ASEAN GUIDELINES FOR THE CONDUCT OF BIOAVAILABILITY AND BIOEQUIVALENCE STUDIES – QUESTIONS AND ANSWERS (Q & A)
(Version 1)
This has been agreed and adopted at the 15th ASEAN Consultative Committee for Standards and Quality (ACCSQ) Pharmaceutical Product Working Group (PPWG), 28th July 2008

Question 1

Under Section 3.5 Reference and Test Product. Para 2 states"

"If the innovator product is not available, an alternative comparator product approved by drug regulatory authority of the country can be used".

Q : What are the criteria that are used in the choice of the comparator, and give examples of alternative comparator products?

A : The criteria used to describe the choice of comparator drug were discussed at the 13th PPWG meeting. The 13th. ACCSQ - PPWG has endorsed the following recommendations made by the Task Force :

The selection of comparator product is as follows:

i. Innovator product and multiple manufacturing sites of the same innovator registered in the country is acceptable.
ii. If the innovator product used as comparator is not registered in the country, justification is required from the generic company to prove its interchangeability with the registered innovator (in vitro or in vivo).
iii. If the innovator product cannot be identified, the choice of comparator must be made carefully and be comprehensively justified by the applicant. The selection criteria of a comparator in order of preference are:
- Approval in ICH and associated countries
- Pre-qualified by WHO

A well selected comparator must conform to compendia quality standards, if applicable.

In view of this, the List of ASEAN Comparator Product is not necessary because the principle of comparator selection has been agreed by all member countries, in accordance with WHO Guidance in TRS 937, 2006, Annex 7.

Additionally, it is advisable to clarify with the regulatory authority regarding the choice of comparator product before the BE study is conducted.

Question 2

4.1 Bioavailability

Q: In the case of new active substances (new chemical entities) intended for systemic action, the pharmacokinetic characterization will have to include the determination of the systemic availability of the substance in its intended pharmaceutical form in comparison with intravenous administration.
When is the situation where the BE studies are automatically waived without the applicant requesting for it ?

A: Refer to Section 5.1.1 of ASEAN Guidelines for The Conduct of Bioavailability and Bioequivalence Studies

Question 3

Absolute BA studies Sec 4.1 (comparison to intravenous administration) are very often difficult studies to get accomplished (for a variety of reasons beyond just a safety issue).

Q: Can the regulatory authority allows flexibility with justifications regarding absolute BA studies? And if justifications are reasonable, can it be considered and accepted?

A: Absolute BA studies are more likely to be conducted for New Drug Application (NDA) rather than generics.

Question 4

3.1. Design

Q: When should the concentration of active metabolite be determined in Bioequivalence Study?

A: Refer to section 3.3, paragraph 1 - 2 of ASEAN Guidelines for the conduct of BA/BE Studies

In most cases evaluation of bioavailability and bioequivalence will be based upon the measured concentrations of the parent compound. In some situations, however, measurements of an active or inactive metabolite may be necessary instead of the parent compound. Such situations include cases where the use of a metabolite may be advantageous to determine the extent of drug input, e.g. if the concentration of the active substance is too low to be accurately measured in the biological matrix by currently (common) available technology, or international standard, product unstable in the biological matrix or half-life of the parent compound too short.

If metabolites significantly contribute to the net activity of an active substance and the pharmacokinetic system is non -linear, it is necessary to measure both parent drug and active metabolite plasma concentrations and evaluate them separately.

Example: Concentration of the active metabolite is 1/10 of the parent drug with activity of 5 times of the parent drug, so the total activity is 1/10 X 5 = 0.5 of the parent drug and both need to pass the criteria

Question 5

3.2. Subject

Q: What is the guidance for using reserve subjects? Should all subjects be analysed or should the reserve subjects be analysed only if there are dropout subjects?

A: Justification should be made by the BE centre and Principal Investigator as according to the study protocol

Question 6

Q: What is the acceptance range for study parameters which are obtained from urine sample?

A: The acceptance range of Bioequivalence will follow the acceptance range for measurement of drug/metabolite concentration in blood samples, ie. Ae follows AUC and (dAe/dt)max follows Cmax.

Question 7

5. APPLICATIONS FOR PRODUCTS CONTAINING APPROVED ACTIVE SUBSTANCES
5.1. Bioequivalence studies.

Q: What are the criteria of changes which need bioequivalence study? (for example change in the source of active substance (raw material), change in formulation, production procedure, etc).

A: If the change is only in the source of the active substance (raw material) but the formulation and production procedure remain the same, a comparative dissolution test should be performed. If equivalent has been established through this in vitro dissolution, the requirements for new Bioequivalence Study can be waived. For changes in formulation and production procedures which are known to influence the bioavailability, a bioequivalence study is required. Kindly refer to USFDA Guidance for Industry on 'Scale-Up and Postapproval Changes' (SUPAC) for more detail.