Taking drug development into the
virtual world

In her series of profiles of bioinformatics companies, Sophia Ktori looks at the work of biosimulation specialist, Certara

Everyone is familiar with the notion of harnessing informatics tools to achieve the truly paperless office, but what about being able to exploit biosimulation and modelling systems to reduce testing in patients during drug development? It may seem a distant prospect, but biosimulation specialist, Certara, is spearheading the drive both to virtualise much of drug development, and to facilitate the optimisation and personalisation of precision medicine at the point of care.

Virtualising drug R&D

While computer-aided modelling and simulation technologies are now mainstream in many areas of industry, including the design of aeroplanes, trains, and automobiles, the use of mathematically based simulation technologies to model, explain, compare, contrast, and analyse biological processes and interventions is far more complex, says Dr Edmundo Muniz, Certara's CEO. 'Nevertheless, the virtualisation of multiple aspects of research and development through the application of *in silico* methodologies and computational and analytical capabilities is a key and significant trend in drug development'. It's a tall order considering that, as Muniz suggests, today, less than 10 per cent of drug R&D, is carried out in silico. 'Yet we are talking about a $150 billion global R&D market, which virtual technologies can feasibly have a huge impact on, significantly reducing drug development timelines, costs, and attrition rates.'

End-to-end *in silico* platforms

Certara offers what it claims is the most comprehensive portfolio of biosimulation software and consultancy services worldwide, spanning discovery, preclinical, clinical, and post-marketing phases of synthetic and biologics drug development. 'Certara software informs key safety and efficacy decisions, identifies, optimises, and validates drug targets, determines optimal

dosing, designs clinical trials, triages compounds, makes comparisons with competitor compounds, and assesses mechanistic drug performance', comments Ellen Leinfuss, chief marketing officer.

Modelling clinical trials design

Using *in silico* approaches to aid the design and optimisation of clinical trials is a major area for Certara's platforms. The firm's model-based meta-analysis (MBMA) platform analyses existing data from in-house and public sources, to help characterise drug class, dose, and response, and so facilitate the design of clinical trials to maximise efficacy, tolerability, and safety. The MBMA platform also allows the comparison of trials, and combination treatments that may not previously have been dosed in parallel in the same trial. 'Using our software, drug developers can model different clinical trial

> ## CERTARA, IS SPEARHEADING THE DRIVE TO VIRTUALISE MUCH OF DRUG DEVELOPMENT

designs to reduce complexity, increase reliability, and optimise outcomes, inform which drugs are likely to fail and, in some instances, replace the need to carry out some human trials – for example, when recruiting subsets of patients will be problematic', Muniz states. 'Our tools can identify the optimal drug dose to achieve the best therapeutic and safety profiles for patient subpopulations, based on genetic profiles, or for subpopulations with co-morbidities, for example. This is really important when you consider that almost 40 per cent of doses selected during drug development are either too high or too low, and can result in unnecessary drug toxicity, reduced efficacy, or drug interactions. Further, the use of biosimulation fulfils an ethical imperative,
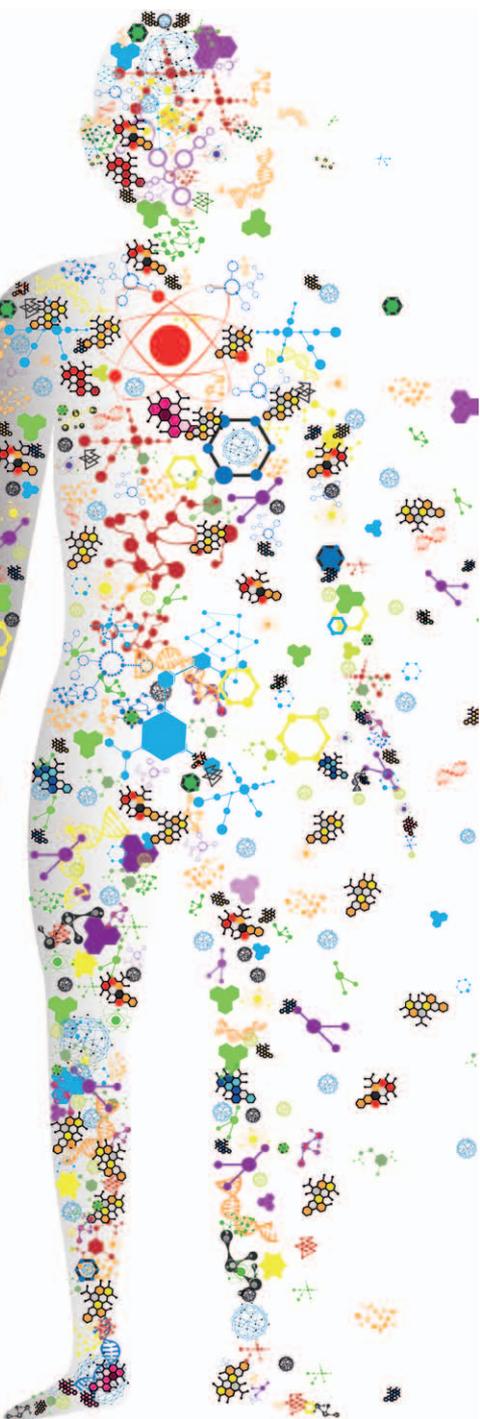
Certara provides end-to-end modelling and simulation to inform decisions on safety and efficacy of potential drugs using virtual populations

➤ especially for patient populations such as paediatrics, and in oncology'.

