

Phoenix IVIVC Toolkit



What is Phoenix WinNonlin

Industry leading PK/PD data analysis tool

Intuitive and easy-to-use spreadsheet style interface

Powerful and fast algorithms

- Noncompartmental analysis of both blood and urine data using methods for rich or sparse datasets
- Four methods for AUC calculation: Linear/Log Trapezoidal, Linear Trapezoidal (Linear Interpolation), Linear Up/Log Down, Linear Trapezoidal (Linear/Log Interpolation)
- Model Fitting / Parameter Estimation
 - Extensive built-in library of predefined models
 - User defined models
- Deconvolution, semicompartamental modeling, nonparametric superposition, crossover design, bioequivalence
- Analysis using fixed and mixed effects linear modeling approaches, and ANOVA
- Descriptive statistics, including weighted descriptive statistics

Flexible data management

- Quick data export to NONMEM®, SAS, S-PLUS®, SigmaPlot® and Excel
- Excel compatible workbooks, including formulas, functions, data import/export, missing value codes, sort, transformations and worksheet merge
- One-click export of results, plots, and tables to Microsoft Word®
- Units definition and conversions, including the ability to specify preferred output units, units for a dosing regimen, and unit conversions
- Support for Excel, SAS Transport, and NONMEM file formats



What is Phoenix IVIVC Toolkit?

Extension of WinNonlin functionality

Separately licensed

Stand-alone tools enable IVIVC workflows

- Deconvolution
 - Numerical
 - Wagner-Nelson
 - Loo-Riegelman
- Convolution
- Levy Plot

IVIVC Wizard facilitates particular IVIVC workflow



IVIVC Tools: Deconvolution

Existing “deconvolution through convolution”

- Improvements include:
- Multiple subject polyexponential UIR
- Dosing per subject

New Wagner-Nelson

- Infers UIR for each profile
- Watch out for flip-flop

Loo-Riegelman

- Takes 2 compt model parameters



IVIVC Tools: Convolution

Unit Impulse Response (UIR) function

- Polyexponential
- Multiple sort keys

Input function

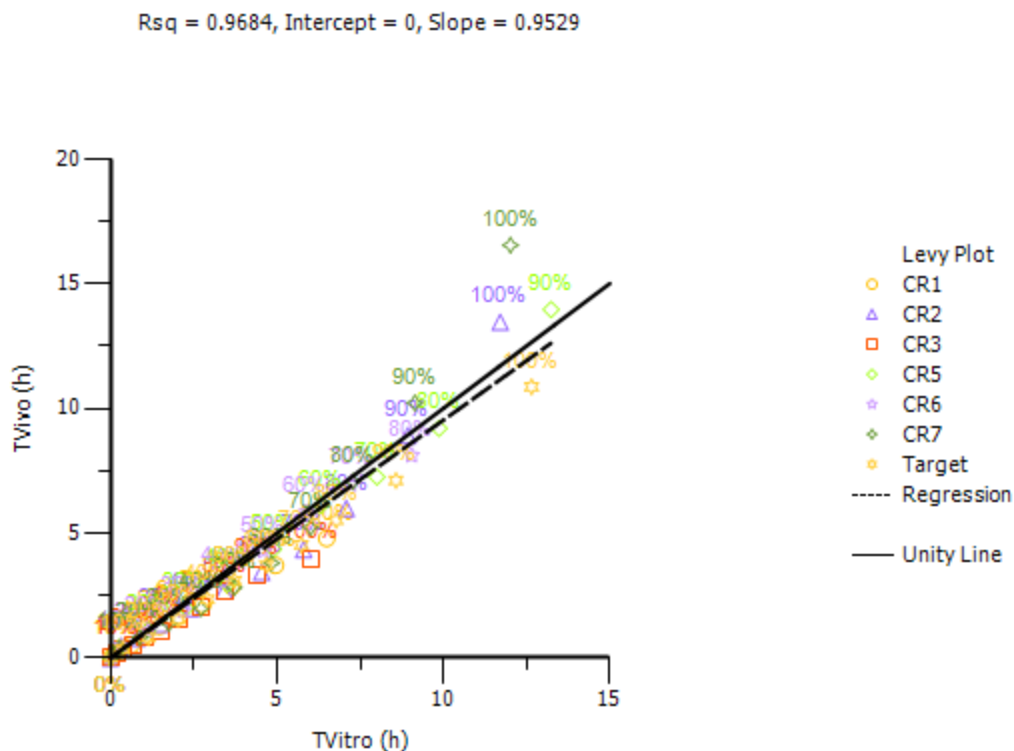
- Rate
- Cumulative (fit with linear splines and derivative used)
- Multiple sort keys

Sort Key Matching

- Map sort keys between UIR and Input
- Will match multiple Inputs per UIR

IVIVC Tools: Levy Plot

Takes two sets of X,Y data and plots X_1 vs. X_2 at matching values of $Y_1=Y_2$





IVIVC Tools: IVIVC Workflow

IVIVC Workflow: Two-stage IVIVC development

- Polyexponential UIR from IV or IR data
- Deconvolution over individual subjects
- Arbitrary IVIVC models could include
 - Dose non-linearity
 - Absorption window
 - Time scaling, shifting
- New Convolution functionality
- Levy plot
- Internal and External Validation of IVIVC model
- Prediction of test formulation PK response

