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<td>Attachment</td>
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**Official Letter from the DOH**

From: DOH

Date: April 2, 2009

Ref. No: 0980316268

Att.: Guideline on BA/BE Studies

RE: The DOH issued an official letter to announce the implementation of the “Guideline for BA/BE Studies” on April 2, 2009 (Ref. No. 0980316265). Please refer to the attachment for the Guideline.
Guideline for Bioavailability & Bioequivalence (BA/ BE) Studies

Chapter 1: General Rules

Article 1  The guideline is established based on Pharmaceutical Affairs Law, Article 42 Item 2.

Article 2  The execution of BA / BE studies should comply with all provisions in the Guideline. Issues not covered by the Guideline are subject to the Guideline for Good Clinical Practice, Guideline for Drug Examination and Registration and other related regulations.

Article 3  Terms used in this Guideline are defined as follows:

1. Bioavailability is a measurement of the rate and extent of an active ingredient of a drug that appears in the systemic circulations and reaches the site of action. If the test drug is not for systemic absorption, use the rate and extent of an active ingredient that is available at the site of action as an index instead.

2. Pharmaceutical Equivalents are drugs that contain identical amounts of the identical active ingredient and in identical dosage forms. The specifications of the finished products shall meet the quality standards set forth by the pharmacopoeia or regulations implemented by the central health competent authority.

3. Pharmaceutical Alternatives are drugs that contain the identical active ingredient or its precursor, but not necessarily in the same amount or dosage form or the same slat or ester. The specifications of the finished products shall meet the quality standards set forth by the pharmacopoeia or regulations implemented by the central health competent authority.
4. Bioequivalence is achieved if two pharmaceutical equivalents or two pharmaceutical alternatives have the same bioavailability when administrated under the same conditions and at the same molar dose.

Article 4 Drug companies should submit the protocol to the central health competent authority for approval before performing any BA/BE studies. The protocol contents should conform to the Guideline for Good Clinical Practice. However, protocols for the BA and BE studies of generic drugs do not need prior approvals.

Article 5 All applications for the approval of protocols and test reports as stipulated in this Guideline should be submitted to the central health competent authority together with completed application forms drawn by the central health competent authority, all related dossiers and application fees.

The above-mentioned application forms include the application form for the protocol of BA test, the application form for the protocol of BE test, the application form for the BA test report, the application form for the BE test report, the application form for the drug dissolution curve comparison study report and any other formula in relation to the application.

Article 6 Reports should be written in the format as specified by the central health competent authority. Complete contents pertaining to the study and test data should be attached to the reports and submitted for review.

Applicants should make a written statement to ensure that the test drug is exactly the one for drug review and approval. The applicant is liable for the quality and integrity of test data.

Article 7 For all medicinal products with systemic actions using non intravenous route, BA or BE studies (hereafter the study) are required if any of the following conditions occurs:
1. The test drug is either a new active substance or is one of the products subject to the Guideline for Drug Review and Approval to conduct such tests. The applicants may submit relevant data to the central health competent authority to grant an exemption from BA/BE studies.
2. The test drug is one of those not under pharmacovigilance but subject to the compliance of BA or BE studies imposed by the central health competent authority.

Generic drugs containing ingredients subject to pharmacovigilance (including investigational drugs and those expired from PMS) should include BE study data when applying for drug review and approval, except for those items qualified for an exemption as approved by the central health competent authority.

Article 8  
BE study can be waived in any of the following conditions:

1. Intravenous injections;
2. Generics in oral solution form with excipients that do not affect the absorption of active ingredients;
3. Generic injection solutions administrated through extra-venous injections whose pH-value is the same as that of corresponding innovative product or as the value specified in pharmacopoeia, also the ingredient compositions (except for preservatives and buffers) are identical;
4. Gas or steam for inhalation;
5. Generic drugs for external dermal uses, excluding drugs absorbed through hypodermic or intradermal routes;
6. Generic drugs for ophthalmic or otic;
7. For applications of drug review and approval of the same oral solid drugs in different doses, or applications for registration alternation of drugs already with BA data and market licenses, BE studies can be substituted by drug dissolution curve comparison studies with the approval from the central health competent authority;
8. Other cases exempted from BE studies as approved by the central health competent authority according to the documents submitted by applicants.
Chapter 2 Bioavailability and Bioequivalence Studies

Article 9  A preliminary study would be appropriate before performing BA/BE studies in order to justify the doses, quantity of blood or urine samples, intervals between sampling time and analytical method. The main study shall be started only after finishing processing all data obtained from the preliminary study.

General final-product tests, and preferably drug dissolution curve comparison studies, shall be performed on drugs used in the BA/BE studies (including test drugs and reference products) beforehand. It would be better to keep the variations in contents between test drugs and reference products to be under 5%.

Except for special situations, test drugs should originate from a batch of at least 10,000 dosage units. In any case, the batch should be at least 1/10 of production scale.

The studies must be performed by professionals with pharmacokinetic background, qualified analysts and doctors (or collaborate with teaching hospitals) at suitable venues for clinical researches and analysis approved by the central health competent authority.