Optimised patient care
Certara's simulation and modelling solutions are also being used at the point of care, to instruct and inform clinicians as to the optimum dosing schedule for individual patients, and so help to improve treatment efficacy and reduce toxicity, unwanted side effects and drug-drug interactions. 'This is something that none of our competitors are doing, yet the utilisation of *in silico* technologies to direct and inform precision medicine – not just at the level of subsets of patients, but for each individual patient – is

❝ CERTARA'S SIMULATION AND MODELLING SOLUTIONS ARE ALSO BEING USED AT THE POINT OF CARE ❞

another significant trend that we believe will influence patient care globally over coming years,' Muniz stresses. 'Biosimulation and modelling could have huge benefits for the global patient care market, especially when you consider the capacity for such technologies to take the guesswork out of prescribing. Yet today, just about zero patient care is currently carried out *in silico*'.

Certara has partnerships with some 1,200 commercial clients, including all the top-tier pharmaceutical companies, the majority of second-tier, 250 academic institutions, and the world's leading regulatory agencies, including the US FDA, the European Medicines Agency, and the Japanese and Chinese regulators. Global regulatory agencies represent major users of Certara's software, Muniz notes. 'They use our software to confirm simulations that companies have already carried out on their drug candidates, or to apply modelling techniques to investigate additional attributes of a drug, and to enhance the level of understanding about drug behaviour in the human body. Regulators also use Certara's modelling and simulation platforms to explore the potential effects of drugs in patient populations for which real world trials may not be feasible, such as neonates or groups of patients with multiple diseases. And they also use our mathematical and computational capabilities to analyse huge datasets.'

Biosimulation informs drug labelling
Drug labelling is a key area that the regulatory agencies are intimately involved with, and in which biosimulation is now increasingly starting to inform drug claims, Muniz says. 'The drug

label is effectively the manual for that therapy, and each claim on that label will directly impact on drug utility at the front end, and thus on profitability. The label is the ultimate result of possibly 10 to 15 years of R&D and billions of dollars of investment. The ability of modern simulation to shape and optimise the final drug label is hugely important.' Certara has been working with companies and with the regulatory agencies to demonstrate the utility of modelling and simulation, using mechanistic modelling and pharmacokinetic-pharmacodynamic modelling, in the derivation of labelling claims. 'It is over the last couple of years that biosimulation has started to have a major impact on label claims,' Muniz suggests. 'FDA's acceptance of physiologically-based pharmacokinetic modelling and simulation has to date led to Certara's software playing a key role in the final wording of some 20 new drug labels. To date, our modelling software has directly informed 80 to 100 statements on drug labels related to safety and dosing.'

Certara works in close collaboration with its clients, to ensure optimum utilisation of its software, backed by its consultancy services. 'Every transaction implies the utilisation of our software and an ongoing partnership around our consultancy expertise. We do not see ourselves as selling software and services. We act as a strategic partner for our clients, and our products help to inform, optimise and verify the most crucial decisions in drug discovery, development and, ultimately, utilisation in the patient. As we believe we are the only company that can provide end-to-end modelling and simulation services, it is important that we collaborate with our partners very early on in the discovery process, and then work closely with them right through to post marketing all the way to the point of care.'

Strategic acquisitions
Established in 2008 through the merger of drug discovery informatics firm, Tripos International, with Pharsight, which specialises in software, strategic and regulatory services for optimising clinical development, Certara has since made a number of acquisitions in the field of modelling and simulation. In 2012 the firm took over Simcyp, which offers a modelling and simulation platform for predicting the fate of drugs in virtual populations. The following year Certara acquired drug development and management consultancy, Great Lakes Drug Development, and in 2014, Certara expanded its regulatory writing and submission capabilities by acquiring Synchrogenix. Then, in January

2015, Synchrogenix acquired ClinGenuity, the only artificial intelligence-assisted medical writing service in the pharmaceutical industry. Most recently, in December 2015, it acquired XenologiQ, a UK-based quantitative systems pharmacology consultancy. The XenologiQ acquisition followed on from Certara's creation, in July 2015, of a global strategic modelling and simulation consultancy, through the merger of its consulting group, Pharsight Consulting Services, with Quantitative Solutions, an international pharmacometrics consulting company.

In the area of pharmacometrics, the company offers the Phoenix platform, which includes WinNonlin for pharmacokinetic/pharmacodynamic (PK/PD) and non-compartmental analysis; NLME for population PK modelling; Connect for data import/export and reporting; the IVIVC toolkit; and the Phoenix Knowledgebase Server, a 21CFR-compliant database and repository. 'Phoenix is used by 1,200 biopharmaceutical companies, 250 academic institutions, and major regulatory agencies,' Leinfuss adds.

Small molecules and biologics
In the rapidly growing discipline of physiologically-based pharmacokinetics (PBPK), Certara's Simcyp simulator for both small molecules and biologics is supported by a unique consortium, which the firm claims includes the majority of leading pharmaceutical companies, key academic institutions and regulatory bodies. Through its XenologiQ purchase, Certara now also provides quantitative systems pharmacology technology, which is used for lead optimisation. The firm's portfolio also includes the Sybyl and Muse Invent software for molecular modelling, and its informatics platform, D360, which facilitates scientific data access, analysis and collaboration across and between departments and researchers within an organisation, and development partners.

'We have transformed a set of complementary, yet fragmented technologies and expertise offered by disparate companies, into an integrated, consolidated and synergistic set of modelling and simulation disciplines. This can model biological processes to facilitate decision making at every stage of drug discovery and development, from target validation, drug discovery and lead optimisation, to preclinical and clinical development,' Muniz concludes. ●