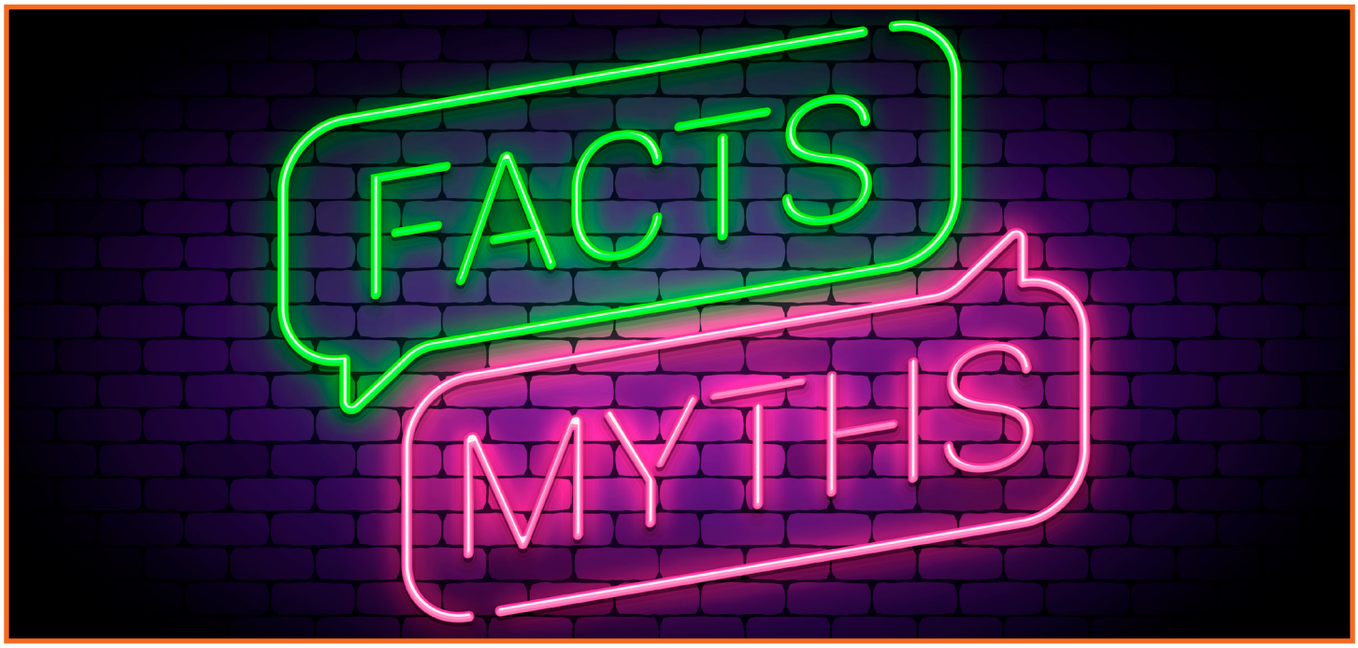

Common Misconceptions About PBPK Modeling

As Physiologically Based Pharmacokinetic (PBPK) modeling becomes more widely used in regulatory submissions, there are some common misconceptions that have been brought to our attention. We would like to dispel or provide clarification on some misconceptions associated with PBPK modeling by diving deeper into these six common myths:

1. PBPK models have limited applications in drug development
2. PBPK models have large and unique data needs
3. PBPK models provide the same information as population PK models
4. PBPK models require clinical data from all relevant populations to make predictions
5. PBPK models can only be used to describe drug PK
6. PBPK models must always be very detailed to be predictive

Myth #1: PBPK Models Have Limited Applications in Drug Development

One common misconception about PBPK models is that they can only be used to address a small subset of drug development questions. While each PBPK model needs to be calibrated to the specific drug under consideration, the applications of PBPK models are numerous.

FACT

PBPK models can be continuously updated based on available data. For any given drug, PBPK models can be developed as early as the pre-IND stage of drug development and can be used for estimating First-in-Human (FIH) doses in Phase 1 studies. The same models can then be updated and used throughout the drug development process for a variety of applications, such as evaluating drug-drug interaction (DDI) potential, estimating doses in pediatric patients, estimating the effect of food on drug absorption, and more.

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Myth #2:
PBPK Models Have Large and Unique Data Needs

While PBPK models have more parameters than other PK modeling techniques, PBPK modeling tools (such as PK-Sim) already contain databases of information and models for estimating most PBPK parameters. These databases greatly reduce the need for new data to be collected before implementing a PBPK model.

FACT

The data required for PBPK modeling can differ based on the reason for which the model needs to be created. In most cases, however, the drug-specific data needed for the model has already been collected as a part of earlier drug development efforts. Similarly, unlike other PK modeling modalities, PBPK modeling does not need extensive clinical concentration-time profiles.

