CERTARA

IVIVC Software: Achieving Regulatory, Formulation and Manufacturing Success

In vitro-in vivo correlation (IVIVC) is a predictive mathematical tool that describes the relationship between an *in vitro* property of a drug dosage form and an *in vivo* pharmacokinetic response. IVIVC is a biopharmaceutical tool used in drug development and formulation optimization. Most important, IVIVC is a surrogate for *in vivo* bio-availability and can be used to demonstrate virtual bioequivalence and support attaining regulatory biowaivers.

IVIVC – A strategic tool in drug development

The US FDA, EMA, PMDA and other global regulatory agencies encourage the use of IVIVC, considering it an important tool in drug development to enhance product and process understanding with the ultimate goal of ensuring consistent performance throughout the product's life cycle[1].

Specifically, IVIVC is leveraged for three purposes:

- **Regulatory**
  - As a surrogate for *in vivo* bioequivalence and to support attaining biowaivers
  - In lieu of certain *in vivo* experiments[2]
  - Pre- and post-approval manufacturing changes
- **Drug development**
  - Initial guidance and direction for early formulation drug development activity
  - To enhance drug product understanding during development cycle
- **Formulation and manufacturing**
  - For testing the impact of each component in formulation and reformulation
  - Prioritization of formulation efforts pertaining to product development
  - Bridging formulations to the pivotal bioavailability or bioequivalence (BA/BE) batch

> "The role of IVIVC becomes more evident as an important tool in drug development to enhance product and process understanding with the ultimate goal of ensuring consistent performance throughout the product's life cycle. IVIVC studies are encouraged."
>
> – US FDA

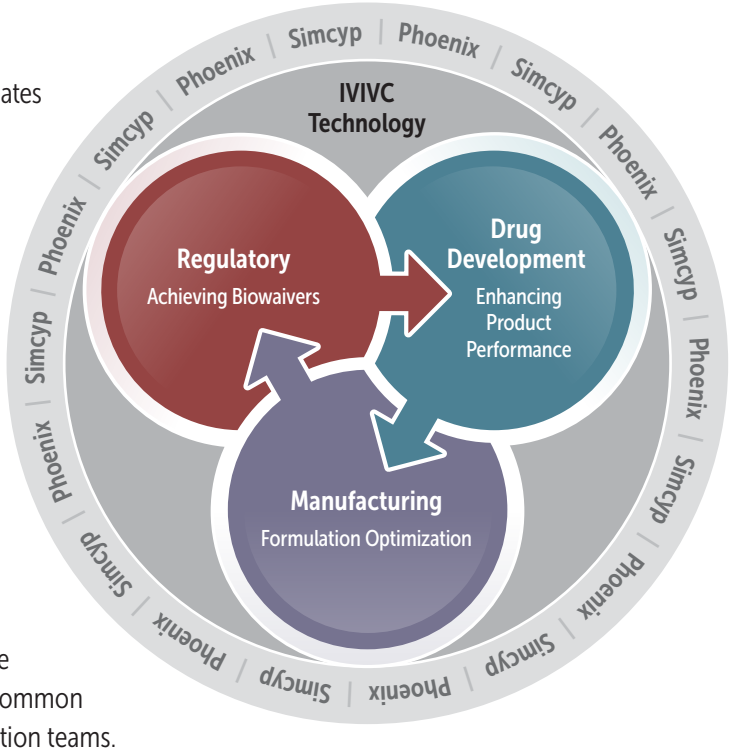
IVIVC – Accelerating drug development and saving costly studies

IVIVC technology allows formulation and manufacturing (CMC) professionals to understand how dissolution parameters affect *in vivo* drug performance. This information can be determined quickly, under inexpensive, controlled lab conditions, to serve as a surrogate for the *in vivo* drug behavior rather than through expensive and time-consuming animal or human BA or BE studies. Each avoided BA/BE study that is replaced by IVIVC analysis can shorten the development cycle by multiple months and hundreds of thousands of dollars. At the same time, IVIVC gives you the knowledge to tweak the formulation to improve *in vivo* performance with fewer iterations and false starts. In other words, a compelling use of technology.

