



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

Executive Issue Brief

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Importance of PK/PD in Early Development

Pharmacokinetics and pharmacodynamics (PK/PD) or 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 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 (MBDD) as a critical path opportunity to improve decision-making. The value of models comes from their ability to improve the prediction and assessment of patient response, and therefore probable success in the market. This permits earlier and less costly failure. Late-stage clinical failure is the biggest reason for increasing drug development costs by far. 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.

Business Case for a PK/PD Data Repository

The business need for a PK/PD data repository starts with an analysis of the workflow of pharmacokineticists and PK/PD modelers. Intense regulation of pharmaceutical development imposes a common structure on the workflow for producing regulatory-compliant PK/PD analyses and reports, so most companies use a broadly similar flow.

Step 1: Analyze PK/PD Data Volume

Time studies reported to Pharsight indicate that 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 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. Even if there have been no mergers, most pharmaceutical and biotechnology companies must deal with multiple data standards that can retard 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 data sets that have been constructed in slightly different ways across various studies, projects, and organizations.

Step 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 data sets, prior to the conduct of the trials.

Step 3: Store the Data in a Secure, Compliant Repository

Once the data are transformed into the desired format, where should the data be stored? Many companies are concluding that 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. The PK/PD scientists can then go the repository to collect data stored in a single,

consistent, nonnegotiable format. PKS Online offers tight integration to PK analytical tools such as WinNonlin, and provides tools (automatic recording of changes, password control, and other features) that permit the building of an efficient, electronic means of regulatory-compliant PK/PD analyses and report production. PKS Online shares its user interface and architecture with Pharsight Knowledgebase Server (PKS), which has been offered for 7 years and has been installed at 25 pharmaceutical and biotechnology companies and in the Office of Clinical Pharmacology at FDA.

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

Step 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 the connector will not simply move data from its source into the repository. Connectors can also perform certain transformations to get the data into the desired analyzable format.

Step 5: Automate PK/PD Data Analysis

PK studies usually result in non-compartmental analysis generating many standard tables and listings that must be incorporated into standardized reports. The analysis is typically performed in WinNonlin, the Pharsight industry standard non-compartmental analysis generation engine 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. Pharsight offers WinNonlin AutoPilot for this purpose. WinNonlin AutoPilot is in use at 11 major companies in North America, Europe, and Japan.

Step 6: Support Model-Based Drug Development

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

Modeling and simulation is a formalized methodology that takes all information into account. This includes not just company-generated PK studies but analog study data derived from literature and other sources. This comprehensive data set is analyzed to deliver, for example, explicit probabilities for 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 are increasingly being called upon to 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.

Step 7: Move TLFs Seamlessly into Word to Automate Data Checking

Once a regulatory PK analysis is produced, whether through automated or manual means, it must be pushed across into another work tool, usually a word processor or presentation software such as Microsoft Word. From there the reports will be logged into a document repository such as Documentum.

Finally, before regulatory documents are submitted it is good practice to check them back against the time-concentration data sets to ensure that no changes in the source data have been made or that the reports are still in sync with the raw data. PKS Reporter from Pharsight automates these last two steps, pushing into Word tables, figures, and listings that have been saved back to the data repository, flagging any reported items that are out of synch with the source data, and permitting rapid “refresh” of reports if necessary to bring the report back into sync with the data.

Summary

The seven steps to value creation in early stage drug development offer most organizations 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 benefits at far lower cost: instant, worldwide access, consistent data standards, automation of data retrieval, automation of standard PK analysis (with WinNonlin AutoPilot), automated data checking and reporting (with PKS Reporter), 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 likely significant contributors to the productivity of early stage development and the health of the drug development enterprise.