The lack of clarity and understanding of the IVIVC concept and practice result in making erroneous claims

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The present day confusion regarding IVIVC comes from a poor understanding of the concept and its presentation in the literature. The commonly presented description of the IVIVC concept in literature is the development of the relationships, or lines, between in vitro (dissolution profiles) and in vivo (dissolution or plasma profiles) results, as described earlier (see link). The confusion comes from both aspects i.e. theoretical, along with its associated mathematical procedures, and the experimental.

Theoretical misunderstandings: In this regard, it should be noted that one does not need to develop a relationship, it always exists. The practice of dissolution testing is based on this fact that this relationship exists (see link). Developing an IVIVC is exactly like being required to develop a relationship between the capacities or quantities of gas (petrol, for the European and Eastern usage) in the tank and the distances the car will travel. There is no need to develop a relationship here, it is a fact that the larger the tank is, or more gas in it, the farther the car will go. Similarly, slower or faster the dissolution rate is, correspondingly in vivo drug availability will be slow and quick, as will be reflected by the plasma profiles. If there is no dissolution (or no gas) there would not be any blood levels/profiles (or car would not run). There is nothing to show or prove here, it is a fact that the relationship always exists. The current literature, and guidances, on IVIVC require developing such a relationship which, as described earlier, is not needed and cannot be used for the development or the evaluation of a product. What is required, however, is the predictability, or a procedure for calculation, of the **actual** distance a car will travel with a tank full of gas or the plasma drug levels for a drug product. That is where modeling or development of an equation is required.

Mathematical considerations: Basically, here the development of an equation/model means having a proportionality constant which could be used to multiply the capacity of the tank or amount of gas present to provide the distance the car will travel. This proportionality constant will be reflective of various factors such as the nature of car engine itself, its size, weight and road conditions etc. So the larger the tank or amount of gas, the further the distance the car will travel, but how large of a distance will travel will the car travel exactly, this will be calculated from the equation/model based on the proportionality constant.

Translating this analogy to our purpose in pharmaceutics, we need to develop an equation (which mathematically known as model) with a proportionality constant that can be used for the prediction of plasma profiles. Reiterating, we do not need to develop relationships or correlations (i.e. IVIVC), which always exist but need to develop an equation/model to predict/calculate plasma profiles (see links 1, 2). That is why I have written that the practice of developing IVIVC is a total waste of time.

Coming back to the analogy of the proportionally constant I referred to earlier, although I referred to it as a constant which gives an impression of a number, in reality this is not a number but an equation reflecting the impact of numerous factors such as car size, road, weather conditions, and so on. Mathematicians like to refer to such a proportionality constant as a "function defined by an equation", but for us, the not so mathematically inclined, the terminology of an equation is perfectly all right.

To predict a distance the car will travel with certain amount of gas, one would require merging (convoluting) the amount of gas available and the proportionality equation/function, hence the name convolution. Understandably, from the calculation perspective, the convolution is bit more complicated than we analysts are accustomed to. However, the fact remains that the underlying principle of convolution is exactly the same as for solving a linear equation, such as the ones we use for calibration purposes (for further detail see the link). By the way, in the convolution area this proportionality equation is referred to as a "weighting function/equation" as well.

To translate this analogy to our dissolution vs plasma profiles topic i.e. to obtain plasma profiles from dissolution results we need to merge (convolute) dissolution results with the proportionality constant, or equation as well, thus it is referred to as a convolution step. The question is how do we get this proportionality constant/equation? Or a more basic question is what does this proportionality constant represent? In pharmaceutics, this proportionality constant is the drug

plasma profile/equation following the administration of a very (infinitely) small dose of the drug. For all practical purposes, this is the elimination rate equation of the drug under consideration. So, when one likes to do convolution one should obtain this equation for the drug under consideration from literature or any standard pharmacology book (for further detail please see the link). By the way, in the convolution area this proportionality constant is also referred to as the "unit dose/impulse factor". So, do not be confused with terminologies, they refer to the same thing but with different names depending which discipline one is following.

There are different ways of such merging or convolution of dissolution results with the proportionality equation, I have suggested a simple procedure in one of my publications (see link). It is to be noted that, the whole product development and evaluation area revolves around conducting the dissolution tests and predicting plasma levels, ***which can ONLY be obtained using the convolution approach*** (link). We do not need IVIVC or even deconvolution at all, however, the majority of literature describes and requires these two practices, unfortunately incorrectly. It is then no wonder that people are so confused and not very successful in predicting plasma profiles from dissolution results. In fact, we will never be successful, if we keep on discussing and requiring the same thing (IVIVC) over and over again, when we, in fact, need a convolution approach or procedure.

Let me clarify another aspect in this regard, that the convolution, and also the IVIVC and deconvolution, are mathematical conversion procedures just like the conversion of UV absorption values of samples to percent drug dissolution/release by multiplying with the proportionality constant/slope while taking into account of a dilution factor, dosage strength, medium volume etc. Convolution is a mathematical procedure often applied in other areas (e.g. engineering), however, in pharmaceutics, it appears that it has not been explained well thus the confusion and frustration in its use. The important thing to remember is that convolution is a data manipulation/conversion procedure, and is not part of the experimental science thus, independent of the apparatus used to generate the data.

The experimental aspect: It should go without saying that no matter how well one explains the concepts and how much easier the described approach of convolution would be, if the data (dissolution results) are not relevant and reliable, then it is all a waste. Therefore, relevancy and reliability of the apparatuses and the data obtained are of critical importance. However, currently suggested apparatuses in particular paddle/basket lack the relevancy. People say that some apparatuses (paddle/basket) provide simplicity while other (flow through) provides flexibility. My question has always been, do these apparatuses provide relevant and reliable results? The answer is most definitely a NO.

An obvious question would be why are these apparatuses not relevant? Without going into further detail, as the detailed discussions have already been provided elsewhere (see links 1, 2), these apparatuses are not qualified and validated apparatuses for their intended purpose (see link). It does not matter that an apparatus is simple to operate or flexible to adapt, if it is not qualified and validated then there is no point in using the results obtained from such apparatuses and drawing conclusion from them, whether for the prediction of plasma profiles and for any other purpose. If someone thinks that I have misjudged these apparatuses or am missing something, please publish or provide some data showing that these apparatuses are indeed qualified and validated. However, based on the data available in literature and my personal experience of over 25 years of research in this area, I maintain my opinion, that these apparatuses cannot be considered qualified and validated for dissolution testing.

Analysts/formulators must, therefore, keep this thought/fact in mind that they are using apparatuses which are not qualified or validated, thus the reliability and usefulness of results, for IVIVC purpose or otherwise, will be questionable at best. That is why I have stated that the current practices of IVIVC are a complete waste of time and I maintain this opinion.

My suggestion of using the crescent shape spindle is based on the above mentioned thoughts and observations. Not only based on my views, but based on the positive feedback I receive regarding the use of the crescent shape spindle and the suggested approach of convolution to predict plasma drug profiles, I strongly suggest that people should try these spindles and see for themselves how interesting and useful dissolution testing will become.