care solutions on an individual basis. That is to say, each individual will have his or her own avatar, just as everyone in the U.S. currently carries a driver’s license or social security number that identifies them as a specific person. That avatar will be used in drug development when the individual is part of a clinical trial, when they are hospitalized, or at the point of care when they are undergoing a specific treatment.

Even better, the avatar will be used for prevention and wellness purposes. Once the specific characteristics of a patient’s cell signaling pathways are understood, and how their polymorphisms can impact those pathways, physicians will be able to maximize that individual’s ability to take medications safely and effectively. They will also be able to ensure that the patient has the right macro and micro nutrients to enhance their wellness and prevent disease.

From Monotherapies to Combination Therapies

The University of Florida’s Lesko also predicts a move away from monotherapies toward combination therapies that better address the multifactorial nature of disease pathology. This will result in an increasing reliance on biosimulation to integrate combination therapies and environmental factors into clinical trials and optimize medical treatments.

As more drugs are added to a patient’s regimen, the number of potential interactions grows rapidly. Biosimulation can help to determine the optimal drug combination, which maximizes benefits whilst minimizing toxicity; it can also identify the best dose, frequency, and timing for each drug.



Using Biosimulation to Enhance Patient Care

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Certara Chief Scientific Officer Amin Rostami, PharmD, PhD, is working with several research centers in the U.S. and the U.K. that are already using biosimulation to inform patient care.

For example, modeling and simulation are being used to define the drug dose changes required for bariatric surgery patients. These patients are undergoing major surgery on their gastrointestinal (GI) tract, which will impact their rate and particularly extent of drug absorption after the operation. Sometimes patients' drug doses need to be increased, as the molecules are now being absorbed through an area of the GI tract that absorbs less.

Biosimulation is also being used to define the appropriate drug doses for pregnant women. Many changes to the body occur during pregnancy, and some women have conditions, such as epilepsy, for which they need to keep taking their drugs. These patients can experience epileptic fits if medications are not getting into their bodies at the intended levels. Biosimulation is used to determine whether their drug dose needs to be adjusted at different stages of their pregnancy.

Furthermore, patients with HIV or hepatitis C infection normally receive multiple drugs, and are thus at risk for drug-drug interactions (DDIs). Biosimulation is being used to preemptively identify potential DDIs. Oncology or elderly patients also often take multiple medications, and require similar assistance.

In addition to providing important drug dosage recommendations for difficult cases at research centers and in clinical practice, biosimulation offers important insights for forensic medicine and helps to test hypotheses in retrospective studies.

Wearable Devices Will Inform Drug Development

Lesko also predicts an increased use of data from wearable devices to complement drug development. These devices currently measure a person's heart rate, sleep pattern, steps taken, and calories burned. In 10 years, they will likely be able to capture almost any physiological data required. Biosimulation will play an important role in this trend because computer modeling will be required to analyze these data.

Most of the patient-related data that are currently used in biosimulation come from measurement devices of some sort, whether in the form of biomarker data, blood pressure readings, the presence or absence of polymorphisms in genes, or the drug levels in plasma. Over the next few decades, those devices will become smaller, much more precise, and portable and wearable.

UCSF's Rowland agrees that biosimulation is going to have an impact at the patient level in terms of improving the individualization of medicines and therapeutics. "People will know a lot more about themselves; they will be aware of features that are either unique to themselves or family characteristics. They will also be more cognizant of their drug responses," he adds.

The Coming Brave New World of Biosimulation

Biosimulation has been widely adopted by sponsors and regulatory agencies alike. It is already playing an integral part in the drug development process, influencing everything from first-in-human dose selection to the language used on the drug label. However, it is destined to play an even bigger role going forward, as sponsors create parallel real and virtual drug development paths to create safer and more efficacious drugs. Each individual will also have a personal avatar on which a proposed treatment will be tested before any real-world intervention is taken. Precision medicine will soon become a reality from which we can all benefit.

Reference

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