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On The Topic of Bioavailability/Bioequivalence-Challenges with Polymorphic Metabolism

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The topic Bioavailability/Bioequivalence (BA/BE) which is a primary driving force for the introduction of generic drugs of small molecules has been discussed for several decades now [1-5]. BA/BE studies also are important for the development of new drugs as API manufacturing process and formulation options keep changing during the entire drug development paradigm. It is needless to say that BA/BE considerations has gone through phases of considerable debate amongst pharmaceutical scientists, academic researchers, regulators and key opinion leaders. While on one hand it could be argued that there is no one single approach that could satisfy the need/requirements for all the stake holders, on the other hand there need to be an uniform yard stick to allow consistency in BA/BE assessment. Hence, the application of average bioequivalence criteria using geometric means of peak concentration (C_{max}), [a measure of rate of absorption] and geometric means of area under the plasma/serum/blood concentration curve *vs.* time (AUC_{inf}) [a measure of the extent of absorption] for the parent compound between test and reference formulation has been well accepted. In order for a test formulation to be bioequivalent with the reference formulation geometric means and the 90% confidence intervals of both C_{max} and AUC_{inf} ratios of test/reference should be contained within 80 -125%.

Along with progressive evolution of BA/BE considerations and associated criteria, debate on other relevant issues such as considerations of drug metabolite(s) and racemates (total drug vs individual enantiomers) in the assessment of BA/BE have also occurred. Straight forward scenarios where metabolite(s) need to be used as surrogates for BA/BE assessment instead of parent compounds include: 1) rapidly converting to prodrugs; 2) highly unstable and/or highly metabolized parent compounds. In some instances, active metabolite(s) in conjunction with parent compounds are being considered for BA/BE assessment - the logic for such comparison stems from the fact that active metabolite contributes largely to the pharmacology/ pharmacodynamics of the drug and therefore, cannot be ignored during a BA/BE assessment.

The focus of this editorial is pertaining to BA/BE of drugs that are prone to polymorphic metabolism. Interestingly, a recent report based on pooled analysis of BA/BE studies for fluoxetine, a substrate for CYP2D6, has documented the enrollment of unsuspected PM phenotypes (approximately 10%) in an Indian population [6]. The regulatory framework is very fluid when it comes to BA/BE assessment of metabolite(s) be it polymorphic or non-polymorphic in nature. However, it is left to a large extent to the discretion of the sponsor as to what one needs to be accomplished in a BA/BE study and if the path taken by the sponsor is outside of the norm it is always prudent to obtain a regulatory buy-in prior to performing the study and the described analysis/assessments.

In a hypothetical situation, the editorial explores options to show BA/BE between a test and reference product for a drug known to undergo polymorphic metabolism. While each option in its own merit seems interesting, it has inherent risks and challenges which need to be carefully weighed in before making a decision on an appropriate option.

First: One of the easy option is to enroll heterogeneous pool of patients without regard to the phenotypes for the polymorphic enzyme. However, due to known pharmacokinetic and disposition differences between poor metabolizers (PM) and extensive metabolizers (EM), this would introduce consider variability in the data set. Therefore, a larger sample size to account for the inherent variability is in order to provide a good chance to demonstrate BA/BE between the two products.

Second: Another interesting option would be to enroll homogeneous pool of patients either EM or PM phenotypes and the statistical power calculations could be based on the known variability of the chosen homogenous pool of patients. In this regard, the work reported by Yuan and Sahajwalla (1999) has suggested that BA/BE assessments using PM phenotypes for CYP2D6 should considerably reduce the number of subjects required for the study since the variability is reduced in PM phenotypes as compared to EM phenotypes (almost a 4-fold reduction in variability in PM vs. EM was reported) [7].

Third: Another rather radical option would be to convert EM phenotypes to PM equivalents by using a cytochrome P450 (CYP) specific inhibitor. This option stems from the fact that while lesser number of subjects of PM phenotypes are required to show BA/BE it may be difficult to enroll all subjects at one time given the frequency of distribution of such PM phenotypes in general population. Hence, use of a single/multiple dose(s) of specific CYP inhibitor can be rationalized to convert EMs to PMs and thus it would be an easier option for study enrollment while keeping the sample size relatively small.

Regardless of the chosen option, the risks need to be completely understood. For instance, in the first option over enrollment of one phenotype over the other and/or differing phenotype of replacement subjects (*vs.* the original) may add up to variance in the data set. In the second option, enrollment of EM phenotypes would require a larger sample size due to its higher variability and the study duration/cost may be much higher; however, enrollment of PM phenotypes may

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have to be only fulfilled by adding additional clinical sites adding cost/timelines to the study. In the third option, while extent of inhibition cannot be confirmed (presumed to be complete) there is a challenge of partial inhibition of metabolism in some subjects and also, one should be cognizant of any safety risks if the chosen inhibitor can also inhibit other metabolic pathways leading to a pronounced level of the parent compound.

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