



**CERTARA**<sup>®</sup>

**Phoenix**<sup>®</sup> Platform

## Phoenix PK/PD Modeling and Simulation Software

Certara's Phoenix® platform is the leading PK/PD modeling and simulation software used worldwide by more than 6,000 researchers at biopharmaceutical companies, academic institutions, and global regulatory agencies, including twelve offices of the US FDA. 90% of novel drugs approved by the FDA are from companies that leverage Phoenix in their R&D programs.

The Phoenix platform includes WinNonlin™, the industry standard for non-compartmental analysis (NCA), pharmacokinetic/pharmacodynamic (PK/PD), and toxicokinetic (TK) modeling. It provides access to the most sophisticated PK/PD workbench tools available today enabling greater ease of use and more efficient pharmacometric workflows, and offers features that support compliance and efficiency. A list of Phoenix Platform technology solutions are below.

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## The Gold-Standard in Pharmacokinetic, Pharmacodynamic and Non-compartmental Analysis

Phoenix WinNonlin™ is the industry standard for the analysis of pharmacokinetic and pharmacodynamics data. The integrated tools for data processing, non-compartmental analysis (NCA), PK/PD modeling, summary and inferential statistics, table creation, and graphics create an all-in-one collaboration workbench for analysts, reviewers, medical writers, and quality assurance team members. The intuitive graphical user interface allows users to spend less time learning the software and managing data and more time to model, interpret, and understand the data. The result? Efficient drug development decisions with more confidence.

### Proven Software with a Vast Global Footprint

Phoenix WinNonlin has a proven 30-year history of providing trusted PK/PD analysis results. It is used by over 6,000 scientists in 60 countries at nearly 2,000 institutions, including the top 50 global pharmaceutical companies. Regulatory agencies, including 12 offices of the US Food and Drug Administration (FDA), Japan Pharmaceutical and Medical Device Agency (PMDA), National Medical Products Administration (NMPA), and the UK Medicines and Healthcare Products Regulatory Agency (MHRA), use Phoenix WinNonlin for analysis and to evaluate drug submissions.

### The WinNonlin Engines Can Do It All

#### The Most Comprehensive Set of Analysis Tools for any Non-clinical or Clinical PK/PD Study

From early non-clinical research to large clinical trials, the NCA engine, individual PK/PD modeling engine, and statistical analysis tools can be used for a wide-range of studies and analyses:

- Single dose or steady-state dosing
- Sparse sampling studies
- Drug concentration data in plasma or urine matrices
- Formulation comparison
- Drug response pharmacodynamics
- Parallel and Crossover study designs
- Dose Proportionality and Parent-Metabolite ratios
- Change in dose regimen simulations
- Bioequivalence and Bioavailability
- Linear regression

### Recent Enhancements

- New Ratios and Differences tool provides automated calculation of NCA ratios
- Additional descriptive statistics
- More flexible charting and plotting capabilities
- Additional new NCA parameters for plasma and urine
- User-defined NCA parameters
- Setting of criteria for the terminal slope calculation in NCA
- Enhanced fully-integrated Phoenix WinNonlin Validation Suite for fast automated software validation in under 30 minutes

## Workflows are the key to consistency across an organization:

- Increase productivity by reusing workflows across multiple projects and analyses
- Output with the click of a button—data processing/formatting, analysis, figure, plots, and tables
- Drag and drop new data into an existing workflow to generate updated results effortlessly
- Eliminate time-consuming analyst work or the need for a separate data programmer

## Statistical Tools Help Answer Critical Questions

Did the new formulation meet bioequivalence criteria? Is the exposure dose proportional? Did the drug cause an increase in a biomarker? Statistical tools in WinNonlin integrate and report inferential analysis of study results. Descriptive statistics have been added, including 2.5% and 97.5% percentiles, user-specified percentiles, sample and population statistics for skewness and kurtosis, and range, min and max when weighting is used.



Bioequivalence



Superposition



Analysis of variance/General linear models



Semi-compartment modeling



Deconvolution



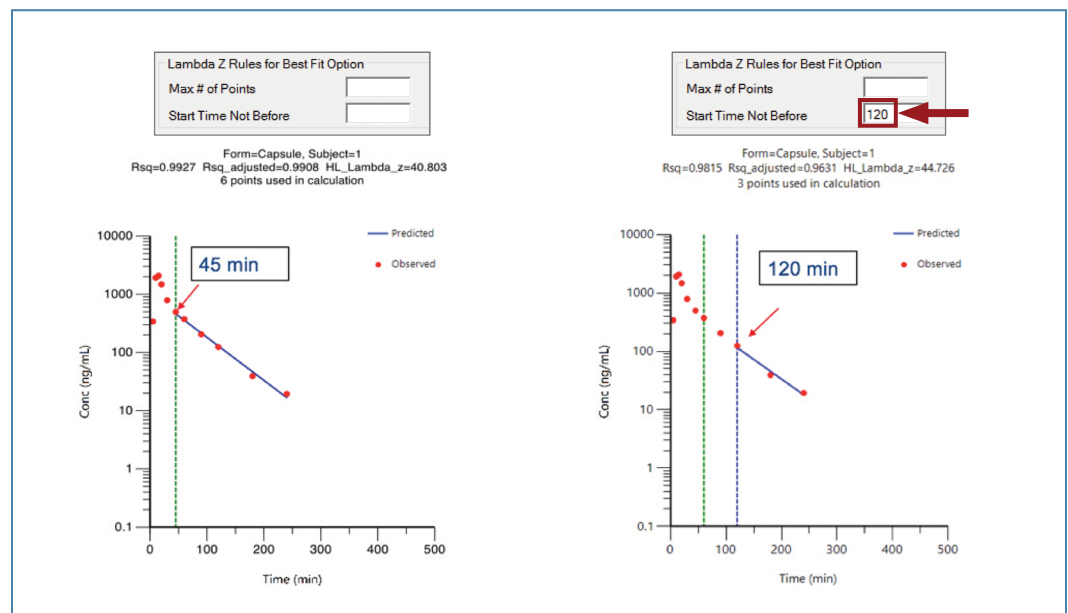
Descriptive statistics

Phoenix WinNonlin takes non-compartmental analysis (NCA) to a new level by adding many commonly calculated NCA parameters to the standard output, providing the ability to define custom NCA parameters, business rules for calculating the terminal slope, and acceptance flags based on terminal slope quality assessments. These new features minimize post-processing work and increase transparency with analysis.

