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GUEST COMMENTARY:
An Ethical Imperative to Use Biosimulation in Drug Development

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The use of biosimulation in drug development has been growing at an exponential pace. The FDA's 2004 Critical Path Initiative report articulated the value of this approach over 10 years ago. Biosimulation informs crucial drug development decisions—informing first-in-human (FIH) dosing, advancing the understanding of drug mechanisms, linking biomarkers to outcomes and optimizing clinical trial design. By using biosimulation, pharmaceutical companies and regulatory agencies expedite bringing new, safer therapies to patients.

Biosimulation: a predictive tool

Biosimulation is sometimes known as model-informed drug development, using both pharmacokinetic/pharmacodynamic (PK/PD) modeling and physiologically based pharmacokinetic (PBPK) modeling. These approaches facilitate a better understanding of a drug's risk/benefit profile. This additional knowledge increases the likelihood of regulatory success.

In the recently published paper "Catalyzing the Critical Path Initiative: FDA's Progress in Drug Development Activities," the agency refers to modeling and simulation (M&S) as "a useful predictive tool for 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 [for determining cardiac safety], and using PBPK modeling in predicting drug-drug interactions (DDIs)."[1]

The ethical case for using biosimulation

In addition to the strong business case for using biosimulation, there is also a powerful ethical case. Now that we know how bio-simulation has proven to inform key drug development decisions, is it ethical to not employ these methods before enrolling patients or healthy volunteers into clinical studies? By using biosimulation, we can determine appropriate dosing and identify and manage possible safety issues, such as drug-drug and drug-food interactions. Biosimulation not only therefore enables drug developers to inform the size and scope of clinical studies, often resulting in smaller and more targeted trials, but may also result in the waiving of specific studies.

The application of biosimulation is particularly relevant for the study of special populations, including pediatric patients, oncology patients, patients with organ impairment and pregnant women.

A learning platform for pediatric drug development

Children are not just small adults. Pediatric drug development must consider their unique biology. Children may have altered PK compared to adults. Their organ size, organ blood flows, tissue composition and the relative abundance of drug metabolizing enzymes all change during development. The bioavailability of drug formulations may differ between children and adults due to differences in gastrointestinal physiology and the enzymes and transporters that impact first-pass loss.

Population PK and PBPK models based on Phase 1 data from adults can be used to develop a drug model that aids with pediatric dosing. These models can predict drug exposure across a wide range of ages and weights taking into account metabolic enzyme maturation and developmental changes in organ function. The predicted drug exposure in pediatric patients can then be compared against observed values in adult subjects in Phase 1 to confirm the models and optimize drug safety.

Guiding dosing in pregnancy

Dramatic physiological and biochemical changes occur during pregnancy. But pregnant women are excluded from clinical trials for ethical reasons. As a consequence, we lack clinical data on how these changes may affect maternal drug exposure. Clinicians often scale doses from recommendations set for men or nonpregnant women. This can lead to suboptimal dosing, with lack of efficacy or a risk of toxicity to the mother or fetus.

The FDA and European Medicines Agency are addressing this issue. They require post-marketing studies of drugs in pregnancy that women of child-bearing age are likely to use. Pharmaceutical companies face two challenges with these studies. They must determine appropriate initial dosing levels, but the dosing will vary depending on the stage of pregnancy. They must also account for changes in drug exposure that may occur over an extended study period.

A full PBPK pregnancy model simulates how drug concentrations change over time in virtual pregnant women. The model reflects changes in weight, blood and plasma volume, feto-placenta volume, CYP450 enzymatic activity and serum albumin levels that occur and may alter over the gestational period. This model is the first to consider time-dependent factors during pregnancy. Drug companies and regulatory agencies can leverage this tool to understand changes in drug exposure throughout pregnancy, determine optimal dosing for pregnant women and help to keep both mom and baby healthy.

