Are bioequivalence (BE) assessments of clinical significance and relevance? Not really!

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A discussion is provided showing weakness of BE assessments for comparing or establishing quality of products such as tablets/capsules. It is argued that in vitro drug dissolution/release testing would provide a better alternative for assessing the quality of such pharmaceutical products.

It is often accepted that if two products provide the ratios of AUC and Cmax within a range of 80-125% (bioequivalence criteria), they would be considered therapeutically equivalent. For example, a good discussion on the topic and its statistical aspect is provided here. The topic is also described in detail in many books and in regulatory guidance documents such as from the US FDA (link).

It is commonly assumed that as a difference of 20% between two treatments would not be recognized by the body as significant therapeutic impact thus such a difference would be considered inconsequential. The literature does not appear to provide evidence in support of this assumption. Therefore, choice of the accepted range is purely an arbitrary standard for regulatory convenience - not from patients' and/or product quality perspective.

The more important question is then what does this 80 -125% range in reality reflect. First of all, it should be clear that this range reflects differences in blood drug levels (which are commonly measured as plasma drug levels, therefore in this article plasma drug levels will mean blood drug levels) from two treatments which could be from two different products (generic vs innovator, variations in manufacturing or formulation of the same product, or in fact repeated administration of the same product in different or the same patient at different times, etc.).

The plasma drug levels are directly linked to the absorption of the drug from solution form in the GI tract, in particular the small intestine. The higher the absorption (which is directly linked to the drug dissolution/release from the product) the higher plasma drug levels and vice versa. This dissolution-absorption-plasma drug levels relationship is commonly referred to as IVIVC (in vitro-in vivo co-relationship), which always exists and is the fundamental underlying scientific principle for the assessment of the plasma drug levels and by extension product quality.

On the other hand, interestingly people always try to develop the IVIVC, which in fact is often regulatory recommendation or requirement. However, unfortunately such IVIVC exercises have seldom been successful. So, the question is, if this relationship exists then why have people not been successful in establishing it. The reason being, the suggested IVIVC models have not been applied correctly. The IVIVC exists between the in vivo dissolution and plasma drug levels however it is commonly applied for in vitro dissolution vs plasma drug levels without showing, validating or equating relationships between in vitro dissolution and the in vivo dissolution.

It is important to note that the appearance of a drug in plasma from a product is at least a three-step process, while in vitro dissolution assumes plasma drug appearance would be a direct or a one-step process. Let me explain. Once a person takes a tablet or capsule, it goes into the stomach, where the process of disintegration/dissolution

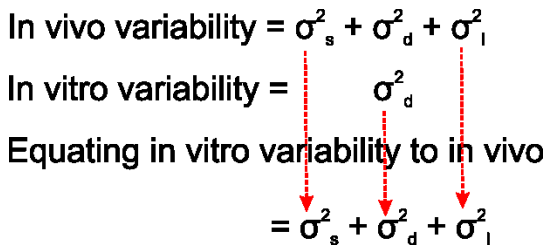
starts. It is important to note that absorption hardly occurs here. To absorb a drug into the body, the drug has to move into the intestine. The transfer of the drug from the stomach to the intestine is dependent on pushing content into the intestine (commonly known as stomach motility or emptying effect). The slower the motility/emptying rate, the slower the drug would be available for absorption and vice versa. It is highly unlikely that the entire drug would appear in the intestine at the same time, especially in different patients. It usually comes in portions. In addition, the drug (or product if it is non-disintegrating type or coated such as enteric) would appear in the intestine at random. It is commonly accepted that the stomach emptying time is about three hours but can vary. So, even if a product is of immediate release type it could take up to 3 hours for the entire drug/product to appear in the intestine/plasma (link). On the other during the in vitro testing, the process is simple and very predictable i.e. when the product is available for dissolution - which is tablet/capsule dropping time into the vessel.

Second, once the drug is absorbed from the intestine, it will pass through the liver before appearing in the plasma/blood, which can metabolize the drug from 0 to 60%+ depending on the nature of the drug and/or its rate of availability to the liver. However, this variability does not exist in the in vitro drug dissolution testing. In vitro dissolution test provides 100% of the drug with minimal variations as it is a simple physical test. Thus, the lack of success in developing IVIVC!

Before moving further, it is very important to note that often observed high variability for in vitro dissolution tests is not related to product characteristics but a reflection of the poor hydrodynamics within the dissolution vessels (link). Therefore, the use of the currently recommended dissolution apparatuses, such as USP, must be avoided if in vivo relevance of the results is desired.