## Business Rules for Terminal Slope Calculation

Organizations can set strict criteria for the calculation of the terminal slope in NCA. Those rules can be implemented directly in Phoenix's updated NCA tool. Users can specify the maximum number of points to be included in the regression or the earliest time to be used (see figure below). The settings are retained and can be reviewed for compliance with organization policies and procedures.

### Example of Lambda Z Rules for Best Fit Option: Before and After Setting "Start Time Not Before"



In addition, users can define acceptance criteria for adjusted  $r^2$ , % extrapolated AUC, or Span (lambda z sampling interval/ $t_{1/2}$ ). All calculated values will be marked as meeting the criteria, not meeting the criteria, or missing. This permits easy post-processing of results based on quality standards for lambda z.

## Parameters for Non-compartmental Analysis

The automated calculation of over a dozen parameters for plasma and urine will save time by reducing manual work and reduce errors with non-compartmental analysis in Phoenix WinNonlin.

- Plasma parameters
  - Swing (single dose and steady-state)
  - %Fluctuation (single dose and steady)
  - $C_{last}$  (predicted)
  - $C_{tau}$  (observed and predicted)
  - Span
  - $AUC_{last}/Dose$
  - $AUC_{Tau}/Dose$
  - $AUC_{Tau}\%Extrap$
  - $\lambda_{z\_intercept}$
  - $N_{samples}$
  - Dose
- Urine parameters
  - $Rate_{last}$  (predicted)
  - $AURC_{last}/Dose$
  - $N_{samples}$
  - Dose
- User-defined parameters
  - Computed concentrations at any time point (uses AUC calculation interpolation)
  - Arithmetic combinations of any NCA parameter (eg, partial AUC/Dose)

## An Intuitive Graphical User Interface

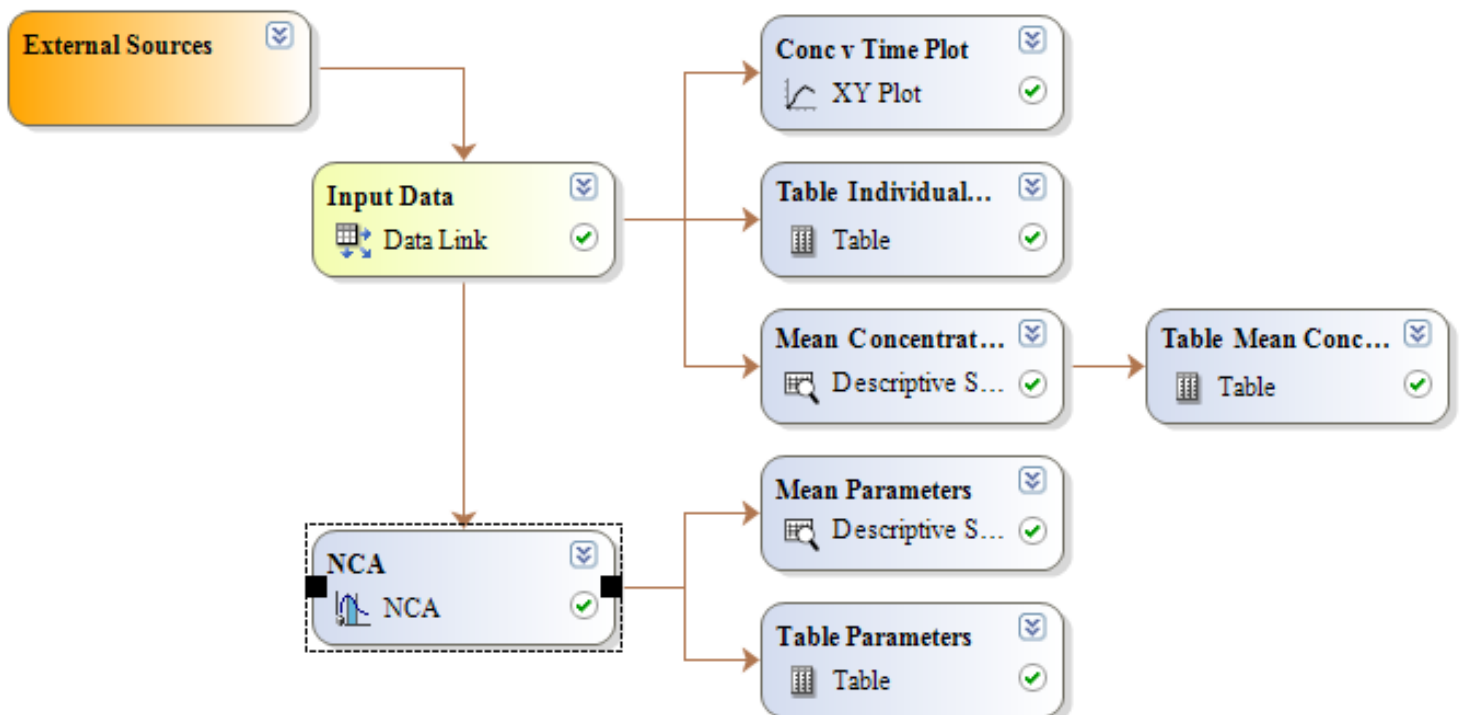
Phoenix was designed to help users efficiently move from data to reporting results using a graphical workflow designed to visualize data flow and analysis pathways. Each workflow contains separate objects for each action—eg, data processing, NCA, PK/PD models, table creation, figures and plot creation, and reporting—which are linked together within an intuitive graphical user interface.

Locking the workflow provides consistent results and eliminates QC checks for approved workflows.

Traceable workflows significantly increase productivity.