The above mentioned professionals with pharmacokinetic background must have at least a master degree in pharmacy-related fields and have publications or researches in pharmacokinetics.

Article 10  The selection of subjects for BA/BE studies should comply with all ethical principles for clinical trials. Except for special situations, subjects are selected from health adult volunteers with considerations of their genders, ages, demographic attributes, etc. Inclusion and exclusion criteria should be described in details in protocol. Subjects should be screened
by means of standard laboratory tests, a review of medical history, physical examinations, etc. Specials medical examination requirements (such as cardiogram) pertaining to the properties of individual drugs should be fulfilled.

There should be at least 12 subjects for each study; and the number of subjects has to be justified by appropriate power calculations. The Institutional Review Board’s approval and subjects’ written consents must be obtained prior to the execution of the studies. The contents of the consent form should comply with the Guideline for Good Clinical Practice. Insurance coverage would be appropriate. In order to protect subjects’ rights, the interval between each clinical trial participating by a subject should meet the requirements on healthy blood donors.

**Article 11** The choice of reference products should meet the following regulations,

1. Reference products of new active substances under pharmacovigilance should be selected from innovative products proved to be original, or the first product on the market approved by the central health competent authority.

2. Reference products of new active substances not under pharmacovigilance should be selected from the following products with justified supporting documents:
   (1) Products from original manufacturers;
   (2) Products already available on the Taiwan market and with known BA results;
   (3) Products having the same BE data or justified therapeutic effects as corresponding innovative products.

3. In addition to the above mentioned choices, any products approved by the central health competent authority as options of reference products.
Article 12  The active ingredients or therapeutic moiety of the reference products for BA studies should meet any of the following conditions:

1. Intravenous injections;
2. Solution or suspension for oral use;
3. Innovator products, or products already available on the Taiwan market and with known BA results;
4. In addition to the above three cases, any products supported by scientific evidences and approved by the central health competent authority.

Article 13  The determinations of BA/ BE studies can be based on the concentration of drug or metabolites in blood or urine (hereafter plasma concentration and urine concentration) or based on suitable matrix of pharmacological or therapeutic effects.

Article 14  The design of BA/ BE studies should be based on randomized two or more way crossover designs or Latin square designs in order to reduce the variation among subjects. If a crossover design is not applicable, then a parallel design can be used as an alternative on the condition that the number of subjects in each group is appropriate.

Before the studies start, all healthy subjects should not take any drugs for at least two weeks. Subject should fast for at least 10 hours before the administration of drugs. In a food effect study, the above mentioned 10-hour fast criterion means that subjects should fast for at least 10 hours before any food intake.

Subjects should continue to fast for 4 hours after the administration of drugs.

Article 15  Regulations on samples and sample collection time are as follows:

1. The sample collection time should cover from the reach of maximal plasma concentration (Cmax) to at least three times
the terminal half-life, and at least seven times the terminal half-life for urine samples.

2. The number of samples should be sufficient to determine the absorption, distribution and elimination of drugs in human body.

3. In principle, the washout period of the second treatment period in a crossover study should be at least five times the terminal half-life.

The washout period of the second treatment period mentioned in paragraph 1 item 3 refers to the interval between the last sample of the 1st treatment and the administration of drugs of the 2nd treatment.

Samples and sample collection time of a multi-dose study are exempted from the first two restrictions listed above. However, the sample collection time should be adequate to assess plasma concentration in steady state.

Article 16  
The analysis of samples for BA/BE studies should comply with the Guideline for Good Clinical Practice and the following regulations:

1. The analytical methods should be able to detect original test drug and its metabolites and have an adequate measurement of the lower limit of the concentration level. The central health competent authority’s prior approval should be obtained if using metabolites as analytes.

2. Bioanalytical method validation should include precision, accuracy, selectivity, matrix effect, sample stability, lower limit of quantification, etc. Issues of system suitability should also be addressed to. Sample stability covers freeze and thaw stability, short term temperature stability, long term stability, stock solution stability and post preparative stability. Exemptions will be granted to special cases approved by the central health competent authority to which the applicants must submit supporting documents and evidences to justify the exemption.
3. For the measurement of accuracy, the average concentration level should be within 15% of theoretical value, and within 20% for lower limit of quantification. For the measurement of precision, the coefficient of variation of concentration should be within 15%, and within 20% for lower limit of quantification.

The following rules should be observed:

1. In cases where blood is one analyte, a comparison of the following parameters is required. A comparison of pharmacokinetic parameters may also be required when necessary.
   (1) Single dose design for immediate release dosage forms: Cmax and area under concentration curve (AUC). For drugs with a long half-life and low intra-individual variability in distribution and clearance, truncated AUC may be used when necessary; however, a prior approval is required.
   (2) Multi dose design for immediate release dosage forms: Cmax in stable state (Cmax, ss) and AUC during a dosage interval in stable state (AUC_{0-\tau, ss}, \tau: a dosage interval).
   (3) Multi dose design for controlled release dosage forms: Cmax in stable state (Cmax, ss) and AUC during a dosage interval in stable state (AUC_{0-\tau, ss}, \tau: a dosage interval).
   (4) Single dose design for controlled release dosage forms (non-replicate) (food effect study for high fat and high calorie foods should also be incorporated into the design): Cmax and AUC. For drugs with a long half-life and low intra-individual variability in distribution and clearance, truncated AUC may be used when necessary; however, a prior approval is required.

