

Regulation of Bioavailability and Bioequivalence Studies

(Amended Date: 2015-03-06)

1.Promulgated on April 02, 2009

2.Amended on January 31, 2013

3.Amended on March 6, 2014. Revised articles include Article 9, 11-14, 17, 18, 26.

This amendment takes effect on January 1, 2016.

Chapter I General Provisions

Article 1 The Regulation is set according to the Second Paragraph of Article 42 of the Pharmaceutical Affairs Act.

Article 2 The execution of bioavailability and bioequivalence and their related studies shall comply with the provisions of the Regulation. Matters not provided for herein should be governed by the Guidelines of Good Clinical Practice, the Regulation for Registration of Medicinal Products, and other relevant laws and regulations.

Article 3 The terms used in the Regulation defined as follows:
1.Bioavailability means the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action. For drug products that are no intended to be absorbed into the blood stream, bioavailability may be assessed by measurements intended to reflect the rate and extent to which the active ingredient or active moiety becomes available at the site of action.
2.Pharmaceutical equivalents means drug

products in identical dosage forms that contain identical amounts of the identical active drug ingredient, and meets either the identical compendial or other applicable quality standards provided by the central competent health authority.

3. Pharmaceutical alternatives means drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Testing specifications of the drug product should meet either the identical compendial or other applicable quality standards provided by the central competent health authority.

Bioequivalence means the absence of a significant difference in the bioavailability between two pharmaceutical equivalents or pharmaceutical alternatives when administered at the same molar dose under similar conditions in an appropriately designed study.

Article 4 Pharmaceutical manufacturers must apply for the approval of the protocol from the central competent health authority before conducting bioavailability and bioequivalence studies. The content of studies should comply with the Guideline of Good Clinical Practices. However, the application of protocol for conducting bioavailability and bioequivalence studies of generic drugs can be waived.

Article 5 Application fees for applying any protocols and reports following the Regulation should be paid, and the completed application forms together with all required dossiers should be submitted to the central health competent authority for assessment. The above-mentioned application forms and

documents include the form of bioavailability study protocol, the form of bioequivalence study protocol, the form of bioavailability study report, the form of bioequivalence study report, the form of dissolution profile comparison report, and/or other forms and documents in relation to the application procedure.

Article 6 Reports should be written in the format required by the central competent health authority, and a complete report with any relevant study results should be submitted for assessment.
Applicants should provide a written statement that test drugs are indeed the registered drugs.
Applicants have the ultimate responsibility for the quality and integrity of study results.

Article 7 Bioavailability and bioequivalence studies should be performed for non-intravenous administrated drug products that cause systemic action under any of the following circumstance:
1.Studies should be performed if requested by new drug application or the Regulation for Registration of Medicinal Products. However, studies can be waived with the approval of central competent health authority if the applicants have submitted relevant information for assessment.
2.Studies should be performed for drugs not under pharmacovigilance that requested by the central competent health authority.
All generic drugs with active ingredients under pharmacovigilance (include those pharmacovigilance period has expired) should submit bioequivalence study reports when applying for registration. However, submission of the study results could be waived with the approval of central competent health authority.

- Article 8 Bioequivalent study can be waived if the drug product meet any of the following circumstance:
1. Intravenous administrated injection product.
 2. Oral administrated generic drug with excipients that do not affect absorption of the active ingredient.
 3. Extravascular administrated injection product, i.e. the injectable solution of generic drug that have same pH value as compendia or brand products. Except for the preservatives and buffers, its formulation should be the same as the brand drugs.
 4. Drug products as inhaled gases or vapors.
 5. Generic drugs with topical uses that are not subcutaneously or intradermally absorbed.
 6. Ophthalmic and otic generic drugs.
 7. For same oral solid drug products with different strength applying for registration, or drug products with approved bioequivalence reports submitting for post-approval changes, the bioequivalence study can be replaced by dissolution profile comparisons if approved by the central competent health authority.
 8. Others that are approved by the central competent health authority according to information provided by the applicants.

