



Common Misconceptions About QSP Modeling

As [Quantitative Systems Pharmacology \(QSP\) modeling](#) is a relatively new field, there are some common misconceptions that have been brought to our attention. We would like to dispel or provide clarification on some of the misconceptions associated with QSP modeling by diving deeper into these seven common myths:

1. QSP modeling always requires a lot of data
2. QSP model construction is always time consuming and expensive
3. QSP models provide the same information as population PK/PD models
4. QSP modeling is not accepted by the FDA
5. QSP models can only be built in early or late stages of drug development
6. QSP models cannot be built if there are unknowns about the compound or its mechanism of action
7. QSP models are only good for determining biomarkers or understanding the mechanism of action of a drug

Myth #1:

QSP Modeling Always Requires a Lot of Data

Creating a QSP model from the ground up does require a good deal of data because you must adequately inform the various parameters of the model. However, not all QSP models need to be built completely from scratch.

FACT

Depending on your program's needs, it might not be necessary to create a brand-new model. There are pre-existing models for specific systems such as renal function, bone metabolism, cardiac action potential, and more. Depending on the desired output of the model, you may be able to use a pre-constructed model. If that is the case, then typically the data requirements are greatly reduced. To use a pre-existing QSP model, you will still need data for the PK of the compound as well as data related to the mechanism of action or potential biomarkers.

Myth #2: QSP Model Construction is Always Time Consuming and Expensive

Similar to the previous myth, QSP model construction is typically only time consuming and expensive if a pre-existing model cannot be found in the literature and you must build the model from scratch.

FACT

If a QSP model that can sufficiently describe the mechanism of action already exists, then the time and costs associated with building the model are significantly reduced. To see this method in action, see our blog, "[Cost-Effective Techniques for Creating QSP Models](#)," which explains how to use existing research and literature sources to successfully create a QSP model.

Myth #3 QSP Models Provide the Same Information as Population PK/PD Models

[Population PK/PD \(popPK/PD\)](#) modeling is a great tool for understanding the variability in the pharmacokinetic profile of a compound based on covariates such as age, weight, and creatinine clearance. PopPK/PD models are useful for evaluating the relationship between plasma concentrations on PK parameters and pharmacodynamic effects or efficacy using empiric or semi-mechanistic models. QSP models, on the other hand, work differently.

FACT

QSP models describe the relationship between concentrations of the drug at the site of action (not necessarily the plasma) and the resulting pharmacodynamic effects of the compound based on a presumed mechanism of action. In this way, QSP models can take into account the fact that the drug effect is related to multiple sequential processes that may be influenced by endogenous substrates and by feedback mechanisms.

For example, a popPK/PD model may be useful for explaining how one drug for diabetes will reduce glucose levels and hemoglobin A1C. However, a QSP model can use the same data to describe what happens to glucose and hemoglobin A1C when subjects receive multiple diabetes drugs with different mechanisms of action administered together.

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Myth #4: QSP Modeling is Not Accepted by the FDA

Since QSP is a new modeling area there are fewer examples of its use in FDA submissions when compared to a more established modeling technique such as popPK/PD.

FACT

Even though QSP modeling is a relatively new field, it has been used to support [NDA](#), [BLA](#), and [IND](#) submissions. In fact, a 2019 publication by [Zineh et al.](#) documents that QSP model submissions to the FDA have been increasing over the years. There are several QSP models that have been used in NDA submissions testing interventions in silico rather than in clinical trials. For example, the [Peterson and Riggs bone and calcium homeostasis QSP model](#) was used to evaluate the dosing regimen of a new drug in a 2014 FDA submission.

Myth #5: QSP Models can Only be Built in Early or Late Stages of Drug Development

Although it is ideal for a QSP model to be constructed during the early stages of drug development, it can be useful during all stages of preclinical and clinical drug development.

FACT

There is no time constraint on how early or late you can start developing a QSP model. As new data is gathered, the model can be updated to reflect the extent of knowledge at that point in time. The applications for QSP models may change as the drug proceeds through the development pipeline.

Early in drug development, a QSP model can be useful to identify drug targets or choose between drug candidates. During the preclinical and clinical stage, a QSP model can be used for determining study design, understanding the mechanism of action, or evaluating the best collection of biomarkers. Later in drug development, QSP models can be used to evaluate different subpopulations or concomitant medications without having to conduct a clinical trial.

Myth #6: QSP Models Cannot be Built if There are Unknowns About the Compound or its Mechanism of Action

There is never a time during drug development or post-approval when there are not unknown questions about a compound because for each question answered within a study, more questions can arise. While it is ideal to have a general idea of the drug's mechanism of action or other properties such as interacting enzymes, this is not a limiting factor to creating a QSP model.

FACT

Conducting a literature search of previously published sources for similar compounds or working with expert consultants to fill in the gaps can allow for QSP models to be built even when there are knowledge gaps about the compound or mechanism of action.

The benefit of using a QSP model is that it is possible to hypothesize a mechanism of action and check the results against data that the Sponsor may have. You can then easily change the model to test different hypotheses. QSP models are also useful to characterize poorly understood biological mechanisms. These models can be built in tandem with in vitro experiments and in vivo preclinical and clinical studies, thereby allowing optimal use of the growing information during drug development programs.

Myth #7: A QSP Model is Only Good for Determining Biomarkers or Understanding the Mechanism of Action of a Drug

QSP models can be quite versatile. Biomarker determination and understanding the mechanism of action of a drug are two major reasons to create a QSP model, but these are by no means the only questions that can be answered with this type of model.

FACT

QSP models can be used for hypothesis testing, animal-human translation, or understanding how a drug can be used within a subpopulation or with other drugs to optimize efficacy and safety through clinical trial simulations. QSP models are highly customizable to

allow for understandable outputs that can be used by scientists and management to help in decision making during drug development.

Conclusions

There are many misconceptions surrounding QSP modeling and how it can be used to answer drug development questions. QSP models are extremely versatile and can be useful at any stage of drug development. The time, money, and data required for QSP model construction does not have to be exorbitant if an existing model can be repurposed from the literature. QSP models are typically only expensive and time consuming if you are building the model from scratch.

QSP models can incorporate evolving nonclinical and clinical data to better inform development decisions such as identifying novel indications, understanding how a drug can be used within a subpopulation or with other drugs, and evaluating a drug's potential to have a clinically meaningful impact for patients.

Nuventra's consultants have many years of experience designing quantitative and translational pharmacology strategies for clients. [Contact us](#) to learn more about [Nuventra's QSP experience and services](#).