2. In cases where urine is one analyte, there should be comparisons of urinary excretion measured at every sample time and cumulative urinary excretion from initial to the end of study. A comparison of pharmacokinetic parameters may also be required when necessary.
3. In cases where the studies are to observe pharmacological effects, the pharmacological effects should be within a range to keep a positive linear relationship with doses. There should also be a comparison of the relationship between the extent of pharmacological effects and time which includes initial point, end point and long pauses.

AUC described in paragraph 1 items (1) and (4) should include area under the concentration curve from time 0 to infinite \((AUC_{0,\infty})\) and area under the plasma concentration curve from time 0 to last sample collection time \((AUC_{0,t_f}, t_f: \text{last sample collection time})\); also, the ratio of \(AUC_{0,t} \) to \(AUC_{0,\infty}\) should not be lower than 0.8.

Comparisons of related statistics should be presented in charts and graphs.

**Article 18**  
BA parameters should be transformed using a logarithmic transformation and analysed using ANOVA with \(\alpha\)-value at 0.05, and followed by calculating the 90% confidence interval of treatment effect.

All parameters from BA studies should be transformed using a logarithmic transformation prior to the calculation of 90% confidence intervals.

In principle, the anti-log of the 90% confidence intervals derived from log-transformed data should be within an interval of 0.8~1.25. With a prior approval, the interval of Cmax may be widened to 0.75~1.33 on the condition that safety and efficacy concerns are justified and it complies with international regulations.

**Article 19**  
BA/ BE study reports of special dosage forms (such as liposome, transdermal or inhalation) are reviewed by the central health competent authority on a case-by-case basis on the consideration of quality and specifications.
Article 20  BE studies of two drugs can be substituted by BA studies together with clinical trials. In general, BE studies have higher priority.

When using BA studies together with clinical trials to substitute for BE studies, the clinical trials should have statistical significance.

Chapter 3 Drug Dissolution Curve Comparison Studies

Article 21  The following regulations should be observed when performing drug dissolution curve comparison studies:

1. Reference products should be chosen according to the objective of the study. Information on formulation, manufacturing and quality control of drugs used in the study has to be available.
2. The drug dissolution curve comparison of test drugs and reference products should be performed under the same test conditions. Appropriate test conditions should be provided, such as using Basket Method with a spinning speed of 50~100 or Paddle Method with a spinning speed of 50~75, and simulating the pH-value of gastrointestinal passage or preparing at least 3 solvents to simulate gastrointestinal passage (pH-value between 1.2 and 6.8), and keep temperature at 37 degree centigrade.
3. If for special reasons the study has to be performed under alternative test conditions, then scientific evidences should be submitted to the central health competent authority for the assessment and approval of the alternative.

Article 22  Data on system suitability and analytical method validation of facilities and analytical methods used in drug dissolution curve comparison studies should be submitted.

Article 23  When substituting drug dissolution curve comparison studies for BE studies, test drugs and reference products used in the studies
should have at least 12 dosage units each. There should also be enough sampling points. The dissolution similarity factor (f2 value) or other adequate statistics should be calculated.

The coefficient of variation of the first samples of test drugs and reference products should not exceed 20%, and 10% for following collected samples.

For studies described in the first paragraph, after 85% of the test drug and reference product are dissolved, only one sampling point is allowed for the calculation of f2 value. In cases where more than 85% of the drugs are dissolved within 15 minutes, the calculation of dissolution similarity factor (f2 value) may not be necessary.

The calculation and the interpretation of dissolution similarity factor (f2 value) are stated in appendix.

Chapter 4 Supplementary Provisions

Article 24

The applicants should retain, or commission the research institution to retain, enough product samples used in the BA/BE studies for at least 5 years after the approval of the report. These samples shall be provided for health authorities for retest and recheck. This regulation also applies to rejected reports.

Article 25

Without the consent from the central health competent authority, the contents of approved protocols or study reports can not be altered.

Article 26

The Guideline take effect from the date of announcement.
Appendix: the calculation and the interpretation of dissolution similarity factor (f2 value)

\[
f_2 = 50 \times \log \left[ 100 \left( \frac{\sum_{t=1}^{n} (\bar{R}(t) - \bar{T}(t))^2}{n} \right)^{\frac{1}{2}} \right]
\]

f2: dissolution similarity factor

n: number of time points

\(\bar{R}(t)\): mean percent drug dissolved of e.g. a reference product

\(\bar{T}(t)\): mean percent drug dissolved of e.g. a test product

\(f_2 \geq 50\) is a necessary criterion for the interpretation of dissolution curve similarity between the test drug and the reference product