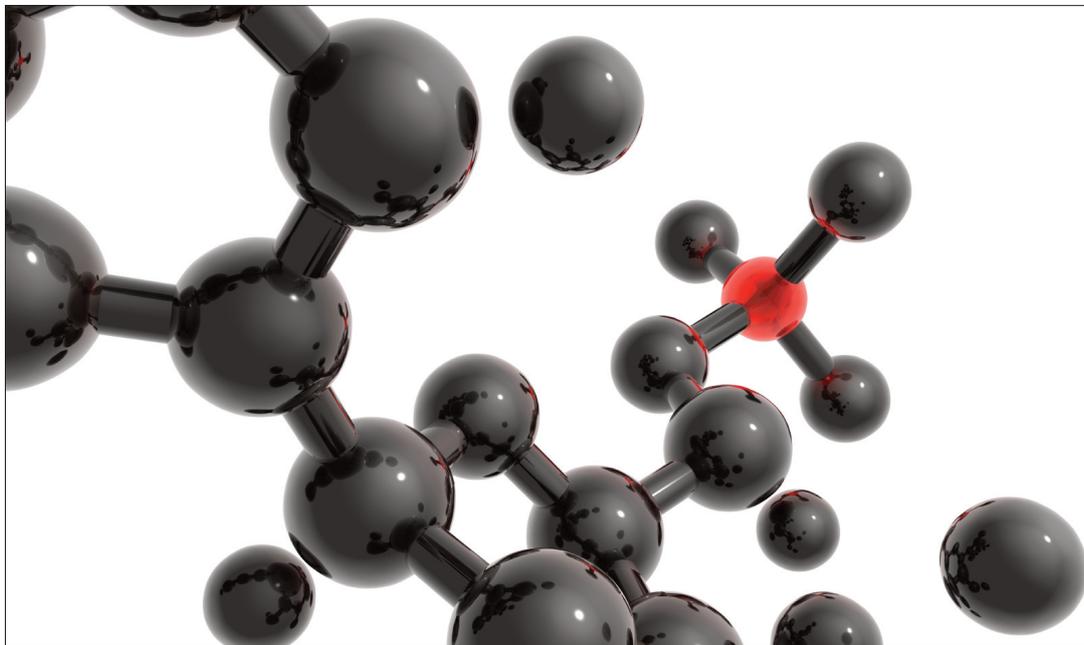


“In situations when pharmacokinetic data may be difficult or impossible to obtain, modelling and simulation will stand alone

Precision dosing takes shape

One size does not fit all, reports Certara's CEO, **Edmundo Muniz**



What do you do when you read a drug label and the dosing information doesn't apply? You have a child in pain and the dose for the analgesic is given for a 2-year-old and a 4-year-old, but she is 3. What do you do? Do you opt for the higher dose or the lower one? And isn't the child's body mass a more relevant metric than her age? Clinicians face similar conundrums on a regular basis.

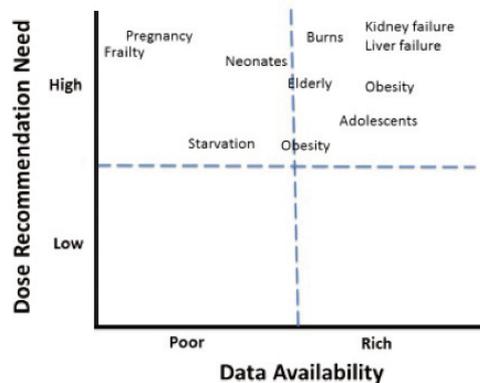
The drug development process includes three phases of clinical trials prior to regulatory approval, each with different goals. During the last phase — Phase III — the drug is given to large groups of people to confirm its effectiveness, monitor any side-effects, compare it with commonly used treatments and collect information that will allow it to be used safely.

Phase III studies involve randomised and blind testing in several hundred to several thousand 'typical' patients. Accordingly, the directions on the drug label are geared to that typical patient population. More complex cases — paediatric and geriatric patients, pregnant women and patients with impaired liver or kidney function — are usually excluded from these trials.

Furthermore, each of these special populations has more complex challenges in determining drug performance. For example, paediatric cases are complicated because absorption rates and enzyme levels change as their bodies mature, whereas geriatric patients are often being treated for multiple conditions simultaneously, making it harder to track the impact of an individual drug.

That said, these specific patient populations could benefit from the drug being tested. If the drug is ultimately approved by a regulatory agency, how does a clinician know what dose to prescribe to a member of one of these untested

Figure 1: Specific population information gaps



patient populations? There is no label information to help, so any prescribing has to be done off-label with the drug dosing based on practice, not science.

Even if the regulatory agency includes a paediatric, geriatric or pregnancy study in the post-marketing requirements, that trial can delay the drug approval by several years or may never get done. In reality, those patient groups often simply do not get the opportunity to benefit from the new therapy. Some of the current knowledge gaps are shown in Figure 1.¹

This is where modelling and simulation comes in. Modelling and simulation combines two transformative technologies: computer-aided mathematical simulation and biological sciences. It uses preclinical and clinical data, together with published industry data, to explain the relationships between drug exposure, drug response and patient outcomes.