Convenience

- Save settings for sharing between colleagues
- Make a change in base data and refresh the entire analysis

IVIVC Workflow Tour: Dissolution Modeling

Setup | Results | Verification

InVitro Data (Sheet1)
 InVitro Formulation
 InVitro Estimates
 InVivo Data (Sheet1)
 InVivo Dosing
 Correlation Estimates
 Plot Values
 Prediction Data (Sheet1)
 Prediction Dosing
 Prediction Estimates

View Source Source
IVIVC.Data.ivivc_vitro.Sheet1

Mappings

	None	InVitro Time	InVitro Dissolution	InVitro Formulation
Form	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>
Time	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>
Fdiss	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>

InVitro | InVivo | Correlation | Prediction | Status | Options

☐ Use raw data

Dissolution Model

☐ Hill ☐ Weibull ☒ Double Weibull ☐ Makoid-Banakar

Generated initial values

☐ Propagate Final Estimates

Phoenix bounds

Weighting Uniform Weighting



IVIVC Workflow Tour: Dissolution Modeling

Locate Workbook and Worksheet with dissolution data

Map dissolution data

- One dissolution profile per formulation

Model dissolution data

- Using sigmoidal models: Weibull, Hill, Double Weibull, Makoid-Banakar
- Can choose weighting model
- Provides for smooth interpolation while building/running models

Partition formulations

- Internal validation and modeling
- External validation
- Target (pivotal or brand), also used for external validation

IVIVC Workflow Tour: UIR and Deconvolution

Setup

Results

Verification

InVitro Data (Sheet1)

InVitro Formulation

InVitro Estimates

InVivo Data (Sheet1)

InVivo Dosing

Correlation Estimates

Plot Values

Prediction Data (Sheet1)

Prediction Dosing

Prediction Estimates

View Source

Source

IVIVC.Data.ivivc_vivo.Sheet1

Mappings

	None	Sort	Independent	Values	InVivo Formulation
Form	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>
Time	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>
Cp	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>
Study	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

InVitro

InVivo

Correlation

Prediction

Status

Options

Unit Impulse Response

Maximum number of UIR exponentials

1

Model Selection

Akaike

Weighting

Uniform Weighting

☐ Include Time Lag

☐ Strip Ka

☒ Use Observed Times for Deconvolution

Generate UIR

Deconvolve

Formulation Information

Reference Formulation

ref

Reference Data Type

IV

Dosing

Units

mg

...

In Vivo Data Options

☐ Generate mean profiles
(validate against mean profiles)

Averaging

Mean

☒ Do not generate mean profiles
(validate against individuals' profiles)

☐ Data already deconvolved and averaged



IVIVC Workflow Tour: UIR and Deconvolution

Locate Workbook and Worksheet with study data

Map study data

- Which formulation was used?
- Which columns identify unique patients?

Specify reference formulation

- Used to fit Unit Impulse Response (UIR) function
- Dosing route (IV, IR)

Fit UIR

- Choose weighting
- Choose model selection
- Will fit polyexponential to each patients reference profile
- With IR reference, we can fit time lag and/or strip 1st order k_a
- With IV reference, we can use bolus or infusion (T_{inf} specified per subject)



IVIVC Workflow Tour: UIR and Deconvolution

Deconvolution

- Numerical deconvolution of each profile (that isn't reference) using UIR for that subject
- Results (Fraction Absorbed, Fabs) averaged per formulation
- Fabs based on administered dose for that formulation

Using other data

- User can provide average Fabs per formulation and UIRs per subject
- Bypasses fitting UIR and Deconvolution
- Must strictly adhere to specified formats
- Why? To use WN, LR or other deconvolution approach with the IVIVC Wizard

IVIVC Workflow Tour: Correlation and Validation

Setup Results Verification

Filter: Validation.

- Validation.Model S
- Validation.Model S
- Validation.Observed
- Validation.Observed
- Validation.Observed
- Validation.Observed
- Validation.Observed
- Validation.Observed
- Validation.Observed
- Validation.Predicted
- Validation.Predicted
- Validation.Predicted
- Validation.Predicted
- Validation.Predicted

