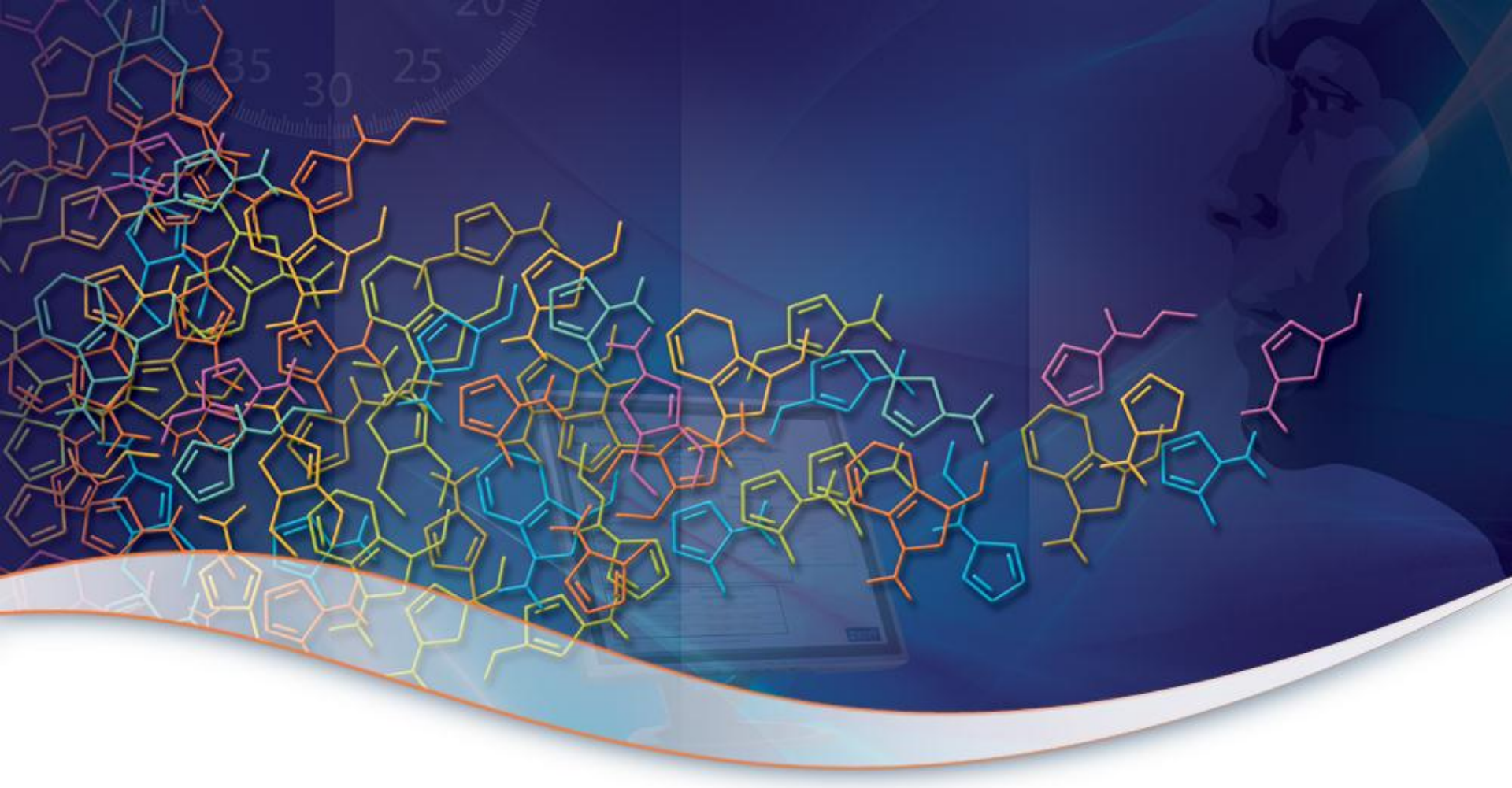


# Phoenix IVIVC Toolkit

Tripos™
A Certara™ Company



Pharsight
A Certara™ Company

# 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, semicompartmental 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

