Choosing the Right Software for PK/PD Analysis
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The methods used to characterize the pharmacokinetics (PK) and pharmacodynamics (PD) of a compound can be inherently complex and sophisticated. PK/PD analysis is a science that requires a mathematical and statistical background, combined with an understanding of biology, pharmacology, and physiology. PK/PD analysis guides critical decisions in drug development, such as optimizing the dose, frequency and duration of exposure, so getting these decisions right is paramount. Selecting the tools for making such decisions is equally important. Fortunately, PK/PD analysis software has evolved greatly in recent years, allowing users to focus on analysis, as opposed to algorithms and programming languages.

One of the principal attractions of Phoenix WinNonlin is that it combines the industry’s strongest set of analytical engines with an extremely intuitive user interface. In a recent survey, more than 98% of the users responded that they were either satisfied or greatly satisfied with the overall quality of WinNonlin and 93% agreed that it saves time over other software tools. The software comes with a thorough online user guide and a set of tutorials that allow a new user to begin using the software very quickly. Pharsight also trains more than 700 users each year at public and private training courses around the globe to provide support from the beginner to the advanced user.

Visualization of data can be easily accomplished with Phoenix Graphics.

Ease of use across the entire workflow

A primary consideration in the selection of PK/PD modeling software is ease of use across the entire workflow. How difficult is it to become fluent with the software? Does it have free online tutorials and a strong help guide? Are training courses or online tools readily available? Can I get help from peer groups?

Drag and drop new datasets onto your workflow to use it again—reduce the next study time by over 75%.

Nobel Prize Laureate Barbara McClintock famously said, “They were so intent on making everything numerical that they frequently missed seeing what was there to be seen,” (Gabrielsson and Weiner, 2000). This paper will focus on key considerations when selecting a software package for PK/PD analysis that will demystify the art and science of mathematical modeling, and allow a scientist to “see what needs to be seen.” A robust software solution should be easy to use and address the three main parts of the PK/PD workflow: data management, analysis, and reporting.

One feature of Phoenix WinNonlin that enhances ease of use is the graphical workflow tool. A graphical workflow provides a visual representation of the data flow and allows the user to store, share and reuse workflow templates, as seen in the following example.
Phoenix WinNonlin allows a user to import from many standard data sources such as .xls, .xlsx, .xpt, .xml, .csv, .xpt or .txt files. The user can import data using the Clinical Data Interchange Standards Consortium Study data tabulation model domain or using an S+ dataframe. It is even possible to import data directly from Watson LIMS™. All of these options make it very easy to get data into Phoenix WinNonlin. Secondly, since it is built on a graphical workflow approach, it is easy to visualize the data flow to make it easier to understand how the data is being manipulated, prior to analysis. For example, users can append worksheets, perform column transformations, and add BQL rules, as well as filter, join, merge and stack data. Functions that had to be performed in Excel® or SAS® in the past can now be performed in Phoenix WinNonlin. This eliminates unnecessary data import/export steps and possible loss of data integrity.

Data import and export

The first step in the workflow is getting the data into the software application. How easy is it to import data? Can it be imported directly from an instrument or standard file type? Can the data be explored directly without having to use a third-party application?

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Data analysis: fit, explore, and validate the model

The next step in the workflow is to analyze the data: to fit, explore and validate the model. One consideration is whether the analytical engines being used to prepare the NCA, PK or PK/PD models are robust and validated. Are they accepted by the regulatory agencies? Are they easy to use and apply? Can the software tool support both non-compartmental and multi-compartment modeling approaches?

Users today have the option of starting with a general mathematical package, such as Excel, SAS or MATLAB®, and programming the algorithms to calculate the parameters of interest, such as the AUC, CI, Cmax, tmax and t_{1/2}. These equations are fairly simple to program for single-dose, NCA, but can get quickly get much more complex. For example, business rules for derivation of IZ or back extrapolation to estimate C0 for IV bolus and NCA analysis of PD data can be tedious and error-prone to program.

When modeling the PK and/or PK/PD of multiple dose administration, the effect of accumulation from the first dose on the second dose needs to be taken into account. And, when the NCA model does not describe elimination properly, a one- or two-compartment model must be used, and may involve linear or non-linear (Michaelis-Menten) kinetics. Having a single tool that supports all necessary methods and allows the user to easily transition between them within the same environment is highly desirable.
The Phoenix WinNonlin software has evolved from the Nonlin software, which was developed in 1984 by Dr. Daniel Weiner as Nonlin84 (which was also based on earlier version developed by Dr. Carl Metzler). The analytical engines are based on a very strong scientific pedigree and are the basis of thousands of clinical study reports. The NCA modeling engines are mature and can support a range of methods from the simple to the very sophisticated. The user interface includes a set of options for model type (plasma, urine or drug effect); dosing (extravascular, IV bolus, IV infusion or user defined); and four calculation methods (linear log trapezoidal, etc.). Bioequivalence studies can also be modeled for both parallel and cross-over studies, and support is provided for both replicated and non-replicated designs.

In addition to the standard NCA modeling, Phoenix WinNonlin has over 80 built-in PK and PD models that support many common study types, such as IV bolus, IV infusion and extravascular administration for one-, two- and three-compartment PK and PK/PD models (including effect compartment and indirect response models). The breadth of computational methods contained in Phoenix WinNonlin has been built up over many years and would be very difficult to replicate in a general user mathematical programming language like SAS or MATLAB, and very difficult to use by anyone other than the primary developer.

As a provider of software that is used by both the FDA and by FDA-regulated customers, Phoenix WinNonlin is built in accordance with a documented software development lifecycle (SDLC). In each phase of the lifecycle, documentation deliverables are created that record the development and
testing of each product, ending with a Release Approval/Validation Completion form. In addition, Pharsight offers a Phoenix WinNonlin Validation Suite™ that automatically runs test data through an exhaustive set of test cases and compares the output to a reference file, saving weeks or months of time.

**Report-ready tables, figures, and listings**

In the last step of the workflow, one must generate several tables, figures and listings of the interim or final parameters to communicate the result of a study. Is it easy to generate report-ready plots and tables without going to a third-party tool? Can all plots and tables be exported?

After the data are imported and the analysis is run, the next critical step is communication of the results. Phoenix WinNonlin integrates strong plotting and reporting capabilities, eliminating the need for dedicated third party graphing tools. Sophisticated plots that were once only accessible through tools like SigmaPlot can now be created in Phoenix WinNonlin, including box and whisker plots, trellis plots, scatterplots and plots with a secondary axis or a categorical X axis.

Furthermore, it is possible to create a workflow that can be reused as a template to recreate all outputs. For example, the PK department could create a set of standard plots and reports applying consistently to each analysis. This approach has been shown to reduce time spent by over 75%. Plots and tables can also be exported in the Word® format for sharing. Example outputs are shown below and on the following page.

**Graphical output from Phoenix WinNonlin.**
Summary

In summary, Phoenix WinNonlin is the best choice for PK/PD modeling, because:

- The analytical engines are industry standard and comprehensive
- The graphical workflows make it easy to create, reuse and share templates
- All major plots and tables can be generated without the use of a third-party graphing tool
- The software can be validated with the support of the Phoenix WinNonlin Validation Suite

Finally, by using a single integrated package to manage data, analyze and create reports, users can save several thousands of dollars per year on total cost of ownership and greatly increase their efficiency.

References

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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