CERTARA

PKS Online: Seven Steps to Building Value in Early Drug Development

Importance of PK/PD in early drug development

Pharmacokinetics and pharmacodynamics (PK/PD), the study of how drugs reach their active site and the effects they produce, occupy an increasingly important role in drug development. Major effort in early development is directed at measuring, modeling, and summarizing the "concentration vs. time" and "concentration vs. effect" data that define the kinetics and dynamics of a drug.

The Food and Drug Administration (FDA) has a long history of applying advanced quantitative modeling. The FDA's Critical Path Initiative calls for more use of PK/PD modeling and model-based drug development to improve decision-making. The value of models comes from their ability to improve the assessment and prediction of patient response. This permits earlier and less costly failures, and therefore increased probability of success in the market. Late-stage clinical failure

is the biggest reason, by far, for increasing drug development costs. PK/PD modeling is usually performed at the end of phase I or in early phase II, when there is sufficient data with which to build the models.

Powerful Solutions From Certara

- D360 can be applied throughout the drug development process from discovery to pre-clinical to clinical and translational science

Business case for a PK/PD data repository

Understanding the business value of a PK/PD data repository starts with an analysis of the workflow of pharmacokineticists and PK/PD modelers and the expense to build and maintain a repository. The cost of a PK/PD data repository can be particularly overwhelming for small and medium sized companies. There are direct costs—such as for the software itself and deployment costs—but

also indirect costs, which are often forgotten—such as IT and domain support and continuous maintenance and revalidation. Software-as-a-service (SaaS) can offer a perfect way to reduce the total cost of ownership—specifically with a data repository that is accessed through a network.

Certara provides its PK/PD data repository, the Phoenix Knowledgebase Server (PKS), for in-house deployment as well as a service through the PKS Online offering. The following steps are critical to implementing a data repository.

1 Analyze PK/PD data volume

Pharmacokineticists and PK/PD modelers spend about one-third of their time retrieving and preparing data for analysis, one-third of their time conducting analysis, and one-third of their time reporting and checking their results to meet regulatory requirements.

Depending on the size of the development portfolio, a pharmaceutical or biotechnology company may perform a few, a dozen, or even hundreds of drug trials per year that generate time-concentration data. Ultimately, a PK/PD scientist or modeler must retrieve (often with help of a SAS programmer) and analyze the subset of the data that contains clinical pharmacology information related to the drug. Outside contractors may be used in place of internal staff at any stage in the process including protocol writing, study conduct, and lab analysis. Most pharmaceutical and biotechnology companies must deal with multiple data standards that can hinder the preparation of analysis-ready datasets. As a result, in a nonstandard environment, much time is wasted by the pharmacokineticist or PK/PD modeler rearranging and transforming time-concentration datasets that have been constructed in slightly different ways across various studies, projects, and organizations.

2 Set and enforce data standards

In order to improve productivity of data retrieval, an organization must first define where and in what form it wishes to store its data. It is best if standards are adopted for the final, analysis-ready formats for the time-concentration datasets, prior to the conduct of the trials.

3 Store the data in a secure, compliant repository

Once the data are transformed into the desired format, where should the data be stored? The best answer is a PK/PD data repository: a single, secure storage medium where all clinical pharmacology information is maintained in a consistent format and where the audit history and changes are tracked automatically.

PKS Online is integrated with PK analytical tools such as Phoenix WinNonlin, and provides features like automatic change tracking and password control for access that permit an efficient, electronic means of regulatory-compliant PK/PD analyses and reporting. PKS Online is based on the PKS, which has been offered for 12 years and has been installed at pharmaceutical and biotechnology companies around the world.

The value of such a repository goes far beyond the automation of data retrieval. The value includes superior organization, faster availability of data, and analysis results, and better decision-making. Most research and development managers would readily acknowledge that these benefits, though substantial, are difficult to quantify.

4 Automate how data moves into the repository

A key question is how the time-concentration data gets into the PK/PD data repository in the first place. Typically, bioanalytical data reside in a laboratory information management system (LIMS). If the pharmaceutical or biotechnology company has a LIMS, then a connector can be built to take the data from the LIMS to the PK/PD data repository. Ideally, a customized data connector moves data from its source into the repository and performs the necessary transformations to get the data into an analyzable format.

5 Automate PK/PD data analysis

Non-compartmental analysis (NCA) of PK studies generates many standard tables and listings that must be incorporated into reports. The analysis is typically performed in Phoenix WinNonlin, the industry standard for NCA, used by over 80% of pharmacokineticists worldwide.

Because FDA guidance and the state-of-the-art in pharmacology reporting is well regulated, the automated generation of standard tables, listings, and figures (the middle third of the PK workflow) offers an additional opportunity for labor and time savings. For this purpose, Certara offers the AutoPilot Toolkit for Phoenix which is used at 11 major companies in North America, Europe, and Japan.

6 Support distributed model-based drug development

Many companies need strategic support of non-compartmental PK analyses. PK/PD modeling and simulation is an important decision support tool in early clinical development. Many large pharmaceutical companies including Pfizer, Novartis, J&J, Roche, and others have built their own M&S organizations to handle standard modeling assignments. In more complex cases or in situations where the client has not built his own internal capability, M&S vendors may be used.

M&S is a method that takes all information into account. This includes company-generated PK studies as well as analog study data derived from literature and other sources. This comprehensive dataset is analyzed to predict the success of an intended clinical program based on choices of dose, duration, comparator, patient inclusion criteria, and measured clinical outcomes.

Enterprise pharmacology data repository applications such as PKS Online support this broader information archiving need. Without a repository of some kind, significant time can be expended pulling together datasets before M&S can take place. In addition, because PKS Online is accessible anywhere, at anytime, by anyone in an organization, it facilitiates collaboration across departments and with external partners.

7 Move TLFs seamlessly into word to automate reporting

Once a regulatory PK analysis is completed, whether through automated or manual means, results must be pushed into another tool for reporting, usually Microsoft® Word®. From there, the reports are logged into a document repository such as Documentum.

Before regulatory documents are submitted, it is good practice to check them against the current time-concentration datasets to ensure that no changes in the source data have been made and that the reports are still in sync with the raw source data. Phoenix Connect from Certara automates these last two steps, pushing tables, figures, and listings (TLFs) into Word, flagging any reported items that are out of sync with the source data, and permitting rapid "refresh" of reports if necessary to bring the report back into sync with the data.

Summary

Most organizations have a powerful business case for investing in a PK/PD data repository. With online repository solutions such as PKS Online, the total cost of ownership is quite low as many validation and installation chores that accompany traditional behind-the-firewall installations are eliminated. This brings the value at far lower cost: instant, worldwide access, consistent data standards, automation of data retrieval, automation of standard PK analysis (with AutoPilot Toolkit for Phoenix), automated data checking and reporting (with Phoenix Connect), faster, surer decisions, and a truly model-based approach to drug development. Some of the benefits are hard savings, where the expense statement will show improvement. Other benefits are harder to quantify, but significantly contribute to the productivity of early stage development and the health of the drug development enterprise.

About Certara

Certara is a leading provider of decision support technology and consulting services for optimizing drug development and improving health outcomes. Certara's solutions, which span the drug development and patient care lifecycle, help increase the probability of regulatory and commercial success by using the most scientifically advanced modeling and simulation technologies and regulatory strategies. Its clients include hundreds of global biopharmaceutical companies, leading academic institutions and key regulatory agencies.

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