



IVIVC Toolkit for Phoenix® WinNonlin® Frequently Asked Questions (FAQ)

Q: What is the IVIVC Toolkit for Phoenix WinNonlin?

A: IVIVC Toolkit for Phoenix WinNonlin is the next generation of the IVIVC toolkit for WinNonlin. The IVIVC Toolkit for Phoenix WinNonlin is an optional add-on to Phoenix WinNonlin that enables the use of Phoenix WinNonlin for in vivo-in vitro correlations. As part of the Phoenix platform, there is a seamless integration with other Phoenix tools whereby the inputs and outputs from Phoenix IVIVC can be easily be linked to other analysis tools within Phoenix.

Q: Why would I want IVIVC toolkit for Phoenix WinNonlin?

A: IVIVC Toolkit for Phoenix WinNonlin is an easy to learn, comprehensive analysis environment for in vivo- in vitro correlations (IVIVC). The goal in developing an IVIVC is to be able to predict human or animal PK from in-vitro dissolution data. This allows for the simulation of clinical trials for new formulations, batches, or dose levels, with an eye toward demonstrating a predicted bioequivalence of the proposed formulation to a pivotal batch or a comparable approved product. Phoenix IVIVC Toolkit facilitates analysis by providing a Wizard to drive every step of IVIVC, facilitates decision making by easily generating figures and results. When used with Phoenix Connect™ (sold separately), you can access the Pharsight® Knowledgebase Server™ (PKSTM), a 21 CFR Part 11 data repository.

Q: What happened to IVIVC Toolkit for WinNonlin?

A: All the same capabilities of the IWIC toolkit for WinNonlin were implemented in the IVIVC Toolkit 2.0 for Phoenix WinNonlin 6.2. The Phoenix platform has a much improved look and feel. Support for IVIVC Toolkit for WinNonlin without Phoenix will continue according to Pharsight's internal policy of 18 months after release of the next version. Contact Pharsight at support@pharsight.com for exact support termination dates for a given version.

Q: Would I get the same answers in IVIVC in Phoenix WinNonlin as for WinNonlin 5?

A: You will usually get the same answers when running analyses in Phoenix IVIVC Toolkit as you did with IVIVC Toolkit for WinNonlin 5.3, however, some enhancements have been made and these could affect results. There will be some cases where the numerical output from Phoenix WinNonlin will differ from the output in WinNonlin 5.3. These small

numerical differences have been documented and they will rarely result in significant differences for IVIVC.

Q:I already have an earlier IVIVC toolkit for WinNonlin version, what is my upgrade path?

A:IVIVC Toolkit for Phoenix WinNonlin is the upgrade path and it is free of cost if you have an existing license agreement and annual license fee.

Q:Must one absolutely have IV data to be able to do IVIVC using the toolkit?

A: Because the IVIVC Toolkit currently supports the two-stage process (deconvolution, then modeling) there must be some kind of reference. One can use IV-bolus, IV-infusion, or oral data as a reference.

Q:What do you mean by "reference"?

A: The reference formulation is the one that is used to establish the pharmacokinetic behavior of the compound. The deconvolution process uses the reference to determine the systemic input (absorption) rate necessary to explain the observed in vivo data.

Q:Are there limitations on what can be used as the reference?

A: An IV bolus, IV infusion, or quickly absorbed oral formulation (solution, suspension, IR Tablet/Capsule) should work well. Their key feature is that the reference absorption rate is not dissolution limited.

Q:What is the "strip ka" option?

A: When fitting a polyexponential function to the reference using the IVIVC Wizard (one of the tools in the Toolkit) there is an option to "strip ka". Selecting this option enforces an assumption that absorption of the reference is a first order process. The benefit is that the fitted function describes the compound pharmacokinetics as if the formulation were an IV bolus. If the assumption is valid, doing this can remove a source of bias in the deconvolution results.

Q:How many formulations are needed to perform a correlation?

A: The Phoenix IVIVC Wizard needs to have at least one formulation (with dissolution and PK data) to build a correlation. Depending on the intended use of the correlation, one probably needs a minimum of two or three formulations with different release rates. Refer to the FDA Guidance for requirements for regulatory submission of an IVIVC.

Q:Can the Phoenix IVIVC Wizard build non-linear correlations?

A: Yes, the IVIVC Wizard provides a very easy method for writing an arbitrary custom model in the WinNonlin modeling language. In this fashion, one can deal with unique combinations of factors such as absorption windows, time dependent dissolution rate, localized gut first pass, and saturated absorption. Remember, however, that use of deconvolution implies linear (first order) pharmacokinetics (though not necessarily absorption).

Q:What deconvolution options are available in the IVIVC Toolkit?

A:Wagner-Nelson, Loo-Riegelman, and Numerical Deconvolution tools are available in the IVIVC Toolkit. The IVIVC Wizard uses the Numerical Deconvolution (Deconvolution through Convolution) routine because of its generality and stability.

Q:Does the FDA have access to the IVIVC Toolkit for Phoenix WinNonlin?

A: The FDA has access to Phoenix WinNonlin and the IVIVC Toolkit for Phoenix WinNonlin through a CRADA with Pharsight. The CRADA also provides FDA access to other Phoenix products including Phoenix Connect and Phoenix NLME.