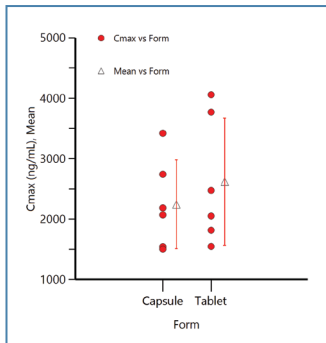
**Workflows enable users to spend less time preparing and manipulating data and results.**

**Scientific and QA reviewers can use tools for rapid error identification to reduce review time.**

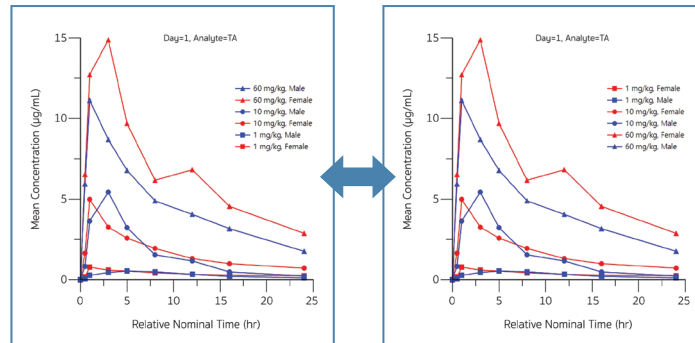


## Powerful Integrated Graphics Engine and Table Generator

The integrated graphics engine in Phoenix WinNonlin automatically creates publication-quality plots and figures and well-organized tables to help create standardized PK/PD reports more efficiently. More flexible charting and plotting tools have been added, including ordering the presentation of categorical axes, allowing for offsets, changing font style and size, customizable legend placement, and more. High native resolution plots and figures can be easily customized to meet user specifications without the need for third party software packages. Do you have standard plots and figures in your organization? Custom plot templates can be shared by everyone and loaded with one command.



**X-Categorical Plot with Error Bars and Offsets**



**Group Label Order Change**

## Tools for Data Processing and Preparation

Analysis dataset preparation is a breeze with Phoenix data processing tools. The Phoenix workflow traces data from the moment it is imported through the final analysis, preventing data loss and costly re-analysis.

Integrated data processing functions—sorting, splitting, filtering, transforming, merging, appending, stacking, pivoting, joining, and more—provide full visibility into the incoming data and the results of each data set.



CDISC Data Preparer



Merge Worksheets



Append Worksheets



Pivot Worksheet



BQL



Rank Worksheet



Crossproduct Worksheets



Ratios and Differences



Data Wizard



Split Worksheet



Enumerate Worksheets



Stacker



Join Worksheets

## Ratios and Differences Tool

The Ratios and Differences tool automatically calculates NCA ratios, including renal clearance, accumulation ratio, linearity index, parent to metabolite exposure ratios, and more.

### Step 1. Select Data

The screenshot shows the Phoenix WinNonlin interface. The 'Object Browser' on the left displays a project structure with 'Data' selected. A 'Send To' context menu is open over the 'Data' folder, and the 'Ratios and Differences' option is highlighted. The background shows a data table with columns: Species, Matrix, Day, Route, Dose (mg/kg), and Dose\_Group.

### Step 2. Map Data and Add Options

The 'Options' dialog box is shown, allowing users to map data columns and filter values. It includes an 'Add' button and a table with the following columns: Comparison, Column, Filter Value, Column, Filter Value, New Column Name, Units, and Description. Two rows are configured for X/Y comparisons using Cmax and AUClast.

Comparison	Column	Filter Value	Column	Filter Value	New Column Name	Units	Description
X/Y	Cmax	Female	Cmax	Male	Ratio Cmax F/M		Cmax where Gender = Female / Cmax where Gender = Male
X/Y	AUClast	Female	AUClast	Male	Ratio AUClast F/M		AUClast where Gender = Female / AUClast where Gender = Male

Use means for X and Y when non-unique

### Step 3. Obtain Results

The 'Results' tab displays the output data table. The table includes columns for Day, Dose\_Group, Analyte, Gender, Cmax (ug/mL), AUClast (hr\*ug/mL), Ratio\_Cmax\_F\_M, Ratio\_AUClast\_F\_M, and Treatment. The data shows results for 24 different experimental conditions.

Day	Dose_Group	Analyte	Gender	Cmax (ug/mL)	AUClast (hr*ug/mL)	Ratio_Cmax_F_M	Ratio_AUClast_F_M	Treatment
1	1 mg/kg	4-Hydroxy-TA	Female	0.20901437	2.9036282	1.8510752	1.6672423	TA
2	1 mg/kg	4-Hydroxy-TA	Male	0.11291511	1.7415755			TA
3	1 mg/kg	TA	Female	0.83465291	9.1618096	1.4765833	1.2342322	TA
4	1 mg/kg	TA	Male	0.56525962	7.4230843			TA
5	10 mg/kg	4-Hydroxy-TA	Female	1.0624565	11.838327	4.6513039	5.0796955	TA
6	10 mg/kg	4-Hydroxy-TA	Male	0.22842122	2.3305191			TA
7	10 mg/kg	TA	Female	5.308485	40.996543	0.97628994	1.0825018	TA
8	10 mg/kg	TA	Male	5.4374063	37.872032			TA
9	60 mg/kg	4-Hydroxy-TA	Female	10.120435	112.16525	8.439756	10.292551	TA
10	60 mg/kg	4-Hydroxy-TA	Male	1.1991384	10.897711			TA
11	60 mg/kg	TA	Female	17.07328	160.89073	1.534125	1.4538612	TA
12	60 mg/kg	TA	Male	11.129002	110.66443			TA
13	14	4-Hydroxy-TA	Female	0.36507452	2.7889805	0.82251062	0.76783037	TA
14	14	4-Hydroxy-TA	Male	0.44385387	3.6322873			TA
15	14	TA	Female	3.2763012	35.291575	1.325344	1.8659947	TA
16	14	TA	Male	2.4720383	18.91301			TA
17	14	4-Hydroxy-TA	Female	4.7414357	29.242751	1.699608	1.5241737	TA
18	14	4-Hydroxy-TA	Male	2.7897231	19.185971			TA
19	14	TA	Female	22.110346	191.55611	1.1326991	1.2023485	TA
20	14	TA	Male	19.520052	159.31829			TA
21	14	4-Hydroxy-TA	Female	20.199662	190.17738	1.6886325	1.7536353	TA
22	14	4-Hydroxy-TA	Male	11.962142	108.44751			TA
23	14	TA	Female	103.40416	1236.6579	1.6995564	2.3777473	TA
24	14	TA	Male	60.841853	520.09644			TA

## Phoenix WinNonlin Makes Compliance Work Much Easier

The analysis of PK, PD, and TK data requires users to follow regulations to ensure compliance with regulatory agencies around the world. Each object includes a validation tab to confirm proper operation, a history tab that keeps an audit trail of changes, and a settings output that records the settings used for analysis.

