Confusion about IVIVC and predicting plasma drug levels

Saeed A. Qureshi, Ph.D. (www.drug-dissolution-testing.com)

As part of a discussion on the LinkedIn Network group (Pharmacokinetics), I posted the following response. For the interest of those who do not participate in the LinkedIn Network, or the particular group, I am posting the response on this blog as well. I hope that you will find the post useful.

Thanks again Simon: [Simon's post is attached at the end of my response]

I do not think we are going in circles, but in my opinion, you are either not following my point or avoiding it. Let me explain it another time.

"The aim of IVIVC is to Predict in vivo behavior from in vitro data." This is incorrect. As the name (or "C") implies, it is not a prediction exercise, but exercise in developing a correlation. For IVIVC, one has to have in vitro (i.e. dissolution) data as well as in vivo (plasma drug levels) data, and to relate them. No prediction what so ever.

"In addition to intended and perhaps undesirable differences ……. it is removed at some rate(s)" This part reflects the pharmacokinetic properties of the ***drug*** and not the product. Therefore, it has to be obtained separate to the product, in particular to product(s) under consideration. This part should be obtained from IV and/or oral solution dose. In general, this part may be summarized by three parameters of ***drug*** (not product) i.e. elimination rate equation, volume of distribution and bioavailability factor. Again, these parameters are obtained from an in vivo study of a ***drug***, but can be, or should be, obtained from literature, thus avoiding any (additional) in vivo (or bioavailability) study.

For prediction purposes, one combines the above mentioned parameters with in vitro dissolution results and obtains the plasma drug levels. There is absolutely no need for developing an IVIVC.

Now, to merge these two i.e. parameters and dissolution curve, you are suggesting the use of a Linear System approach by (dissolution) curve fitting/modelling which is a perfectly valid approach, but complex and difficult to understand, use and also may be expensive (one has to buy sophisticated software e.g. Phoenix). However, in my suggested approach one can achieve the same end results (predicted plasma drug level) using Excel spreadsheet software based on simple arithmetic calculations. Perhaps you may like to include that approach in your software as well, it is free (lucky you!)

So, in short, I can say that it is only the convolution approach which can provide predicted plasma levels and developing IVIVC would be of no use or help.

Greatly appreciate your time and look forward to hearing from you.

++++++++

Saeed, we seem to be going in circles here as I thought we went through this on another thread. (http://www.linkedin.com/groupAnswers?viewQuestionAndAnswers=&discussionID=250075776&gid=1909401&commentID=146228158&trk=view_disc&fromEmail=&ut=1Az0Dn4TaABRQ1)

Furthermore it is difficult to explain these concepts without diagrams etc, but to summarise.

The aim of IVIVC is to Predict in vivo behavior from in vitro data.

In addition to intended and perhaps undesirable differences in the formulations themselves, there are notable differences between people and dissolution apparatus;
Dissolution conditions e.g. High variability in people, Very complex "media", Time variance of solubility, hydrodynamics
Absorption e.g. Additional step to get into "water" also Distribution, Metabolism and Excretion: Drug doesn't just "hang out" in our "water", it is removed at some rate(s)

So we split the problem up and, using Linear Systems Theory, if we know the response of a system to a known input we can predict the response to a different input. How does the IVIVC wizard help you manage these steps well here are the main steps (each is a separate tab in the tool)

1) Find a Model to describe the Dissolution Profiles well

2) Estimate absorption, this is where you can use model-dependent approaches e.g. Wagner-Nelson (single – compartment) or Loo-Riegelman (two – compartment) or *Deconvolution*

3) Use Levy Plots etc. to propose and test the Correlation model, Phoenix allows you to easily select sets for both internal and external validation of the model; the latter process involves 'holding back' one or more sets from the model selection and building process and then running the processes of *deconvolution* and *convolution* to confirm your predicted profiles are within acceptable limits of actual observed profiles

4) Prediction, using the IVIVC model and convolution we can now predict in vivo profiles for *new formualtions which have not yet been tested in man/in vivo*. This is the power that building an IVIVC gives you.

Simon.

PS We have made many free to view videos to show how to use our software and/or approach modelling problems here is one of them;
Introducing the IVIVC™ Toolkit 2.0 for Phoenix® WinNonlin®
http://www.pharsight.com/events/eventsonline_archive.php#replay_048
Speaker: Jason Chittenden, M.S., Director, Product Development

Join this webinar to learn how the IVIVC Toolkit can improve your bioavailability and bioequivalence studies. During this webinar you will learn how to create correlations via the use of an IVIVC Wizard; perform numerical convolution and deconvolution; create tables and figures, including Levy plots; predict pharmacokinetics from new in vitro data. You will see how all of these operations can be performed in a single, integrated, regulatory compliant software tool.

ALternatively there are some shorter but less detailed Youtube videos e.g.
http://www.youtube.com/watch?v=VeVaSbABptw
http://www.youtube.com/watch?v=-AYnWrWsAXo