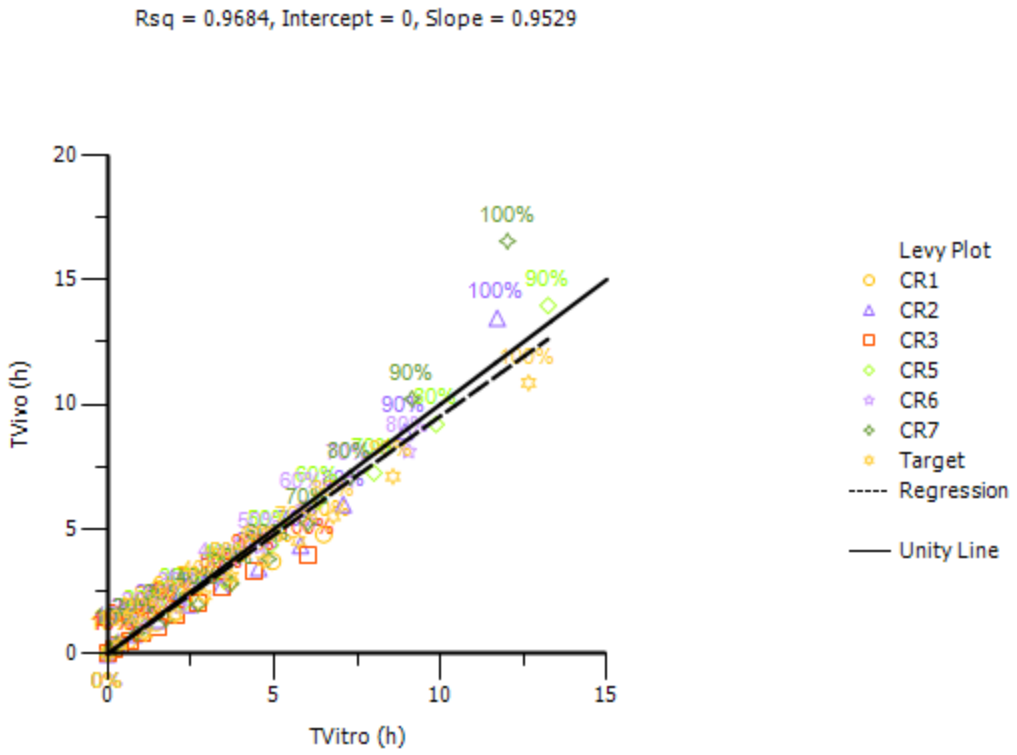
- Rate
- Cumulative (fit with linear splines and derivative used)
- Multiple sort keys