For example, Certara's Simcyp Population-based Simulator draws from proprietary information and the company's knowledge of human biology, anatomy, physiology and genetics to create virtual patient populations. It then uses preclinical/clinical data and information about a drug's physiochemistry to create a computer model showing how that drug would be distributed throughout the human body.

Those results can then be used to predict differences in pharmacokinetic and pharmacodynamic response between individuals. Pharmacokinetics describe how a drug moves through the body during absorption, distribution, metabolism and excretion. Pharmacodynamic information looks at the relationship between drug concentration and effect.

In short, the simulator allows drug developers to predict drug performance in 'untestable' patient populations and recommend dosing and prescribing directions.

Noting the unmet needs of the earlier untested populations, Certara has produced models specifically for paediatric, pregnant, obese, hepatic- and renally impaired patients. The company is now working with key opinion leaders from academia, industry and regulatory bodies to determine a framework that would allow dosing guidelines for these special populations to be included in the initial drug label.

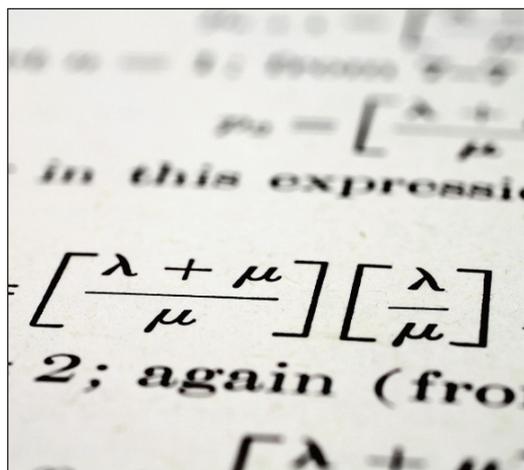
This approach will likely take a 'predict and confirm' format, whereby modelling and simulation is used to demonstrate the expected drug response, which is then confirmed in a much smaller number of patients. This would be particularly useful in rare diseases (including many types of cancer) for which patient numbers are naturally small. In situations when pharmacokinetic data may be difficult to obtain, such as during pregnancy, or impossible in the case of complex comorbidities, modelling and simulation will stand alone.

Adoption by global regulatory agencies

Today, modelling and simulation is being included in most new drug candidate development programmes. Its application is actively encouraged by global regulators such as the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA), which use the resulting data to inform drug labels.

FDA reports: 'Modelling and simulation has served as a useful predictive tool for dose selection for pivotal trials, dosing in select populations such as paediatrics, the optimisation of dose and dosing regimens in a subset patient population, predicting the efficacy and dosing in unstudied patient populations in clinical trials and predicting drug-drug interactions.'

Modelling and simulation insights are now being used by biopharmaceutical companies to inform many drug development decisions. They include go/no-go portfolio and drug decisions, selecting first-in-human, final dose and dosing regimen, comparing drug candidates for safety and efficacy, developing safer, more targeted and efficient clinical trials, determining optimal and



alternative drug formulations, and identifying drug-drug and drug-food interactions.

Future of precision dosing

Although improving dose selection for special populations is an incredibly important step forward, Certara wants to progress this concept further and identify the right dose for individual patients in clinical care. As a result, thought leaders are pioneering precision dosing and helping to ensure that individual patients get the right drug at the right dose at the right time.

Their goal is to determine the drug dose that maximises therapeutic benefit for the patient, while also reducing risk. By employing modelling and simulation, it is possible to account for individual variability in drug reactions. Mathematical modelling and the wealth of genomics and biomarker data that are now available can help to ensure that individual patients get the best possible treatment.

Certara cohosted the first-of-its-kind Health Care Summit on Model-Based Precision Dosing with the University of Manchester in May 2016. Included on the agenda were 15 case studies that demonstrated the successful use of modelling and simulation in the hospital research environment in eight different countries. These examples showed modelling and simulation employed with patients who had experienced heart failure, undergone bariatric surgery or had received a kidney or cell transplant. They also demonstrated its successful use with pregnant women, neonatal and paediatric patients, and those in psychiatric care. There is no doubt that precision dosing will become a mainstream healthcare practice in the near future.

REFERENCE

1. I.R. Younis, *et al.*, 'Utility of Model Based Approaches for Informing Dosing Recommendations in Specific Populations: Report from the Public AAPS Workshop,' *J. Clin. Pharmacol.* doi: 10.1002/jcph.787 (2016).

FOR MORE INFORMATION

Dr Edmundo Muniz, MD, PhD, is Chief Executive Officer at Certara, a leading provider of decision support technology and consulting services to optimise drug development and improve health outcomes (www.certara.com).

Pharmacokinetics describe how a drug moves through the body during absorption, distribution, metabolism and excretion