As a drug advances through its life cycle, there is a need to establish bioequivalence at many junctions. The formulation may be changed for many reasons, including altering the timing of release, improving solubility and absorption, reducing manufacturing cost, extending shelf life, preventing adverse events such as stomach upset, improving taste and smell, and holding the tablet together. Further, new formulations many be needed multiple times during a drug's life cycle because of new manufacturing supplies, process changes, dosage form changes, or other factors.

Conventional IVIVC using Phoenix IVIVC Toolkit

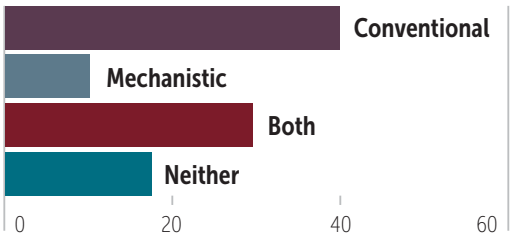
The IVIVC Toolkit™ for Phoenix® WinNonlin® is a software tool that creates and substantiates the Level A correlation outlined in the FDA guidance to correlate the *in vitro* dissolution profile of a dosage form with the *in vivo* pharmacokinetic (PK) profile. It can be used to predict the impact a change in formulation will have or predict the dissolution rate that is necessary to achieve a desired PK profile. The Level A IVIVC can support a biowaiver for changes in manufacturing site, raw material suppliers and minor changes in formulation.



Phoenix IVIVC is a 'gold standard' for predicting pharmacokinetic parameters from *in vitro* dissolution data—it is widely used in regulatory filings to support biowaivers. It uses deconvolution methods such as Wagner-Nelson, Loo-Riegelman, numerical deconvolution and modified deconvolution to estimate the rate of input of a drug into the systemic circulation from observed plasma drug concentrations to the oral formulation. Seamless transfer of the PK and IVIVC parameters within the Phoenix workbench provide a common collaboration platform between the drug development and formulation teams.

Mechanistic IVIVC using the Simcyp Simulator

A complementary approach to IVIVC that is gaining interest from a regulatory perspective is mechanistic IVIVC that leverages physiologically-based pharmacokinetics (PBPK) using the Simcyp® simulator. This approach considers and separates the various mechanisms involved in absorption, such as the transit time, gut wall permeability, gut wall metabolism and hepatic first-pass metabolism from dissolution rate. By integrating the anatomical and physiological parameters of the gastrointestinal tract with the physicochemical properties of drug substances, mechanistic IVIVC has great capabilities for designing and evaluating the performance and safety of new drug formulations.



In a recent survey, we asked leading pharma companies to comment on preferred IVIVC methodology. The results show the benefits of both the conventional and mechanistic tools, and affirm the benefits of both for regulatory, drug development and formulation.

References

1. Suarez-Sharp, Sandra et al. "Regulatory Experience with *In Vivo In Vitro* Correlations (IVIVC) in New Drug Applications." *The AAPS Journal*, August 2016.

2. Fortuna, Ana et al. "*In Vitro In Vivo* Correlation (IVIVC): A Strategic Tool in Drug Development." *Journal of Bioequivalence & Bioavailability*, August, 2011.

3. Margolskee, Alison et al. "Deconvolution and IVIVC: Exploring the Role of Rate-Limiting Conditions." *The AAPS Journal*, December, 2015

4. Mistry, Bipin et al. "Examining the Use of a Mechanistic Model to Generate an *In Vivo/In Vitro* Correlation: Journey through a Thought Process." *The AAPS Journal*, June, 2016.

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.

For more information visit www.certara.com or email sales@certara.com.

BR Nov 2016 v1 110716