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

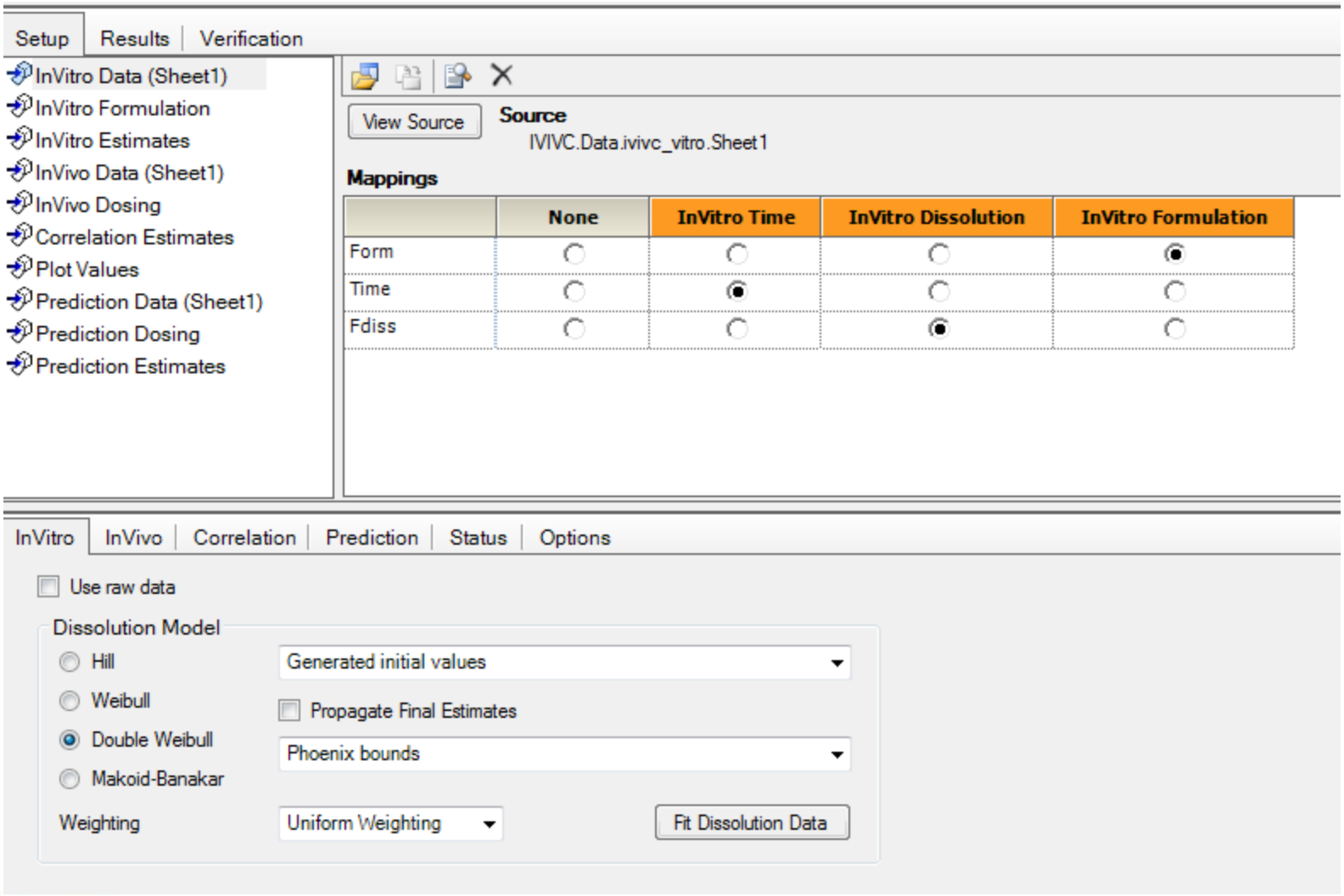
IVIVC Workflow: Two-stage IVIVC development