	Formulation	Parameter	Predicted	Observed	%PE	Ratio
1	CR1 Internal	AUClast	7349.4431	7545.575	-2.5992975	0.97400703
2	CR1 Internal	Cmax	597.75503	617.75	-3.2367414	0.96763259
3	CR2 Internal	AUClast	6864.2487	6652.7375	3.17931	1.0317931
4	CR2 Internal	Cmax	469.35765	474.17	-1.0148997	0.989851
5	CR3 External	AUClast	7176.7298	7935.435	-9.5609781	0.90439022
6	CR3 External	Cmax	634.87609	684.08	-7.1927128	0.92807287
7	CR5 Internal	AUClast	5452.8576	5430.7325	0.40740531	1.0040741
8	CR5 Internal	Cmax	373.68918	378.78	-1.3440044	0.98655996
9	CR6 External	AUClast	5721.5336	5249.135	8.999552	1.0899955
10	CR6 External	Cmax	401.60553	414.11	-3.0196011	0.96980399
11	CR7 External	AUClast	6769.7763	6627.8975	2.1406309	1.0214063
12	CR7 External	Cmax	463.19769	429.45	7.8583514	1.0785835
13	Avg Internal	AUClast	6555.5164	6543.015	2.0620043	1.0019107
14	Avg Internal	Cmax	480.26729	490.23333	1.8652152	0.97967081

InVitro InVivo Correlation Prediction Status Options

Correlation

☐ Fabs = Diss(Tvivo)
☒ Fabs = AbsScale*Diss(Tscale*Tvivo)
☐ Fabs = AbsScale*Diss(Tscale*Tvivo-Tshift)
☐ Fabs = AbsScale*(Diss(Tscale*Tvivo-Tshift)-AbsBase)
☐ User Specified # parameters 3

Generated initial values
Phoenix bounds

Tcutoff* 12

*Diss stops increasing for Tvivo>Tcutoff

Build Correlation Check Syntax

Plots

☒ Tvivo vs. Tvivo (Levy)
☒ Fabs vs. Fdiss

Generate Plots Validate Correlation

Validation

AUC AUClast Calculation Method Linear_Trapezoidal_Linear_Interpol Averaging Mean



IVIVC Workflow Tour: Correlation and Validation

Exploratory Plots

- Fabs vs. Fdiss
- Levy Plot (Tvivo vs. Tvitro)

Correlate deconvolved Fabs with Fdiss

- Built-in equations, eg: $Fabs = Fa * Fdiss(tscale * time - tshift) - Foffset$
 - Fdiss modeled or interpolated from raw data
 - Absorption cutoff optional
- Custom equation built on user ASCII models
 - Only using modeled Fdiss
 - Can incorporate dose

Validation Grid

- Runs correlation and convolution on dissolution data.
- Cmax and AUC are computed for individuals (if included in analysis) then averaged over the formulation.
- Shows prediction error (% ,ratio) of Cmax and AUC for each formulation and average over all formulations (internal and external) - compared to observed data for each formulation.

IVIVC Workflow Tour: Prediction

Setup Results Verification

Filter: Prediction.

Output Data

- Prediction.Baseline
- Prediction.Conv.Ex
- Prediction.Conv.Re
- Prediction.Corr Sim
- Prediction.Corr Sim
- Prediction.Corr Sim
- Prediction.Corr Sim

	Formulation	Parameter	Predicted	Target	%PE	Ratio
1	Test1	AUClast	5525.4853	5550.255	-0.4462799	0.9955372
2	Test1	Cmax	429.28491	435.13	-1.3432974	0.98656703
3	Test2	AUClast	4945.0465	5550.255	-10.904157	0.89095843
4	Test2	Cmax	338.88786	435.13	-22.11802	0.7788198

InVitro InVivo Correlation Prediction Status Options

☐ Use raw data

Target Formulation Target

Dissolution Model

- ☐ Hill
- ☐ Weibull
- ☒ Double Weibull
- ☐ Makoid-Banakar

Generated initial values

☐ Propagate Final Estimates

Phoenix bounds

Weighting Uniform Weighting

Fit Dissolution Data

Predict PK



IVIVC Workflow Tour: Prediction

Locate Workbook and Worksheet with dissolution data

Map dissolution data

- One dissolution profile per formulation

Specify dose per formulation

Model Dissolution Data

- Or use interpolated raw data (with built-in models)

Predict PK

- For each test formulation
 - Run correlation
 - Convolve with UIRs from target formulation
 - Uses individual UIRs, then computes means by formulation.
 - Show prediction error (% ratio) of C_{max} and AUC - compared to observed target data for each formulation.












IVIVC Workflow Tour: Projects

Colored bullets highlight status of project

- Red - not completed
- Yellow - needs to be updated
- Green - completed

Designed so Prediction Tab can be used independently of model development workflow

Easily collaborate with co-workers

Status Panel		
View		Specify InVivo data
View		Specify InVivo data
View		Fit Dissolution
View		Generate UIR
View		Deconvolve
View		Build Correlation
View		Validate Correlation
View		Fit Prediction Dissolution
View		Predict PK



Use IVIVC Toolkit to:

Assist Formulation design

Evaluate dissolution experiment

Set dissolution specifications

Investigate absorption

Explore correlation models for 1-stage IVIVC



Benefits

Incrementally leverage your existing investment in WinNonlin

Powerful IVIVC exploration and development capability

Visualize the in-vitro in-vivo relationship with new plotting features

Improve collaboration between Clinical Development and Formulation

Easy application of correlations to predict PK from new in-vitro data