Validation Suite, now fully integrated into Phoenix WinNonlin, eliminates the need to install a separate application. Automatic execution of detailed test scripts completes the validation of WinNonlin in minutes, not days. Validation is completed in less than 30 minutes with locked PDF reports containing links to saved reference files, user output files, and difference files. Updated validation template documents are aligned with the latest regulatory guidances for computer system validation.

Full integration of Phoenix WinNonlin with *Certara Integral*, a secure and pre-validated data and model repository, enables the management of clinical and non-clinical PK and PD data and analyses in compliance with the US FDA electronic records and signatures regulation (21 CFR Part 11).

## Flexible and Powerful Compartmental Modeling Tools

WNL Classic Modeling and Phoenix Modeling tools provide beginner to advanced users with suitable options. WNL Classic Modeling has several built-in models including Dissolution, Indirect Response, Linear, Michaelis Menten, PD, PK, and PKPD models, and an option for user-defined models in ASCII format. Built-in, Graphical Editor and Textual editor options are available for Phoenix Modeling.

## Access to Continuing Education and Support

Coming up to speed on WinNonlin is simple and easy with the graphical user interface. We provide a wide range of education and support tools to get users started and up to date with the most important advancements in modeling:

- Step-by-step user guide and examples
- Classroom and on-demand e-learning training courses available through Certara University ([www.certarauniversity.com](http://www.certarauniversity.com))
- The new Certara Professional Certification program offers online accreditation of user competency and proficiency analysis of PK/PD data using Phoenix WinNonlin 8.0, 8.1 and 8.2 ([www.certara.com/cpc](http://www.certara.com/cpc))
- Webinars from world-renowned investigators and modelers
- White papers, educational blog posts, and access to an active user forum community ([support.certara.com/forums](http://support.certara.com/forums))





Phoenix NLME™ is the premier PK/PD modeling engine that powers Certara's industry-leading Phoenix® software, and is now available as a stand-alone software that can be driven by programming in R. In both implementations, NLME is user-friendly and easy-to-learn. Phoenix NLME is the most powerful non-linear mixed effect modeling engine available to scientists today and is used by 1,400 scientists, 18 of the top 20 pharmaceutical companies in the world, renowned academic institutes, and multiple regulatory agencies, including the US Food and Drug Administration (FDA).

NLME includes a full suite of algorithms for non-linear mixed effects models including QRPPEM, the most advanced expectation maximization algorithm available. In tested models, QRPPEM was found to be consistently the fastest to converge among EM methods, demonstrating the advantage of this approach<sup>1</sup>.

## Included Algorithms

Individual and Pooled Data Analysis	Population Analysis	
	Parametric Method	Non-parametric Method
<ul style="list-style-type: none"><li>• Naïve Pooled</li></ul>	<ul style="list-style-type: none"><li>• FO</li><li>• FOCE-LB</li><li>• FOCE-ELS</li><li>• IT2S-EM</li><li>• Laplacian</li><li>• AGQ</li><li>• QRPPEM</li></ul>	<ul style="list-style-type: none"><li>• Non-parametric Engine</li></ul>

Built from the ground up on the Phoenix workbench architecture, Phoenix NLME enables users to focus on modeling, and not on the tools or coding required to implement the modeling. The result is more time for analysis and strategic decision-making. Plus, Phoenix NLME is the first PK/PD modeling software to be out-of-the-box grid-enabled, supporting remote parallel execution on compute platforms.

## Most User-friendly PK/PD Software Available

Phoenix NLME uses a modern, intuitive graphical user interface (GUI) that provides a seamless transition between modeling ideas and modeling execution.

- Select from a complete library of built-in models or use the graphical model editor for quick customizations. In either case, the full model code is available using Phoenix Modeling Language (PML), a modern modeling language that is easy to read and understand.
- Informative diagnostic messages are provided during model building and execution to quickly and easily identify and remedy errors in a model. Phoenix NLME automatically produces the required diagnostic tables and plots, enabling instant evaluation of model results.
- Along with the Model Comparer tool, the model selection process can be automated with Run Options such as Covariate Search, Covariate Shotgun, and Scenarios.
- Model validation can easily be performed using Bootstrap and Visual Predictive Check (VPC). The user-friendly VPC interface provides stratification and binning options to create easy to interpret plots with confidence bands.

Combining these innovative features for modeling with data preparation, data formatting, statistics, table, and plotting tools built into the Phoenix workbench makes Phoenix NLME a modern tool for today's PK/PD modeling scientist.

## Recent Enhancements

- Model delayed outcomes using the automated and fully integrated discrete and distributed delay functions
- Greater flexibility and broader applicability with the Visual Predictive Check function
- Significantly reduce model run times via parallelizing jobs on remote compute platforms
- Seamlessly pair Phoenix NLME with your Compute Grid to accelerate model runs

The power and flexibility of Phoenix NLME makes it suitable for many demanding PK/PD studies including:

- Translational modeling
- Extrapolating PK data from animals to humans
- Enabling sparse sampling strategies
- Predicting the pharmacodynamics in humans based on *in vitro* models
- Combining PK and PD data from multiple studies
- Enhancing study designs to minimize animal use

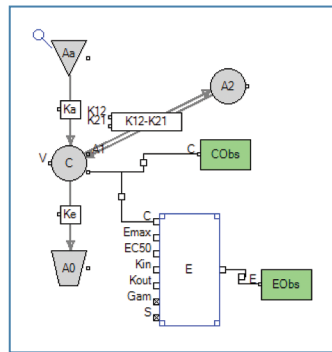
## Powerful and Widely Used for Regulatory PK/PD Submissions

Phoenix NLME was developed for optimal performance and maximum flexibility. Both beginners and advanced users can leverage the power of NLME for PK/PD analysis. NLME has integrated support for parameter estimation, simulation, automated covariate searches, bootstrap parameter estimation, and visual predictive checks give a user the flexibility to conduct all phases of a PK/PD analysis with a single intuitive tool.

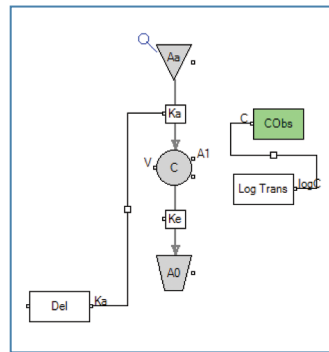
## Guided Model Development

Phoenix NLME provides full 1-to-1 mapping between the development of an optimal modeling strategy and corresponding tools required to perform the analysis. Often the most difficult part of PK/PD modeling is building the right model for the study. Phoenix NLME makes that easy with a graphical model building interface called the Drug Model Explorer (DME) that can easily create custom models including multiple absorption or clearance pathways, parent-metabolite models, and complex exposure-response models. The DME also writes PML code for users, helping new users learn model coding. Combining these innovative features of the software with step-by-step examples and classroom/online training courses at Certara University makes Phoenix NLME easy to learn for beginners, self-guiding for novice modelers, and optimized for advanced users.