- 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



# IVIVC Workflow Tour: Dissolution Modeling

Locate Workbook and Worksheet with dissolution data

Map dissolution data

- One dissolution profile per formulation

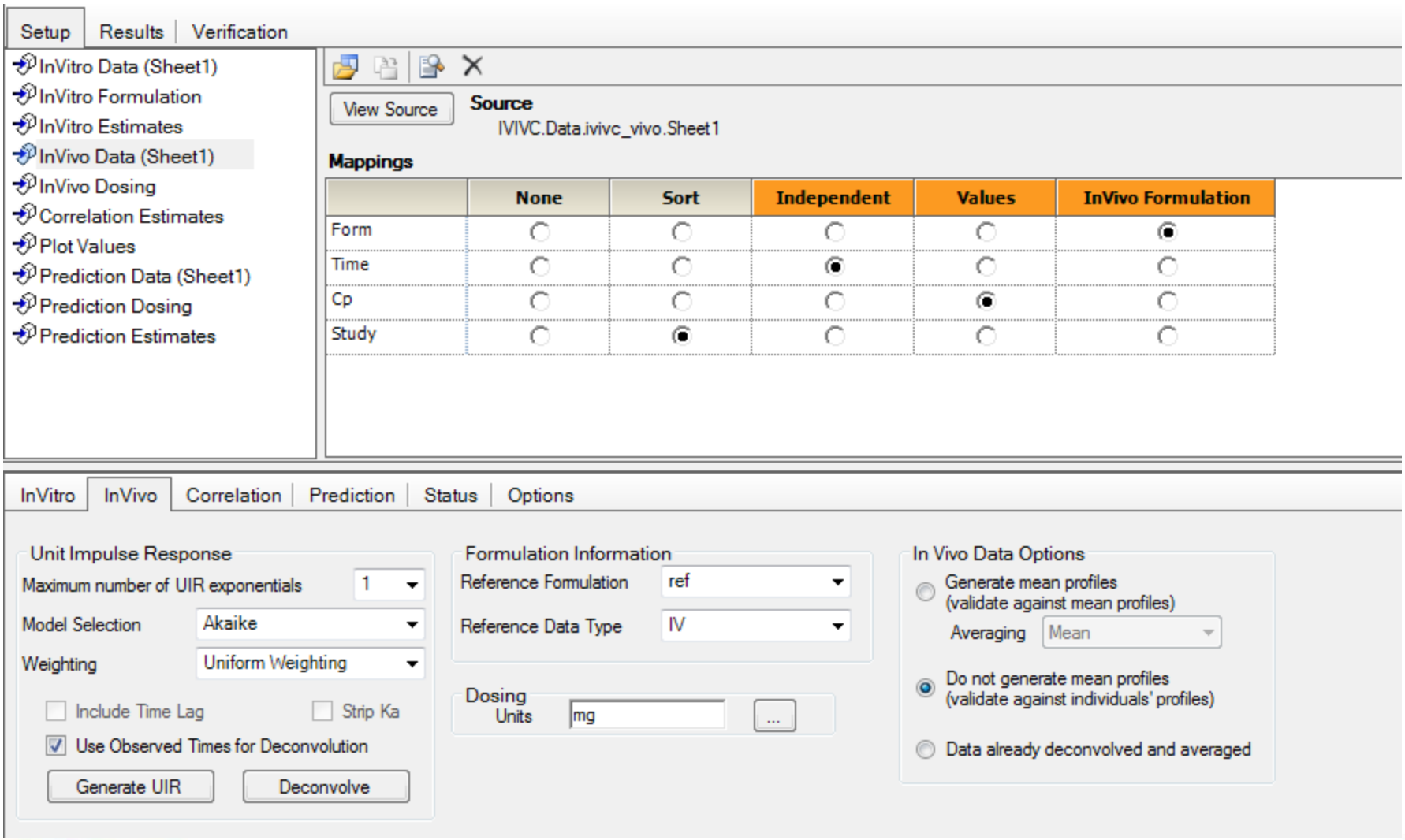
Model dissolution data

- 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



# 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 1$^{st}$ order ka
- With IV reference, we can use bolus or infusion (Tinf specified per subject)