Chapter II Bioavailability and bioequivalence studies

- Article 9 A pilot study is recommended to determine appropriate dosage, volume of blood samples, intervals for blood or urine sampling, and methods for sample analysis before a pivotal bioavailability or bioequivalent study proceed. Testing specifications of drug products, including

test and reference products) should be completed before the study proceeds. A dissolution profile comparison is also recommended. Difference of the drug content between the test and reference products should not exceed 5 %.

The test product should originate from a batch of at least 1/10 of production scale and no less than 100,000 dosage units. In case of a production batch smaller than 100,000 dosage units, a full production batch will be required. In other cases, applicants should explain the reason and provide supportive documents for the central competent health authority to justify.

Pharmacokinetic professionals, appropriate analytical scientists and physicians (or cooperation with participant teaching hospital) should be employed to perform the studies. Sites for study and sample analysis should also be certificated by the central competent health authority.

The pharmacokinetic professionals should at least pertain to master's degree in Pharmaceutics, and have experience or publications in Pharmacokinetic research areas.

Article 10 While implementing bioavailability and bioequivalence studies, choice of subjects should comply with ethic codes of clinical studies. Normally the study subjects should be adult healthy volunteers, unless otherwise justified. Factors such as gender, age and ethnic groups should also be considered. The inclusion and exclusion criteria should be clearly stated in the protocol. Subjects should be screened by means of standard laboratory tests, medical history and physical examination. Depending on the characteristic profile of the drug product, special

medical investigation may be carried out (i.e. ECG).

The number of evaluable subjects in a bioequivalence study should not be less than 12. Prior to execution, studies should be approved by institutional review board (IRB) and written informed consent from subjects should be insured. Time intervals between studies of a subject shall conform to the standards of blood donors in order to protect the interest of the subject.

Article 11

The selection of reference product in a bioequivalence study should comply with the following rules:

1. For drug products with active ingredients under pharmacovigilance (even the pharmacovigilance period has expired), brand product with identification documents or the first approved domestic drug product should be selected.

2. For drug products with active ingredients not under pharmacovigilance, the selected reference product should be confirmed with documents that identify following characteristics in preference order:

(1) Brand products.

(2) An approved domestic drug product with established bioavailability.

(3) A drug product that is bioequivalent to the brand product or has been proved as clinically effective.

3. The reference products that are specified by the central competent health authority are applicable, excluding the preceding circumstance described previously.

For reference product selected according to the preceding Subparagraph 1 and 2(1), but different in manufacture sites as approved in Taiwan, the

applicants should provide with proper supportive data to proof the quality of selected reference product and explain the reason for selection.

- Article 12 The selection of reference product used in a bioavailability study shall comply with one of the following circumstances in regards to the active ingredient or the therapeutic moiety:
1. Intravenous injections dosage form.
 2. Oral solution or suspensions dosage form.
 3. The brand products or an approved domestic drug product whose bioavailability has been established. For reference product selected according to this criteria but different in manufacture sites as approved in Taiwan, the applicants should provide with proper supportive data to proof the quality of selected reference product and explain the reason for selection.
 4. Products that are scientifically justified and certified by the central competent health authority, excluding the preceding circumstances described previously.

- Article 13 Bioanalytical data from concentrations of active ingredient or its metabolites in blood (plasma, serum or whole blood) or urine, (hereinafter referred as blood concentrations or urine concentrations) can be used as biological sample for assay in a bioavailability or bioequivalence study. If this is not feasible, validated pharmacodynamic and clinical endpoints may be used.

For the use of blood or urine concentration, following rule should be complied:

1. Blood concentration of the active ingredient should be used as first priority. In case of the active ingredient was difficult to detect in blood

and the bioanalytical data is therefore difficult to generate, then blood concentration of the metabolite could be used.

2. For active metabolite with safety and efficacy concerns, the blood concentration of the drug ingredient (prodrug) and the active metabolite should both be used.

3. For drug ingredient (prodrug) and active metabolite that are mainly eliminated by urine and not detectable in blood, urine concentration could be used.

Using assays measuring individual enantiomers of the drug is acceptable in bioavailability studies.

Generally, the achiral compound should be measured in bioequivalent studies. Measuring all enantiomers of the drug according to pharmacokinetic considerations might be required.