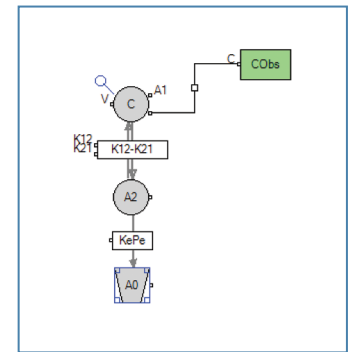
## Custom Models Created by Drug Model Explorer



PK/PD Model with Emax Pharmacodynamics Response



PK Model with Modified Ka and Log-transformed Concentration Data

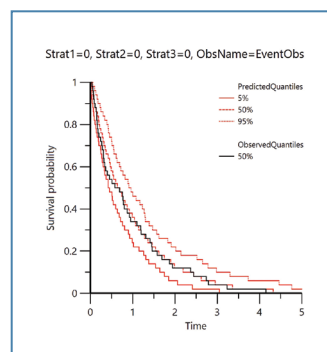


2-Compartment PK Model with Elimination from the Peripheral Compartment

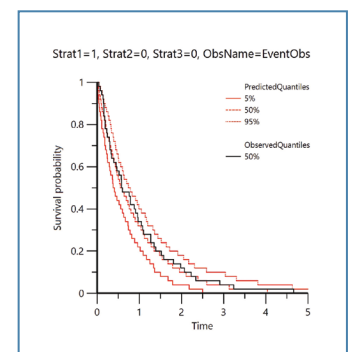
## Visual Predictive Check

Visual Predictive Check (VPC) is a graphical comparison and analysis of observations and simulated predictions.<sup>2</sup> VPC in Phoenix NLME provides broader applicability and flexibility for users. These enhanced functionalities include the ability to perform separate analyses for different data types such as continuous data, including Below Quantification Limit (BQL), and discrete observations such as categorical, single time-to-event, and count data. Other improvements include separate Visual Predictive Check and Simulation modes and VPC Stratification for categorical covariates.

## Single Time-to-event with Stratification



Stratum Value 0



Stratum Value 1

## Out-of-the-box Grid-enabled

One challenge of population PK/PD modeling is the need for computing power to solve complex models in a reasonable time frame to support drug development decisions. NLME features parallelization for almost all run modes, versus command line and manual execution, and the ability to run on powerful remote compute platforms, reducing run times from days to minutes.

NLME uses an algorithm that automatically maximizes the number of cores for each run to minimize run times without any user intervention. For example, a standard laptop computer has 4 CPU cores available for model fitting, but a grid configured with 100 cores will run an NLME job 25 times faster than the laptop computer. After sending a NLME job to the grid, the results are automatically downloaded when the job is finished. Users can disconnect and reconnect to running jobs and view interim run results to catch and fix any mistakes. NLME also enables a user to initiate an NLME job on a remote/parallel compute platform directly from the desktop application without the need to install NLME on the remote computer.

## How Does Automatic Algorithm for NLME Parallelization Work?

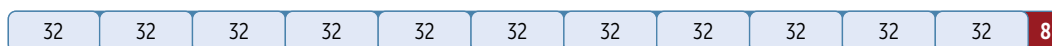
### Example 1: Simple run with sort variable (360 cores, 400 subjects, 3 unique sort keys)

With 400 subjects and 3 unique sort keys using a 360-core grid, the automatic algorithm selects the optimal number of cores to maximize the use of all 360 cores.



### Example 2: Log-likelihood Profiling (360 cores, 10 perturbations, 300 subjects and no sort keys)

The total number of models (n) equals (# perturbations + 1). The automatic algorithm runs 11 models in parallel with 32 cores each.



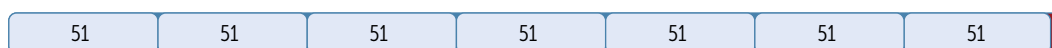
### Example 3: Covariate Search Stepwise (360 cores, 8 covariate-parameter relationships, 300 subjects, 3 covariates in final model)

The algorithm calculates the optimal parallelization at each stage of addition and deletion.

Round 1: Baseline + 8 covariate models, forward addition



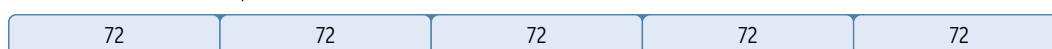
Round 2: 7 covariate models, forward addition



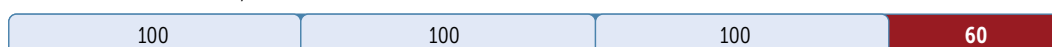
Round 3: 6 covariate models, forward addition



Round 4: 5 covariate models, forward addition



Round 5: 3 covariate models, backward deletion



## Faster Model Runs with NLME Parallelization

- All run modes are parallelized on remote platforms, except Sim./Pred. Check
- Automatic algorithm uses the maximum number of cores for each run to minimize run times without any user intervention
- There are no additional license fees to access remote platforms to run NLME models
- Disconnect and reconnect to running jobs, and view interim run results to catch and fix any mistakes
- Settings for remote computational grids are included in the Preferences section of Phoenix

## Cutting-edge Science

Phoenix NLME is the first PK/PD modeling engine to offer integration of discrete and distributed delay functions, eliminating the need to add complex lines of code. This methodology can be used to replace transit compartments, dual absorption models, effect compartment models, or even indirect response models, providing a more accurate evaluation of these models. The new delay functions greatly simplify modeling delayed outcomes, an important function in several therapeutic areas such as oncology, diabetes, and arthritis.<sup>3,4</sup> A delay function can be added with a single Phoenix Modeling Language (PML) command, avoiding inefficient workarounds and approximations.<sup>5,6</sup>

## Interoperability

Phoenix NLME is interoperable with any PK/PD modeling paradigm. Phoenix also provides interoperability with software packages such as SAS®, R, SigmaPlot®, NONMEM®, PSN, Watson LIMST™, and more. This allows users to integrate specialized software tools into a Phoenix workflow to ensure compliance and data traceability. Phoenix NLME is designed to easily export analysis results for incorporation into PK/PD reports. Any plot, figure, or table can be exported to a Microsoft® Word document with a single click. Using the Phoenix Reporter tool, users can compile a series of plots, figures, and tables into a single Microsoft Word file with customized numbering and headers. This output can then be quickly and easily attached to a PK/PD report for communicating results internally and to regulatory agencies.