# IVIVC Workflow Tour: UIR and Deconvolution

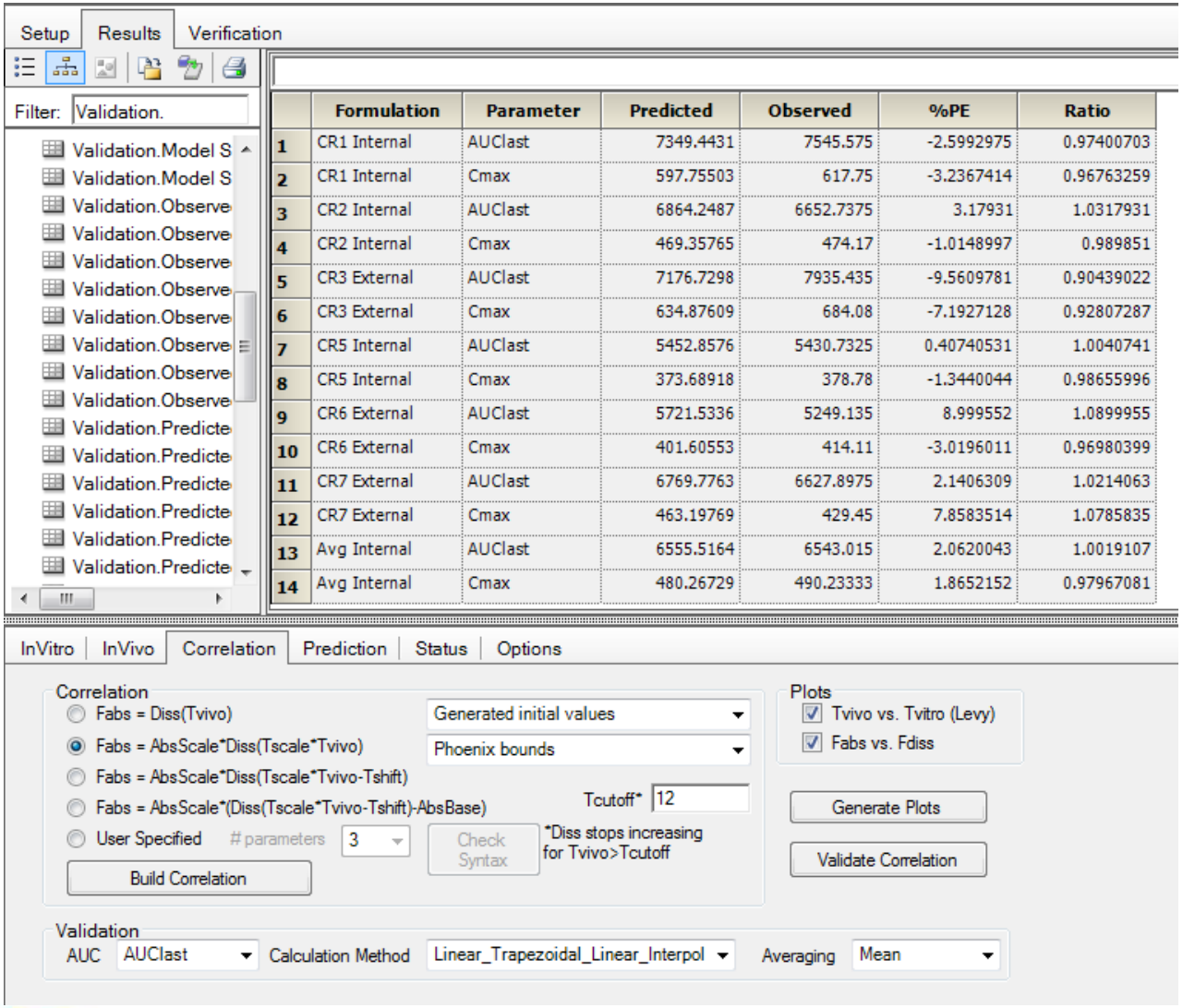
## Deconvolution

- 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




| | 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 |

# IVIVC Workflow Tour: Correlation and Validation

Exploratory Plots

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

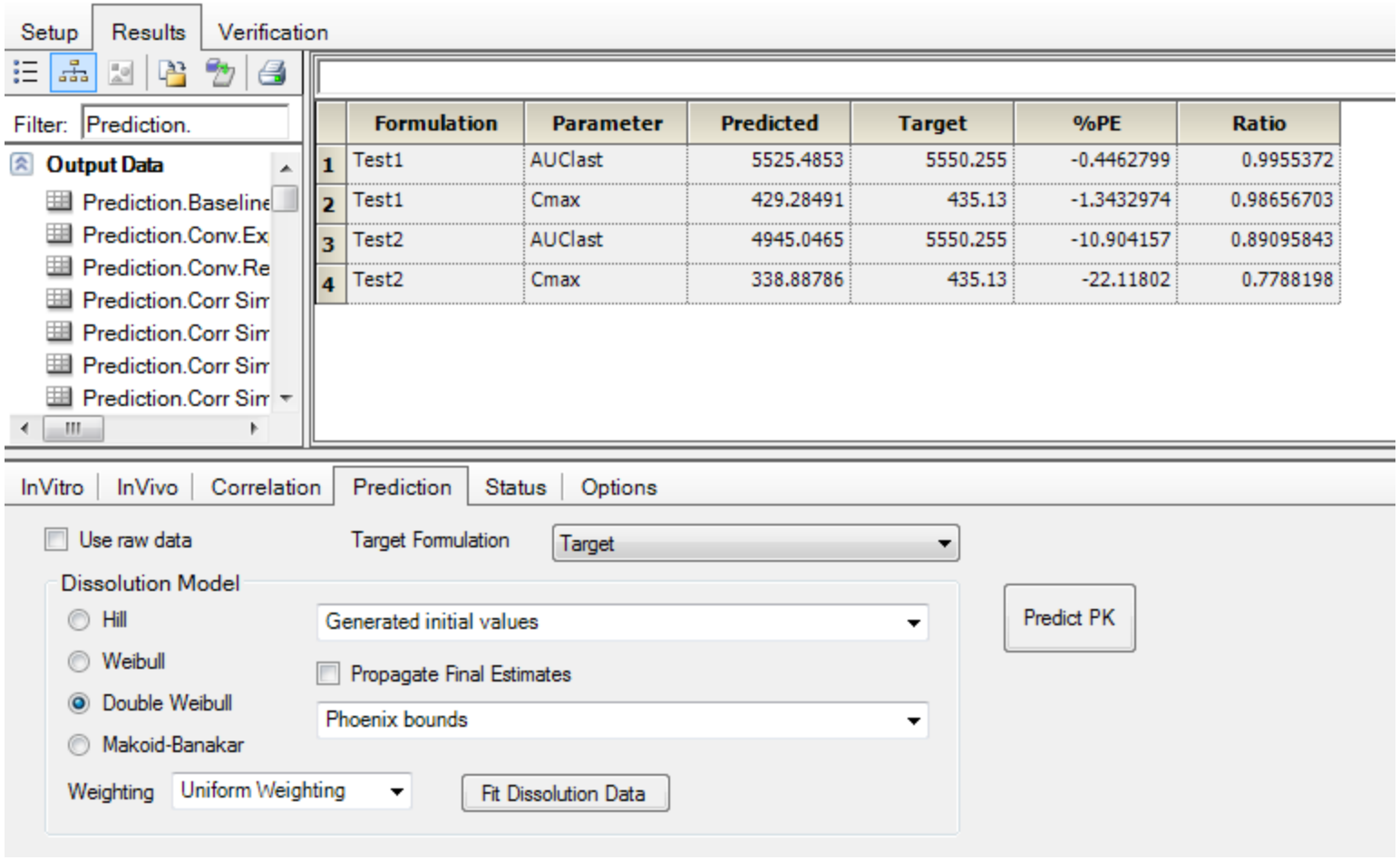