Article 14 A randomized two or more way crossover designs or Latin Square Designs is recommended to reduce the intersubject differences for bioavailability and bioequivalence studies. Under certain circumstances, parallel designs can be adopted and the number of subjects in each arm should be properly determined.

Healthy subjects should abstain from any medicines for at least two weeks before the study. Subjects should fast for at least 10 hours prior to administration of the drug except for a food-effect bioavailability or bioequivalence study. If Food Effect study is conducted, subjects should fast at least 10 hours before food intake.

A standard meal should be provided no less than 4 hours after drug administration.

In addition to the preceding Subparagraph 1, for immediate-release products, a single dose-fasting

study should be conducted. In the case of the administration with food is recommended according to package insert of the reference/innovator products, a single dose-fed study should be conducted instead. In addition to paragraph 1 in this article, for modified-release products, both single dose-fasting and single dose-fed studies should be conducted, unless otherwise justified.

- Article 15 The sampling times for bioavailability and bioequivalence studies should follow the rules below:
1. Blood sampling shall be continued for at least three or more terminal half-lives of the drug after reaching its maximum plasma concentration (C_{max}). If urine samples are used, appropriate urine sampling times should be taken.
 2. Blood samples should be taken at appropriate times and sufficient frequency to adequately characterize the absorption, distribution, and elimination phases of the drug.
 3. The predose concentration of drugs should not exceed five percent of the maximum plasma concentration (C_{max}) in a crossover design. The typical randomized cross-over design with appropriate washout periods, normally at least 5 elimination half-lives between each treatment, is recommended.
- In a multiple-dose study design, appropriate sampling shall be carried out to document attainment of steady state.

- Article 16 The bioanalytical part of bioavailability and bioequivalence studies should be performed in accordance with the principles of Good Laboratory Practice, and comply with the

following requirements:

1. Bioanalytical method used in bioavailability and bioequivalence studies should be able to measure the parent compound or its metabolite with adequately justified lowest concentration to adapt the aim of the study. If a metabolite as a surrogate for a parent compound is the biological sample of the analysis, it should be approved in advance by the central competent health authority.
2. Validation of a bioanalytical method should include determination of precision, accuracy, selectivity, matrix effect, stability and the lowest limit of quantification. They must be compatible to system suitability. Stability tests shall include freeze and thaw stability, short term temperature stability, long term stability, stock solution stability, and post preparative stability. Under special circumstances alternative approaches may be used. In such cases, the applicants must provide relevant documents to support such claim and gain approval from the central competent health authority.
3. For accuracy determination, the mean concentration should be within 15% of the nominal values for each concentration level, except for the lower limit of quantification which should be within 20% of the nominal value. For precision determination, the coefficient of variation value should not exceed 15% for each concentration level, except for the lower limit of quantification which should not exceed 20%.

Article 17 Bioanalytical data of bioavailability and bioequivalence study, including raw data and bioavailability parameters from different assessments, should meet following criteria:

1. If the drug concentration in blood is the

biological sample for assay, the following parameters should be compared. When necessary, other related parameters based on pharmacokinetics should be compared.

(1) For single dose study of immediate-release dosage form: the maximum plasma concentration (C_{max}) and the area under the concentration time curve (AUC). For long half-life drug that demonstrates low intrasubject variability in distribution and clearance, a truncated AUC can be used.

(2) For multiple-dose studies of immediate-release dosage form: the maximum plasma concentration at steady-state ($C_{max, ss}$), and the area under the curve of a dosing interval at steady-state ($AUC_{0-\tau, ss}$, τ : a dosing interval).

(3) For multiple-dose study of modified-release dosage form: $C_{max, ss}$ and $AUC_{0-\tau, ss}$.

(4) For single dose study of modified-release dosage form (conducted with both fasting and high fat and high calorie fed studies): C_{max} and AUC.

(5) For subjects with predose concentrations $> 5\%$ of C_{max} , such data should be excluded from calculation. The number of remaining qualified subjects shall comply with the provisions of Article 10.

2. If the urine is the biological sample for assay, amount of drug excreted in each sampling interval and accumulated amount from the beginning till the end of study in urine should be compared. Other relevant pharmacokinetic parameters may be performed for comparison if necessary.