## Compliance

PK/PD modeling requires users to follow regulations to ensure compliance with regulatory agencies around the world. Phoenix NLME does the compliance work for users. Each object includes a validation tab to confirm proper operation, a history tab that keeps an audit trail of any changes, and a settings output that records the settings used for analysis.

## Leverage your Experience with Phoenix WinNonlin

Since it is built on the Phoenix workbench, Phoenix NLME leverages the same GUI that users rely on when using WinNonlin. Combining Phoenix NLME with WinNonlin creates a comprehensive analysis package that can be used for optimal PK/PD modeling and simulation through all stages of drug development, including regulatory submission. The integrated tools for data processing, PK/PD modeling, post analysis statistics, table creation, and an integrated graphics engine create a single all-in-one collaboration workbench for scientists, reviewers, medical writers, and quality assurance team members.

## Leverage your Experience with Phoenix WinNonlin

We provide a wide range of education and support tools to get you started and keep you up-to-date with the most important advancements in modeling, including step-by-step guides, classroom and on-demand e-learning courses available through “Certara University”, thought-leadership webinars, educational blog posts and access to an active user “support forum” community.

### References

1. Liu X & Wang Y. (2016). Comparing the performance of FOCE and different expectation-maximization methods in handling complex population physiologically-based pharmacokinetic models. *J. Pharmacokinetics and Pharmacodynamics*, 43, 359–370.
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4. Koch G, Krzyzanski W, Pérez-Ruixo JJ, & Schopp J. (2014). Modeling of delays in PKPD: Classical approaches and a tutorial for delay differential equations. *J Pharmacokinetic Pharmacodyn*, 41, 291–318.
5. Hu S, Dunlavy M, Guzy S, & Teuscher N. (2018). A distributed delay approach for modeling delayed outcomes in pharmacokinetics and pharmacodynamics studies. *J. Pharmacokinetic Pharmacodyn*, 45, 285–308.
6. Krzyzanski W, Hu S, & Dunlavy M. (2018). Evaluation of performance of distributed delay model for chemotherapy-induced myelosuppression. *J Pharmacokinetic Pharmacodyn*, 45, 329–337.



## PK Submit™ – the First and Only Technology Solution to Automatically Generate PK CDISC Domains During Non-Compartmental Analysis (NCA)

Ensuring compliance with regulatory agencies' electronic submission guidelines for preclinical and clinical data is required – for the FDA as well as the PMDA. These guidelines, including the use of CDISC study data standards, apply to any new drug application (NDA), investigational new drug application (IND), abbreviated new drug application (ANDA), and certain biologics license application (BLA) filings. Preparing data in these standardized formats requires that scientists either become experts in CDISC implementation or otherwise delegate this task, which can introduce inefficiency. Moreover, the many tedious, complex, time-consuming, and error-prone steps involved in creating Study Data Tabulation Model (SDTM) and Standard for Exchange of Nonclinical Data (SEND) datasets requires a great deal of quality control.

PK Submit is integrated with Phoenix WinNonlin® and supports the automatic generation of a complete electronic PK regulatory submission package, including all necessary CDISC domains, during the normal process of setting up and executing an NCA – all from the same source, by a PK scientist who is not a CDISC expert, and within minutes.

### Solve data management issues faster with PK Submit

- Creates a complete electronic PK regulatory submission package
- Automatically generates CDISC domains while executing an NCA with no additional effort
- Allows users to easily apply exclusions and comments
- Remains current with CDISC controlled terminology and implementation guides
- Automatically configures the NCA
- Provides an intuitive, simple, single interface
- Supports all study designs and types
- Increases data standardization and quality and therefore confidence in your data
- Developed by Certara, a CDISC Platinum Member and experts in PK analysis using Phoenix WinNonlin, the gold standard for PK/PD analysis

### PK Submit allows you to:

- ✓ Optimize R&D productivity
- ✓ Reduce risk of errors and audits
- ✓ Easily collaborate with CROs

## SDTM and SEND CDISC Domain Generation

Automatically create regulatory compliant CDISC domains in **less time, with fewer resources, and with fewer errors.**

PK scientists can use PK Submit to generate all required SDTM and SEND CDISC domains at the source – a solution that is integrated into their workflow.

After uploading and combining data in PK Submit, the software validates the output into the desired version of SDTM or SEND. The user requires only an understanding of the imported data.

### Intuitive, Simple, Single Interface

Achieve the full submission through one interface – built with PK scientists in mind and eliminating the need to become experts in the nuances of CDISC implementation and uses database technology to efficiently store user settings to minimize repetitive tasks.

### Complete Electronic PK Regulatory Submission Package

To decrease the opportunity for errors and potential regulatory audits, the reports and electronic records should be generated from one source. Therefore, PK Submit was designed to create the entire PK regulatory submission package, including the CDISC domains, validation report, study data reviewers guide, and define file.

#### CDISC domains generated by PK Submit

- PC
- PP
- RELREC
- POOLDEF
- CO

Easily load, harmonize, append, and merge data from multiple sources.

Stay current with CDISC controlled terminology and implementation guides.

Use with all study designs and types.



## The Clear Choice in Drug Development and Formulations for Obtaining Biowaivers

*In Vitro-In Vivo* Correlation (IVIVC) is a predictive mathematical tool that describes the relationship between the *in vitro* property of a drug dosage form and an *in vivo* pharmacokinetic (PK) response. Developing IVIVCs for solid dosage forms, especially for extended release formulations, is encouraged by the US FDA<sup>1</sup>, EMA, PMDA and other regulatory agencies. It is considered an important tool for supporting biowaivers and has become a surrogate for *in vivo* human bioequivalence (BE) studies.<sup>2</sup>

The Phoenix IVIVC Toolkit™ from Certara provides enhanced tools for *in vitro-in vivo* correlation studies used by formulation and pharmaceutical scientists to improve the success of BE studies. The IVIVC Toolkit approach requires less assumptions, as compared to other methods, and helps the user define the correlation observed from real *in vivo* profiles as compared to the dissolution profiles.

