Quality generic products without bioequivalence (BE) assessment – a simple and practical approach!

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Considering the weakness (non-specificity) of BE assessments it is suggested that in vitro drug dissolution/release testing would provide a better alternative to establish quality of pharmaceutical products such as tablet and capsule. It is argued that the use of in vitro dissolution test should be the method of choice for developing and monitoring improved or better quality generic products because BE assessment focuses only on equivalence and not on the improvement of the product quality. Other significant advantages of using an appropriate in vitro dissolution test in lieu of BE assessment are described.

Bioequivalence (BE) studies are conducted, which are often a regulatory requirement, to establish quality, and by extension safety and efficacy, of the pharmaceutical (drug/medicinal) products such as tablet and capsule. The BE assessments establish whether two or more products provide the same or similar blood/plasma drug profiles/levels in humans from the tested drug products. The underlying understanding for such assessments is that if two or more products provide the same/similar drug levels then their therapeutic outcome would be the same i.e. their efficacy and safety would be the same as that of the reference (e.g. innovator's) product. This forms the basis of world-wide regulatory approval of generic products for human use. In reality it is an assessment to establish drug release characteristics of the products in humans which leads to the observed plasma drug levels. In this regard, a BE assessment is a typical analytical test or assessment, however often referred to as clinical evaluation or test as the analyzed blood samples are from humans. Otherwise there is practically no difference between such "clinical" evaluations from any other analytical test of average complexity.

An important thing to note is that the BE assessments do not establish quality, by extension safety and/or efficacy, of the drug/medicine but only of the drug or medicinal products i.e. the assessment is only for drug/medicinal products such as tablet and capsule. One has to be clear on this differentiation as confusion exists in literature and in the minds of scientists and practitioners who consider these (drugs/medicines and drug/medicinal products) one and the same thing. A simple way to differentiate this aspect is by noting that a consumer/patient needs a drug/medicine (often a pure chemical compound) however buys or is prescribed a drug/medicinal product (often a composite of multiple ingredients along with the drug/medicine). Therefore, from the quality aspect a drug product (tablet/capsule) must fulfil consumers'/patients' need which is - the product must release the drug/medicine from the product as expected, which BE assessment establishes. Thus, for all practical purposes a BE becomes a quality assessment test for the products and the drug release characteristics as the quality attribute. It is important to keep this thought in mind that BE is in reality a drug release test based on the evaluation of human plasma samples and forms the basis of establishing quality of the products.

As for any typical analytical test, to be valid and acceptable a BE test must also follow some

fundamental requirements which unfortunately it does not. For example, a fundamental requirement for any analytical test is that it must be specific and unbiased, ***which the BE assessment is not!*** As noted above, the BE test assesses drug release characteristics as reflected by human plasma drug levels, however, the results are confounded with other physiological processes/variables such as stomach emptying and liver metabolism. As explained previously [1], it could be argued that the current BE assessments as conducted or required may not provide accurate drug release characteristics of the products thus product assessment and/or its quality. It may not be incorrect to say that BE assessment as currently used would be a scientifically invalid test and its use and/or requirement should be reconsidered.

In addition to scientific invalidity of this test, it seriously hinders the development of the products with improved quality because a BE test focuses only on providing "equivalent" quality products not improved or better ones. Thus, with BE assessments one does not have an option to manufacture improved or better products, no matter how the claims are made.

Considering ethical and large monetary and extended time requirements, drug release assessments are usually conducted using an in vitro test known as drug dissolution test. This in vitro test does not require the use of human subjects and is less expensive, simple and faster to conduct. This test is conducted on the basis that for a drug to be absorbed, and to appear in plasma, it must be released from the product and dissolved in the GI tract content, in particular intestinal, which is water based at body temperature having pH around 6. As this (dissolution) test deals only with the drug release characteristics and free from confounded variabilities of physiological factors as noted above for BE assessments, by definition the test becomes specific and unbiased. Therefore, the test provides a better alternative to human BE assessments.

Unfortunately, the dissolution test as practiced, and required by the regulatory authorities, suffers a serious deficiency which is, it does not provide scientifically valid dissolution results. The recommended testers have never been qualified and/or validated for their intended purpose. In addition, most commonly recommended testers (paddle/basket) are simply not capable of providing relevant dissolution results because of their flawed design. In fact, if given a blinded tablet or capsule sample it is not possible to determine dissolution characteristics of any product.

There is significant scientific literature available indicating poor hydrodynamics within the dissolution vessels and inability of these testers to provide relevant and predictable dissolution results. On the other hand, if the lack of stirring and mixing (poor hydrodynamics) aspect could be addressed then the drug dissolution testing can become an accurate and relevant dissolution test measuring drug release characteristics of the products. In this regard, a modified stirrer has been suggested providing relevant dissolution characteristics of the product [2, 3]. Thus practice of BE evaluation may now easily be substituted using an in vitro drug dissolution.

If desired, two simple approaches may be used to complement and/or enhance the credibility of dissolution results with regard to in vivo bioavailability assessment: (1) Plasma drug levels may directly be predicted from dissolution data

using a suggested convolution method and comparing these predicted results with the ones available in the literature from human studies [4]. (2) Conducting a bioavailability study with the ***test product only*** and comparing trend of obtained pharmacokinetic parameters with the ones provided in literature.

There are number of advantages in conducting such in vitro dissolution studies and establishing quality of products: (1) one can determine accurate and unbiased dissolution characteristics of the products; (2) one does not require reference products, which are often difficult to obtain, to conduct comparative BE studies to evaluate the test products; (3) It provides the ability to manufacturers and the regulatory authorities to independently develop and regulate better quality generic products not just equivalent. (4) The drug manufacturing and evaluation process would become significantly simpler and efficient thus saving time and money for their development.

If you would like to have further information or discussion on the topic, please do not hesitate to contact me by sending an email at principal@pharmacomechanics.com.