Correlate deconvolved Fabs with Fdiss

- 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



# 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 Cmax and AUC – compared to observed target data for each formulation.

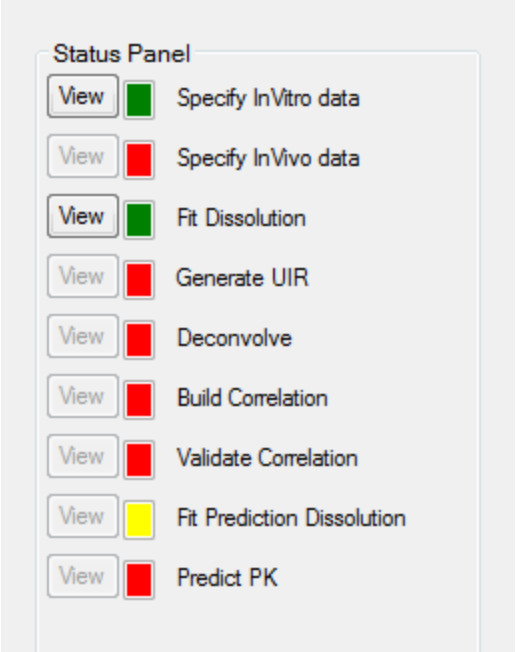
# IVIVC Workflow Tour: Projects

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



# 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