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Quantitative Systems Pharmacology Brings Value To Drug Development

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Quantitative systems pharmacology (QSP) sits at the interface between pharmaco-metric modeling and simulation, and systems biology. It uses mathematics to describe biological processes. While pharmacokinetics describes what the body does to the drug, pharmacodynamics quantifies what the drug does to the body; the pharmacological response. QSP is a mechanistic modeling approach and an emerging technology, which mathematically integrates pharmacokinetics, pharmacological response and disease progress/modulation.

An understanding of the underlying mechanisms that determine pharmacological response, facilitates the development of mathematical models that can be used to predict likely outcomes in as yet experimentally unexplored scenarios. For example, if you have a mechanistic model describing a particular form of cancer, you can explore likely drug combinations that may have the best chance of modulating or stopping that disease, prior to performing clinical trials. You may also gain a quantitative understanding of how that cancer may manifest in patients with other diseases or of different gender or ethnicity.

Mechanistic modeling enables you to study "what-if" scenarios and ask questions that are difficult to study experimentally. For example, you can use modeling to assess what would happen if a specific disease were to occur in patients with renal or hepatic impairment or with multiple health issues. QSP modeling can be used throughout the drug development process from discovery through to clinical development.

Great Potential Leads To Early Adoption

QSP is a relatively new discipline but has enormous potential to improve pharma R&D productivity and most major pharma organizations are investing in it. QSP may also be able to take advantage of the enormous amounts of data we now have access to including those arising out of the genomics and proteomics arena.

When Simcyp Consortium member organizations were surveyed last year, the majority (60 percent) of respondents had built (40 percent), or were in the process of building (20 percent), IT infrastructure for QSP modeling and simulation. Furthermore, 52 percent of them already had dedicated QSP modelers. The majority of the top-40 pharma companies (including all of the top 10) are members of the Simcyp Consortium.

QSP can be used from the early stages of discovery onwards, helping identify biological pathways and determinants of disease. You can ask questions such as: "Does drug A or drug B have a better pharmacological profile?" If you determine that drug A has a stronger impact on biological path Y than biological path Z, is that going to be more effective than drug B which has a stronger effect on biological path Z than Y?

QSP modeling allows investigation of a wide range of what-if scenarios to determine what the likely efficacy of the drug is going to be, without having to do clinical investigation and facilitating lead optimization very early on in the discovery process.

Later down the development line, you can use QSP to evaluate the most likely effective dose of a medicine in different patient populations. It enables you to optimize clinical trial study designs by getting an initial understanding *in silico* of the dose that will likely be required in patients. This is a much safer and more efficient approach than the traditional method of conducting a dose ranging or dose escalation study to identify experimentally what the optimum dose will be. QSP will enable sponsors to remove a lot of the costly serendipity from the drug development process.

From an ethical point of view, QSP will lead to less speculative research within the patient population, allowing sponsors to make sure, as best they can, that patients who participate in Phase II or Phase III studies benefit from their participation. Historically, they knew that some of the patients that participated in these studies were going to receive drug doses that were ineffective or could result in an adverse experience.

Predicting The Effect

While pharmacokinetic analysis tells a sponsor how much drug will reach its site of action, QSP offers insight into what the drug will do when it gets there. The drug could produce a beneficial effect and prove to be an efficacious product or create a toxic effect and generate adverse events in patients.

As a result, QSP holds great promise in helping pharma companies overcome the major challenge of Phase II attrition. Phase II trials mark the point at which new drugs are tested in patients for the first time and the stage at which about 80 percent of the novel entities being tested fail.

QSP has the potential to help identify drugs that are likely to fail earlier in the development process, thus saving substantial revenue and staff time.

Furthermore, in some cases, the Phase II failure may not be due to the company picking the wrong target. They could have chosen the wrong dose or dosing frequency or perhaps should have considered a combination therapy. QSP can be used to explore those elements in advance of the design and execution of the pivotal Phase II trial.

In terms of therapeutic areas, it is likely that QSP will have the greatest impact in those areas that present the greatest challenges to study via clinical experimentation such as oncology, immunology, metabolic diseases and some of the neurological illnesses.

A combined effort by pharma, academia and the regulatory agencies will be required for QSP to be fully adopted and reach its full potential. But that process is already underway with the regulatory community already recognizing the potential benefits of QSP modeling.

About one year ago, FDA published its use of a QSP model on its website for the first time. FDA used a QSP bone model when reviewing the biologics license application for NATPARA, a recombinant human parathyroid hormone, being evaluated for the treatment of hypoparathyroidism. As a result, FDA proposed a different dosing regimen from the one suggested by the sponsor.

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