To summarize the in vivo dissolution-absorption-plasma drug levels discussion, it can be stated that it is dependent on three variables: (1) stomach emptying, (2) drug release/dissolution from the product (3) liver or hepatic metabolism. The in vitro drug dissolution test only reflects the #2, i.e., drug release/dissolution, which is often the least variable of the three. This means that for all practical purposes, BE assessments are measuring or reflective of variabilities of the biological system (stomach motility and hepatic variability), not that of product dissolution/release *per se*. However, the BE studies are being considered or promoted as the evaluations of choice for assessing the in vivo drug release characteristics.

In the statistical terminology, this is represented as follows:



To convert the in vitro dissolution variability as it would appear in vivo from the drug levels in blood, one requires adding variability components corresponding to the stomach emptying (σ_s) and the liver metabolism (σ_l) to the observed/experimental in vitro drug dissolution variability (σ_d). Note that stomach and liver variabilities are independent of the product but

specific to the patient (physiological) and drug, respectively. Thus, if one even reduces the in vitro dissolution or manufacturing variability of a product to extremely low or zero, plasma drug levels will still show their high variabilities depending on the physiological and drug components. So, for all practical purposes, the BE assessment range of 80-125% represents non-product-related variability. Another way of saying this is that plasma drug levels assessment (which is BE) is a poor model or predictor, in fact inaccurate, for assessing drug release characteristics (or quality) of the product or at least non-specific to assess the in vivo product dissolution/release characteristics.

Usually, clinical BE studies are conducted in multiple human subjects. Let us assume that a test study is conducted on 24 subjects. Further, assume that each subject is given a single tablet, thus 24 tablets which have insignificant or zero variability for the drug content and its release (dissolution). In vitro one can consider these 24 subjects represented by 24 dissolution vessels, where each vessel receives one tablet at different times, reflecting the variability of stomach emptying time. In the end, an analyst will have 24 dissolution profiles scattered, reflecting stomach emptying time. Accordingly, drug levels from every subject (represented by individual dissolution vessel results) will be metabolized/reduced in the range of bioavailability factor - and at random. This in vitro metabolism component can be simulated using a filter of random absorbability, which would hold some amount of drug in the filter going into a sampling tube. Following this process, one would have 24 dissolution profiles with reduced blood level equivalents as per the drug bioavailability factor. Adding all these blood drug levels with common time scale, as commonly done for human BE studies, will result in average plasma profiles with associated variabilities/spread of plasma drug levels for every sampling time. The resulting profile (shown in Figure 1) will look similar to the

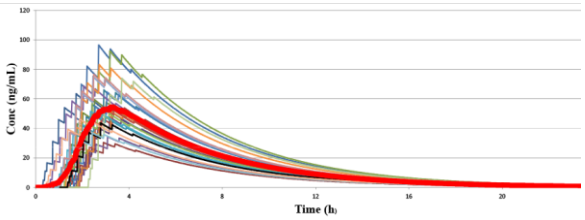


Figure 1: Predicted plasma drug levels obtained/simulated from drug dissolution profiles of a 60 mg diltiazem IR tablet product. Thin lines represent results for individual subjects while thick line represents mean values for each sampling time

The details of this virtual experimental model are described here (link), which clearly shows a high variability of plasma drug levels (~29% RSD) without any contribution from the product or dissolution results. Therefore, this strongly indicates that the commonly observed variability in the BE studies reflects the combined effect of stomach emptying and metabolism. Further, it may be assumed that as the 80-125% range is arbitrary, and may be conservative, i.e. not reflecting higher expected variability of the physiological system, thus BE results should often fall outside the criteria without any involvement of product/dissolution deficiency.

Furthermore, it is very important to note that considering the dependency of the plasma drug levels on stomach emptying and liver metabolism components would make the BE assessment a non-specific assessment. This clearly demonstrates the weakness of BE assessment for in vivo or in vitro dissolution evaluation of the product and, by extension quality of the product.

On the other hand, an independent in vitro drug dissolution test could be considered a specific test for such purposes as it is free from the stomach and drug variability components thus should be used if dissolution characteristics or quality of product assessment is required. However, as noted above, care must be taken in using currently suggested drug dissolution testers as these cannot provide relevant dissolution testing because of their design problem and lack of validation. A vessel-based dissolution tester using a modified stirrer, such as a crescent-shaped spindle, may provide a better alternative (link).