### Streamline development time, standardize the process, and reduce costs of expensive bioavailability/bioequivalence (BA/BE) studies

In most cases, a large amount of available dissolution and PK data will be used to develop and test a robust and predictive IVIVC. By using the IVIVC Toolkit, scientists can accelerate the analysis and documentation of IVIVC to support regulatory filings.

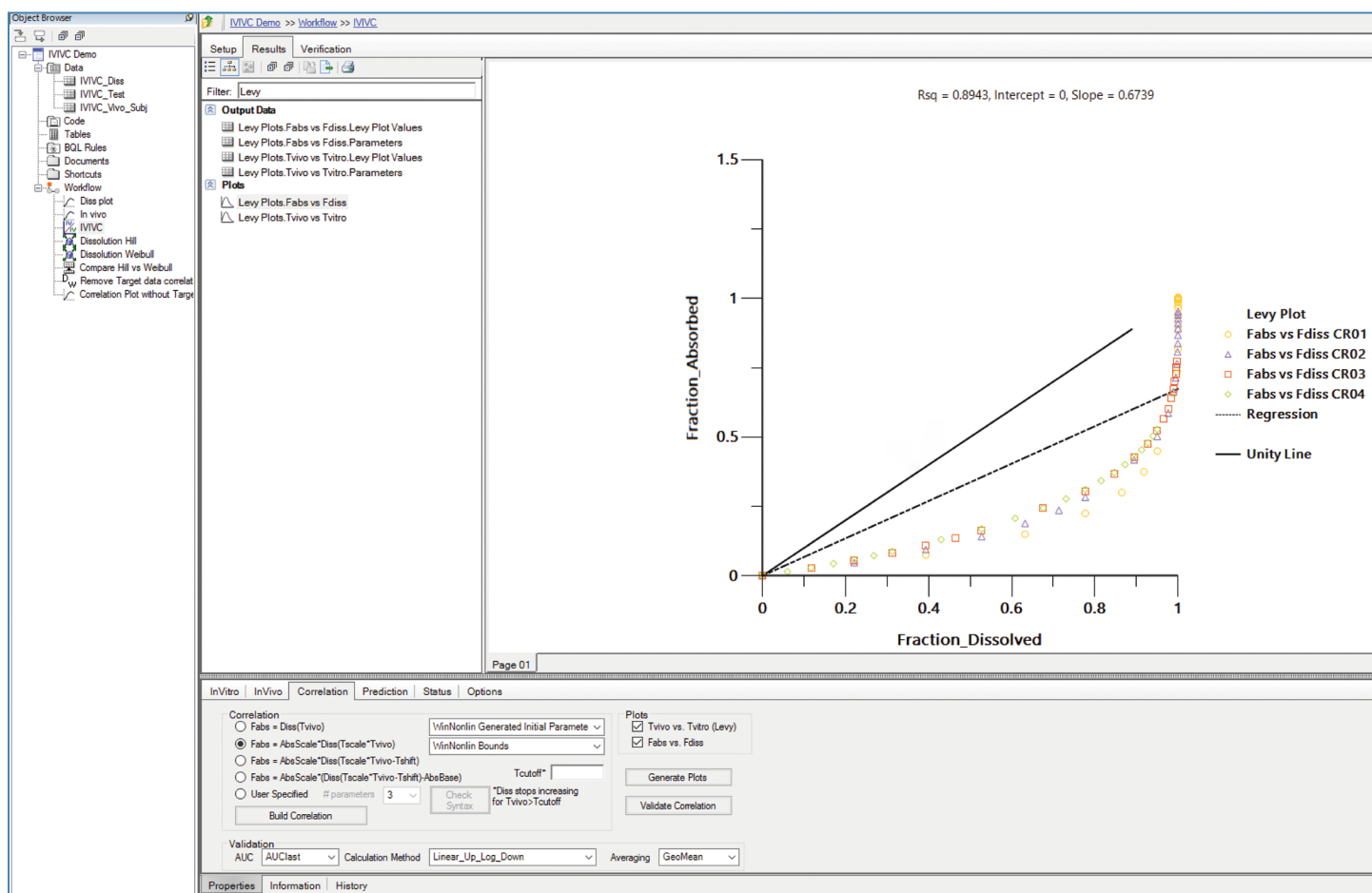
- Decreases the number of costly BA/BE studies by quickly generating IVIVC results using workflows and high quality outputs
- Organizes and simplifies the process, saving time and reducing error every time an IVIVC is needed
- Shortens the typical IVIVC development effort from weeks to days, dramatically lowering cost and bringing the drug to market quicker
- Facilitates collaborations—entire projects can be stored in a single file that can be easily shared internally or with external partners

## Standardize and simplify the IVIVC workflow

The Phoenix IVIVC Toolkit is specifically designed to efficiently manage this highly specialized workflow required to obtain IVIVC results. The IVIVC Toolkit provides numerous features that enable scientists to arrive at the right conclusion.

- Dialog-guided wizards and tools to streamline the IVIVC workflow processes
- Automatic estimation of Unit Impulse Response (UIR)
- Workflow support for a complete, 2-stage IVIVC with the ability to extend to a 1-stage IVIVC using the Phoenix model engine
- Levy Plots to assess time-scale of dissolution experiments
- Wide range of programmed and validated tools, including NCA, interpolation, deconvolution, convolution, PK modeling, model selection criteria (AIC), data merge and join
- History and Settings information for each workbook preserves auditability
- Access to continuing education and domain support