3. If pharmacological endpoint is used in bioavailability and bioequivalence studies, pharmacological response should be in the range proportional to the concentration of drugs. The

relationship between the intensity of the pharmacological effects and duration of drug should be compared, including those of onset, end point and suspense, etc.

The AUC described in item (1) and (2) of the preceding Subparagraph 1 should include AUC from time zero to infinity ($AUC_{0-\infty}$), and AUC from time zero to the final blood sampling point (AUC_{0-t} , t: final blood sampling point, where blood concentration is detectable). The ratio of AUC_{0-t} to $AUC_{0-\infty}$ shall not be smaller than 0.8. All data analysis and statistical results should be illustrated by graphs and figures.

- Article 18 The data should be transformed using a logarithmic transformation prior to ANOVA analysis at the 5% significance level, and then the treatment effect in 90% confidence interval is calculated.
- A 90% confidence interval is obtained from the log-transformed of the parameters under statistical consideration in bioavailability assessment. This confidence interval is then back-transformed to obtain the desired confidence interval on the original scale. The 90% confidence interval for the ratio of the test and reference products should be contained within the acceptance interval of 80.00-125.00%. For drugs with high intrasubject variability and not classified with narrow therapeutic index, the acceptance criteria for the confidence interval of C_{max} can be widened to 0.75 to 1.33; in such case, the implication of international guidelines and clear statement in the study protocol will be required.

- Article 19 Bioavailability and bioequivalence studies and

reports for special dosage forms (such as liposomes, transdermal, and inhalation) will be reviewed in a case-by-case basis by the central competent health authority depending on its quality and specification.

Article 20 Bioequivalence study between two products can be substituted with bioavailability and clinical studies. In principle, bioequivalence studies are preferred. If a substitute (i.e., the bioavailability combined with clinical studies) is preformed; the clinical trials should demonstrate with statistical significance.

Chapter III. Test of Dissolution Profile Comparisons

Article 21 When performing the test of Dissolution Profile Comparisons, the followings should be applied:

1. An appropriate reference product needs to be selected based on the purpose of the studies. The formulation, manufacturing, and quality data of test product should be available.
2. Dissolution profile comparisons of test products and reference products should be carried out under the same and adequate test conditions. For example, using the basket method, the agitation is 50-100 rpm; with the paddle method, it is 50-75 rpm. An aqueous medium at 37 °C and with pH values to mimic gastrointestinal conditions or at least three aqueous medium simulating gastrointestinal conditions (with pH range 1.2 to 6.8) should be carried out in dissolution testing. Under certain circumstances dissolution be tested in other conditions, scientific evidences shall be provided and reviewed by the central competent health authority.

- Article 22 Instruments and analytical methods used for dissolution profile comparison shall be documented for system suitability and analytical methods validation, respectively.
- Article 23 When dissolution profile comparisons is used to waive bioequivalence requirements, the number of test drugs and reference drug in dissolution profile comparison shall be at least 12 dosage units each with sufficient sampling points. The values of similarity factor (f_2 value) or other appropriate statistical results should be provided. The percent of variation coefficient of test and reference products at the first sample point should not be more than 20%, and at other time points should not be more than 10%.
Only one measurement should be considered after 85% dissolution of both the products in f_2 value calculation. If more than 85% of the drug is dissolved within 15 minutes, dissolution profiles may be accepted as similar without further mathematical evaluation.
The method to calculate dissolution similarity and result interpretation are provided in the attachment.

Chapter IV. Supplementary Provisions

- Article 24 Applicants shall voluntarily or commission an agency who implements bioavailability and bioequivalence studies save samples of drugs (including test and reference products). Sufficient samples should be retained for at least five years after report is approved. Applicants should cooperate with the competent health authorities

for retest and inspection. Applicant should do likewise even the study report has not been approved.

Article 25 Any approved study protocol and report cannot be modified, unless modification is approved by the competent health authorities.

Article 26 The Regulation takes effect starting from the date of promulgation.
The amended articles announced on 6th Mar, 2015 take effect starting from 1st Jan, 2016.