In fact, PBPK models can even be built using non-clinical concentration-time profiles and then extrapolated to humans for estimating a FIH dose. Similarly, species-specific physiological data and quantitative structure-activity relationship models (QSAR) can be readily obtained from published literature. Software tools such as PK-Sim contain collated databases from these sources. This further reduces the amount of data needed for creating drug-specific and species-specific PBPK models.

Myth #3:
PBPK Models Provide the Same Information as Population PK Models

In some sense, PBPK models can be viewed as more descriptive versions of population PK (popPK) models. Both models utilize mathematical descriptors to predict drug distribution parameters. PopPK models are useful for identifying the clinically relevant sources of variance from a drug PK profile in multiple subjects. PBPK modeling can be used to simulate drug concentration in specific tissues and the impact of physiologic differences on these tissue specific concentrations.

FACT

PopPK models describe drug distribution by dividing the body into hypothetical central and peripheral compartments. PBPK models, on the other hand, are made up of compartments that incorporate the physiology of actual tissues within the body. This enables PBPK models to be used for determining exposure to tissues outside of systemic circulation. The added physiologic details enable the model to predict tissue specific clearance and absorption mechanisms.

The effects of age, disease state, and genetic backgrounds can then be incorporated in the model to get an accurate picture of drug disposition for different populations. Similarly, some applications such as estimating target tissue concentrations or evaluating the impact of non-oral or non-IV dosing routes on drug PK can be much more readily investigated using PBPK modeling. Overall, PBPK models are more detailed than popPK models, but are also applicable to more scenarios while requiring less scenario-specific data.

Myth #4:
PBPK Models Require Clinical Data from all Relevant Populations to Make Predictions

Many common modeling techniques rely heavily on having population-specific clinical data to make predictions. This is not always necessary when utilizing a PBPK model.

FACT

Other PK modeling approaches assume that most biological variability is encompassed in the concentration-time profiles collected during clinical studies and then use these data to make predictions surrounding the drug PK. PBPK modeling utilizes a bottom-up approach for model development. This means that all the physiological details of any given population are incorporated in the model, and then the model is simulated to predict concentration-time profiles. Therefore, PBPK models can, in direct contrast to other modeling techniques, simulate drug PK in populations where no clinical studies have been conducted.

Due to this bottom-up approach, PBPK models can predict FIH doses from non-clinical PK data or can extrapolate dose to pediatrics (or other sensitive

populations) with a limited amount of clinical PK data. This versatility in PBPK modeling makes it an excellent tool for studying special populations in which data collection can be difficult or not as complete as in healthy populations. Clinical data collected later in the drug development pipeline can easily be incorporated into existing PBPK models further increasing their predictive capacity.

Myth #5: PBPK Models Can Only be Used to Describe Drug PK

PBPK models provide information on drug distribution in different tissues and can, therefore, be used for more than just describing a drug's PK characteristics. Pharmacodynamic models, like Quantitative Systems Pharmacology (QSP) models, simulate drug effect on the target tissue. The two modeling applications are complementary to each other and using them together can often provide distinct advantages in drug development.

FACT

Using PBPK and QSP models in conjunction can provide a stronger modeling portfolio. For example, a PBPK model can be used to predict drug concentrations in a particular tissue which can then be used to inform QSP model parameters to make mechanism-related predictions. Linking QSP and PBPK models in this way can provide more informative parameter values especially when literature information is sparse.

Myth #6: PBPK Models Must Always be Very Detailed to be Predictive

The defining characteristic of a PBPK model is inclusion of physiological rather than empirical parameters to predict drug distribution. Depending on the level of detail incorporated, the models can either be classified as very detailed (whole-body) PBPK models or very minimal PBPK models. Both types can be used for predicting drug PK. The whole body is represented in a detailed PBPK model so that specific and mechanistically driven predictions can be made. However, not all PBPK models must be whole-body.

FACT

PBPK models can either define each major tissue as a separate compartment, resulting in a whole-body PBPK model, or combine multiple tissues with similar volume to blood flow characteristics, resulting in a minimal PBPK model. PBPK models can be further customized solely to have target tissues as separate compartments while all other tissues are lumped into a single compartment. While the amount of data required of a whole-body PBPK model might seem higher, most PBPK modeling tools already incorporate relevant databases to parameterize such models.

The decision to implement a minimal or whole-body PBPK model is driven by the application, the modeling tool of choice, and the amount of available data. Taking these criteria into consideration, Nuventra can customize the PBPK model to fit the program's needs.

Conclusions

Misconceptions surrounding PBPK modeling fall primarily into two categories: 1) that either the data requirement is too large or 2) the applicability is too small. PBPK models can be used throughout a wide range of applications such as DDI predictions, FIH dose selection, and age-based dosing predictions. The data necessary for PBPK modeling is confined mainly to the physicochemical properties of the drug and can be supplemented with non-clinical and clinical PK data as these data become available. The versatility and low data requirements of PBPK modeling make it an ideal tool for any phase of drug development.

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