### Example of a Levy Plot Generated in the Phoenix IVIVC Toolkit



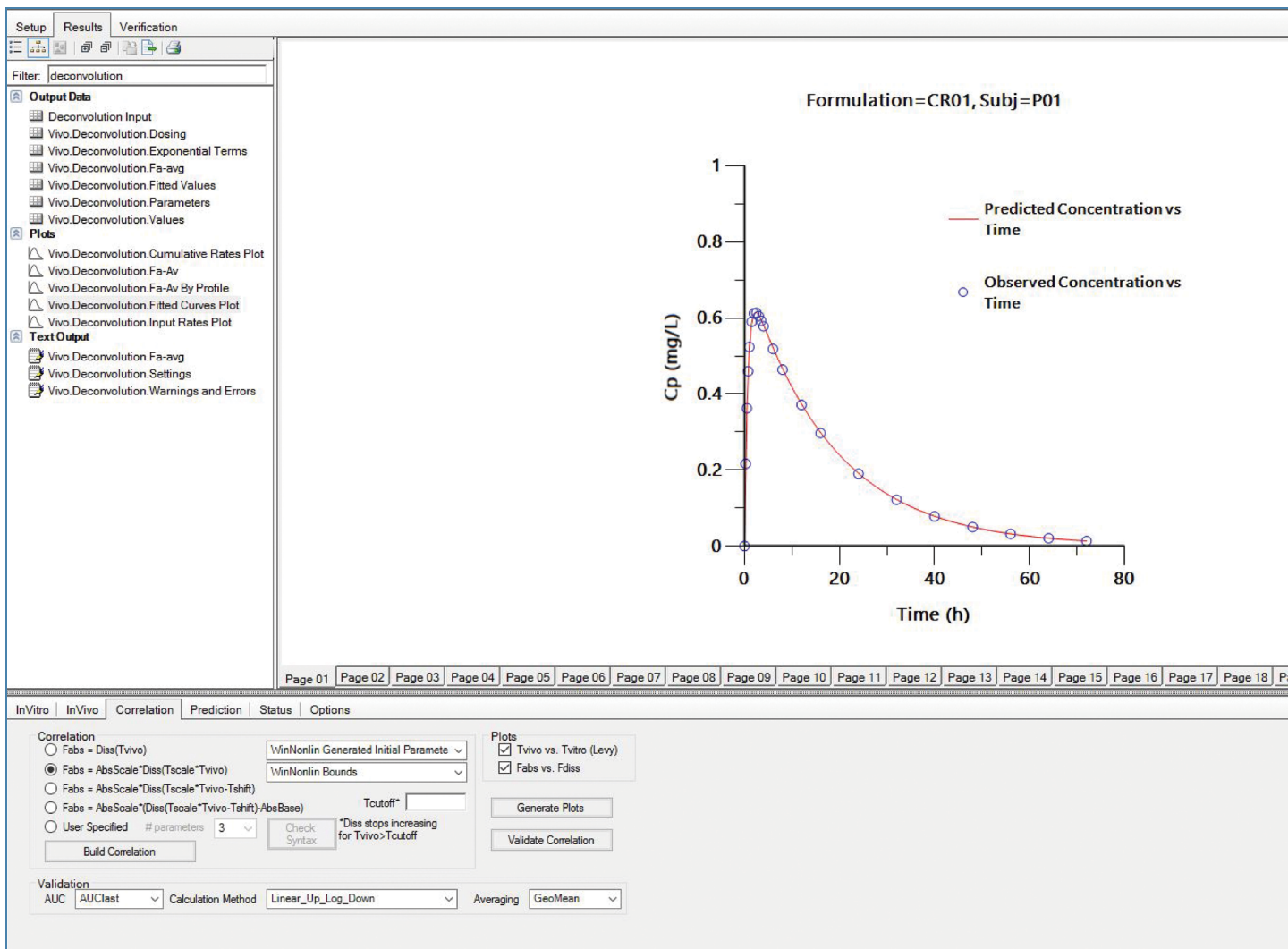


## Phoenix IVIVC Toolkit

Modeling Capabilities	Workflow Management	Reusable Workflow Templates	High Quality Outputs	Compliance and Validation
<ul style="list-style-type: none"><li>• Deconvolution<ul style="list-style-type: none"><li>– Wagner-Nelson</li><li>– Loo-Riegelman</li><li>– Numerical</li></ul></li><li>• Convolution</li><li>• IVIVC Wizard</li></ul>	<ul style="list-style-type: none"><li>• Visualize data flow and analysis pathways</li><li>• Store analysis steps and documentation in a single project</li><li>• Simplify QA</li></ul>	<ul style="list-style-type: none"><li>• Save up to 75% of time spent on routine analysis with templates</li><li>• Make changes without rebuilding the whole analysis project</li><li>• Create a corporate library of workflows and templates for standardization and training</li></ul>	<ul style="list-style-type: none"><li>• Create report- and publication-quality tables, listings and figures</li><li>• Assess the time-scale of dissolution experiments with Levy Plots</li><li>• Reuse favorite plots with new datasets</li><li>• Utilize export and overlay features</li></ul>	<ul style="list-style-type: none"><li>• Verification tab indicates status of object execution and errors</li><li>• Settings output indicates which options were selected</li><li>• History output shows when objects were executed</li><li>• Toolkit was built in accordance to software development lifecycle (SDLC)</li></ul>

### The Phoenix IVIVC Toolkit is differentiated from other commercial software for *in vitro-in vivo* correlation studies

- **Affordability**—Low start-up expense and add-on costs make Phoenix IVIVC Toolkit an affordable choice
- **User Interface**—Dialog-guided tools and wizard provide unique time savings
- **Quick Learning Curve**—The easy-to-learn Phoenix interface includes examples to get users up to speed quickly
- **Navigation**—IVIVC wizard provides an easily navigable interface that walks users through the process of creating a Level A IVIVC; informative status indicators signal completion, missing information or out-of-date steps
- **Deconvolution Methods**—Numerical deconvolution is a documented method known for its stability and accuracy, and overall is less susceptible to study design variations
- **Fitting the Correlation**—IVIVC Toolkit provides Level A correlation; unlike other software packages, Level B and C can be done using WinNonlin
- **Custom Models**—Unlike other IVIVC software, the Toolkit provides the flexibility to use built-in correlations or the ability to develop a custom correlation model
- **Dissolution Modeling**—Built-in models better interpolate dissolution data, resulting in accurate interpolation that can make the difference between failure and success
- **Proven Phoenix Workbench**—Trusted powerful workbench can easily handle the large amount of data that an IVIVC can generate



## Numerical Deconvolution Setup Tab and Outputs from the Phoenix IVIVC Toolkit

### References

1. US Department of Health and Human Services, Food and Drug Administration, and Center for Drug Evaluation and Research (CDER). Guidance for the Industry. Extended Release Oral Dosage Forms: Development, Evaluation, and Application of *In Vitro/In Vivo* Correlations. September 1997.
2. Suarez-Sharpe, M. Li, J. Duan, H. Shah, and P. Sen. Regulatory Experience with *In Vivo In Vitro* Correlations (IVIVC) in New Drug Applications. *The AAPS Journal* (2016). 18 (6):1379-1390.

## 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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