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Three Questions

Piet van der Graaf, Certara

CW Weekly presents this feature as a way to put the spotlight on issues faced by executives in the clinical trial space. Staff writer Ron Rosenberg interviewed Piet van der Graaf, Pharm.D., Ph.D., vice president of quantitative systems pharmacology at Certara and former director of XenologiQ, a QSP consultancy.

Q With Certara's acquisition of XenologiQ for its quantitative systems pharmacology (QSP), please explain this emerging biosimulation technology and how it supports the company's precision medicine vision?

A Quantitative systems pharmacology (QSP) is a relatively new discipline with the potential to have a very significant impact on pharma productivity and R&D.

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Piet van der Graaf, vice president of QSP, Certara

The biggest pharma challenge—and opportunity for biosimulation—is to tackle phase II attrition. Phase II is the milestone in pharmaceutical R&D where new medicines get tested for the first time in patients. It's also the point where we see a lot of failure: approximately 80% of the novel entities that move into phase II fail, often because the new molecule doesn't show any efficacy.

There are three pillars that form the basis for a successful phase II trial. Pillar I is target exposure, or exposure of the drug at the site of action. That area is well-understood, using physiologically based pharmacokinetic (PBPK) modeling and simulation. Pillar II is target binding—the drug needs to do that in the right way. Pillar III is target expression—the drug needs to activate or stop a particular pathway. QSP is taking biosimulation from a pillar I concept to a pillar II and III one.

We are expanding the PBPK models that Certara's Simcyp division has developed and creating models that predict pharmacological effects—the efficacy that will modulate a particular disease or, equally importantly, the safety and the toxicology effects that we don't want.

QSP can give companies more confidence to invest heavily in a particular program and take it to phase II or make the decision not to. It enables them to make a better-informed decision years earlier, saving dollars and resources. Furthermore, a lot of phase II failures may not be due to the companies picking the wrong target, but rather the wrong dose or dosing frequency, or perhaps they should have considered a combination therapy instead of a single-target therapy. Those elements can be brought out by QSP years before the pivotal phase II trial, allowing the company to change their phase II strategy and alter the trial design or patient population.

Q Please explain how QSP has evolved to where it integrates quantitative drug data with knowledge of the drug's mechanism of action. What are some of the challenges with QSP and who is using this technology now?

A QSP focuses on the area between PK and systems biology; it translates PK or exposure into pharmacological effect.

PBPK answers pillar I questions like, "If someone takes a drug, how much of it will actually reach the organ of interest?" It also examines whether that drug level will be the same in elderly and pediatric subjects, or in patients and healthy volunteers.

We are building on that knowledge with QSP and asking, "Okay, once we know how much drug there actually is in the site of action, what will it do? What pharmacological effects will it have in that particular organ?" QSP allows us to extend our knowledge around drug impact to individuals versus patient groups, moving us toward the goal of precision medicine.

QSP has gained significant interest and traction in the pharma industry because people see it as an opportunity to really utilize the tremendous amount of data that is now being generated from genomics, proteomics and metabolomics [sometimes referred to as the systematic study of the unique chemical fingerprints that specific cellular processes leave behind]. QSP models and biosimulation tools will really help us integrate all that new data into pharma R&D to discover novel medicines.

When we surveyed the Simcyp Consortium—which includes the majority of the top-40 pharma companies—most of the members interviewed indicated that not only did they have an active interest in QSP, but they had investments in terms of dollars and resources in it.

About one year ago, the U.S. Food and Drug Administration (FDA) published on its website for the first time its use of a QSP model. FDA used a bone model to evaluate the dosing regimen proposed in the biologics license application for NATPARA, a recombinant human parathyroid hormone, being reviewed for the treatment of hypoparathyroidism. As a result, the FDA proposed a different dosing regimen than the one suggested by the sponsor in its filing.

Q Which complex disease areas does evaluations with QSP benefit the most?

A In principle, QSP can be applied to any disease or any area of safety or toxicity effects. However, there are four areas where QSP approaches can be applied immediately and with the greatest impact. They are: oncology and, in particular, immuno-oncology; immunology and indications like arthritis; cardiovascular and metabolic diseases like diabetes; and CNS indications such as Alzheimer's disease, schizophrenia and Parkinson's disease.