Assessing the impact of eliminating organ impairment on PK

Patients with eliminating organ (kidneys and liver) impairment have a high risk of drug-related adverse events. PBPK models can help assess the impact of organ impairment on PK without subjecting vulnerable individuals to unnecessary clinical trials. Hepatic impairment models incorporate information on demographics, changes in hepatic blood flow, liver size, changes in metabolizing enzyme abundance, plasma protein binding and renal function. The model allows for the Childs-Pugh categorization of hepatic impairment and a study by Johnson, et al.[2] showed good agreement between simulated results and observed values for a range of drugs. Mechanistic models of renal impairment have also been developed and evaluated for numerous drugs including those with complex kinetics.[3]

Evaluating drug-disease PK interactions using PBPK models

PBPK M&S is also useful for evaluating drug-disease interactions that alter PK. For instance, researchers developed a PBPK model to evaluate PK changes in cancer patients.[4] These patients differ significantly from healthy adults. They are generally older than healthy clinical trial volunteers and have lower levels of drug-metabolizing enzymes compared to their younger peers, which may result in lower drug clearance.

Likewise, certain disease states impact drug binding to plasma proteins. The two most common drug-binding plasma proteins are alpha-1 acid glycoprotein (AAG) and albumin. Cancer patients have higher levels of AAG and lower levels of albumin compared to their healthy peers, a change which may manifest as significant pharmacokinetic differences between the two groups. Simulation of pharmacokinetics in oncology patients needs to take into account differences in the age-sex distribution, relative abundances of binding proteins and drug metabolizing enzymes when using PBPK models originally developed for a healthy volunteer population

Case study: How biosimulation supported the development of a novel antibiotic for patients with drug-resistant infections

At least two million people become infected with drug-resistant bacteria in the United States annually. At least 23,000 die as a result. Many more lose their lives to conditions complicated by the infections.[5] Antibiotic resistance is on the rise, and there is a low rate of new antibiotic approvals.[6]

Zerbaxa (ceftolozane/tazobactam) is a novel antibiotic for diverse populations with varying demographics, renal function and complicated infections. Biosimulation (model-based analyses) incorporated clinical data to support go/no-go decisions, to improve understanding of drug exposure in these diverse populations and to anticipate and address regulatory concerns for the drug's expedited review and approval.

Zerbaxa's toxicokinetic profile was characterized from preclinical data. In Phase 1 trials, the PK profile of ceftolozane and tazobactam (TAZ) was assessed in healthy volunteers given each drug alone and together.[7] PK analysis showed that ceftolozane clearance was similar whether the drug was administered alone or with TAZ. This suggested that TAZ did not affect ceftolozane clearance.

Based on Phase 1 and 2 study data, a population PK model was created for Zerbaxa in healthy adults and for patients with renal impairment and complicated bacterial infections.[8] The population PK models helped predict the probability of attaining target drug exposures in populations with varying demographics, renal function and infection status. The results also indicated that Zerbaxa could be an alternative to the current treatments for complicated urinary tract infections (cUTI) in patients with renal impairment, especially for drug-resistant infections.

As a treatment for serious or life-threatening infections, Zerbaxa was eligible for Qualified Infectious Disease Product (QIDP) status. This status also qualifies Zerbaxa for five extra years of market exclusivity. The FDA granted it priority review under the Generating Antibiotic Incentives Now (GAIN) title of the FDA Safety and Innovation Act.[9] In December 2014, the FDA approved Zerbaxa to treat adults with cUTI, including kidney infection.

Conclusion

The above examples support the ethical case for using biosimulation in drug development. This is especially true for research involving special populations. FDA pediatric ethicist Robert Nelson opined that "We have evolved a view that we must protect children from research to a view that we must protect children through research,"[10] and also "It is no longer acceptable to treat children or other special populations as 'therapeutic orphans.'"

The principle of scientific necessity is a fundamental tenet of bioethics. It states that clinical trials cannot involve children or other special populations unless there is no other option. Biosimulation is that option. It minimizes or even eliminates the need for clinical trials in special populations while informing the development of new therapies. Using biosimulation is an ethical imperative for the pharmaceutical industry.

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