Benefits & Uses of QSP in Drug Development

Quantitative systems pharmacology (QSP) is an exciting and powerful convergence of biological pathways, pharmacology, and mathematical models for drug development. QSP has the potential for delivering significant impact to modern medicine through the discovery and utilization of new molecular pathways and drug targets in the pursuit of novel therapeutics and individualized medicine.

Individually, the concepts and components of QSP (studies of biology and drugs) are not new. However, merging these disciplines is generating considerable interest in the pharmaceutical industry to maximize predictions from a pharmacodynamic (PD) perspective and with the use of advancements in computing power, QSP is now able to improve outcomes in drug development.

Many drug candidates fail in Phase 1 due to poor pharmacokinetic (PK) properties or fail in Phase 2 due to less than expected efficacy. QSP offers the ability to evaluate critical aspects related to the efficacy of a drug candidate and provide a 'road map' to designing Phase 2 clinical studies to potentially improve outcomes. Ideally, QSP would be applied throughout the drug development process, from preclinical through clinical development, to harness it's true power and capacity.

What is Quantitative Systems Pharmacology?

QSP is a computational model that examines the interface between discrete experimental data (i.e., studies of the drug/compound) and the "system." The "system" can be any biological process related to the disease such as the physiological consequences of a disease, a specific disease pathway (e.g., signal transduction or up/down regulation of a pathway, increased heart rate), or any of the "omics" (i.e., genomics, proteomics, metabolomics).

Tapping into the "omics" generates substantial opportunity to learn from big data systems by looking for intersecting themes. While "omics" data are not likely to lead to definitive directions during drug development on their own, their coupling with QSP can result in powerful insights that decrease uncertainty at key decision points in the development process. QSP can help guide appropriate study design or suggest what additional experiments might be needed to make more informed choices. Similarly, QSP can greatly reduce missteps that might prolong the drug development process or even result in an unnecessary failure.

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For example, one way that utilizing big data in QSP can glean powerful insights into drug development is by integrating regulative and metabolic biological pathways with novel drug compound mechanisms to accelerate the pace of innovation with the identification of overlapping moieties. These insights can aid in exploiting possible additive or synergistic effects, planning around potential set-backs and redesigning experimental direction at critical times during early stages of the drug development process to help thwart unnecessary failures.

As previously unknown and intersecting disease pathways are discovered, QSP can be leveraged to identify new targets, verify current targets, understand potential adverse effects of novel pathways, and repurpose existing drugs to new targets. QSP has built on the insights gained in developing physiological based pharmacokinetic (PBPK) models (ex. blood flow rates, organ volumes, transporter expression, etc.) and has truly taken the power of understanding drug action to a new level.

Quantitative Systems Pharmacology vs. PBPK

QSP and PBPK are similar in that both systems are developed with a "bottom-up" approach. However, the difference between QSP and PBPK is that PBPK predicts PK outcomes in patients populations, whereas QSP predicts PD and clinical efficacy outcomes in patient populations. QSP uses biological systems of the therapeutic target for PD outcomes (i.e. predicting heart-rate changes, muscle growth rate, etc.). This is especially important for decision making based on scaling PD outcome from animal models to humans and recommending clinical doses in trials.

When to use Quantitative Systems Pharmacology

QSP can be employed at all stages of drug development (preclinical to Phase 3). Given the amount of experimental data generated for diseases, genetics, drug binding, metabolism, polymorphisms, biological pathways, inter-relationships between systems, information from big data, and more, coupled with the availability of necessary computational power, QSP is primed to change the landscape of drug development.

Key factors to consider that can be explored with QSP:

- **Mechanism of Action** – new and old drugs, possible repurposing
- **Simplifying Pathways** – distinguishing between relevant and irrelevant pathways in complex biological systems
- **Important Determinants of Exposure** – pharmacogenomics (rapid/normal or reduced metabolizer of various drug-metabolizing enzymes; transporter expression); drug-drug and drug-gene interactions
- **Efficacy** – define interspecies differences in the expression levels and characteristics of biological targets leading to improved translational understanding of PK/PD responses across species, for better prediction of clinical outcomes from preclinical models
- **Comorbidity** – impact and implications on the PD response such as liver disease, kidney disease, heart failure, gastrointestinal variations, etc.
- **Special Populations** – forecasting results of perturbations to the system (such as in pediatrics where receptor expression or endogenous pathways may still be developing relative to adult populations) in a population of in silico patients – verifying actions of responses to novel targets and therapeutic agents
- **Dosing Regimen** – choosing doses, rational selection of combination therapies, and dose frequency for different patient populations

Examples of When to Use QSP

1. PREDICTING DRUG RESPONSE

One major use of QSP is to forecast drug responses resulting from perturbations in the system in populations of in silico patients before running clinical trials. For example, perturbations might include deteriorating liver function or the biological effects of pregnancy. Responses to these pertubations might include alterations in drug metabolizing enzyme expression or receptor occupancy needed for therapeutic effect, causing possible alterations in outcomes on clinical trial endpoints.

This can be proactively analyzed using computer models to predict PD responses and verify predictions in animal models of disease to predict outcomes in healthy volunteers and other patient populations. Confirmation of clincial responses to biomarkers in healthy volunteers further improves predictions and study design for Phase II trials, in special populations or in selecting appropriate target populations.

2. INTEGRATIVE MODELS

QSP has also been shown to be useful in intergrative drug-disease models within academia, the pharmaceutical industry, and the FDA for disease areas such as oncology, metabolic disorders, neuro, cardio, pulmonary, and auto-immune diseases, to name a few. The scope and application of QSP, specifically within oncology ranges from combination regimens, immunotherapy and exploring specific pathways such as VEGFR, ERK, PD-(L)1, MEK, AKT, BRAF and others.

3. EFFICACY & SAFETY

Another capability of QSP is to highlight efficacy and safety concerns through the interactive evolution of a QSP model. This has been used to predict cardiovascular effects using blood pressure and heart rate, identify peripheral resistance, predict hERG mediated Qtc prolongation, linking biomarkers to cell injury and renal dysfunction, or explaining drug-induced liver injury and how to avoid it.

Benefits of QSP for Drug Development

QSP can save valuable resources during drug development, and importantly, reduce the time to getting therapies to the patients in need. QSP can facilitate the decision-making process in order to get the right drug, to the right patient, for the right disease, at the right time, and in the right dose.

In programs where the first clinical study will be in a patient population such as in a rare disease or in cell and gene therapies, the need to predict a therapeutic dose for the first in human dose is crucial. QSP offers the ability to help make these critical and ethical decisions with more confidence. Having an early understanding of what QSP can provide can guide the design of therapeutics from the very beginning of the drug discovery process.

Conclusions

QSP can help guide critical choices for valuable resources by providing important and timely pieces of knowledge. With QSP we now have the ability to predict how a patient might respond or provide further therapeutic understanding that was previously unknown which is extremely valuable throughout the entire drug development process.

QSP is becoming an increasingly powerful component of drug development. The power of combining experimental, biological, and physiochemical data for model-informed decision making is just beginning to be harnessed. Others are surely to follow as our knowledge and understanding of the potential of QSP continues to develop. Contact us to learn more about Nuventra's QSP experience and services.

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