

발 간 등 록 번 호
11-1470000-001738-14



Guidance Document for Bioequivalence Study

영문 생물학적동등성시험기준

2008



의 약 품 안 전 국
생물학적동등성평가과

머 리 말

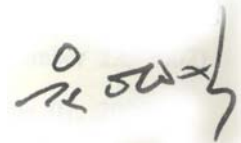
2000년 7월 우리나라에 의약분업이 실시되면서 국가의 건강보험재정 안정화와 제네릭의약품의 품질, 안전성 및 유효성 확보를 위해 생물학적 동등성시험이 본격적으로 활성화되었습니다. 2001년 8월 약사법이 개정되어 생동성이 인정된 제네릭의약품에 대해서만 대체조제를 할 수 있도록 되어 생물학적동등성시험의 중요성이 더욱 부각되었습니다. 또한 한·미 FTA 협상으로 인하여 제네릭의약품 허가 상호인정을 위하여 우리나라 생물학적동등성시험의 신뢰성 확보와 제도의 선진화가 절실한 실정입니다.

이러한 환경 변화에 대응하고자 의약품안전국에서는 학계 및 관련 업계 전문가와 부단한 논의를 거쳐 생물학적동등성시험기준을 새롭게 마련한 바 있습니다. 이는 ‘의약품임상시험관리기준(GCP)’ 및 ‘비임상 시험관리기준(GLP)’을 반영하고 특히, 시험기관의 분석데이터 생산 및 관리가 체계화되도록 한 것으로 국제적으로 통용되기에 손색이 없는 합리적인 규정으로 생각됩니다.

국내 제네릭산업은 짧은 시간에 비약적인 발전을 이루었으며, 이 시기에 영문 생물학적동등성시험기준을 발간하는 것은 매우 의미있는 일이라 하겠습니다. 영문 생물학적동등성시험기준의 활용을 통하여 국내 생물학적동등성시험 결과를 국제적으로 인정받고, 국내 기술을 외국에 수출하여 국익에 기여할 수 있기를 바라며,

끝으로 국내·외 학계 및 연구소·제약업계의 생물학적동등성시험 관계자께서 영문 생물학적동등성시험기준을 적극 활용하시기 바라며, 나아가 우리나라 제네릭 의약품 개발과 국가 경쟁력 제고에도 기여될 수 있기를 기대합니다.

의 약 품 안 전 국 장



Guidance document for Bioequivalence Study

발 행 일 : 2008년 12월

발 행 처 : 식품의약품안전청 의약품안전국

발 행 인 : 의약품안전국장 운영식

편집위원장 : 의약품평가부장 김대병

편 집 위 원 : 생물학적동등성평가과, 의약품안전정책과

자 문 위 원 : 서울대학교 이명걸 교수, 오정미 교수, 정석재 교수,
경희대학교 이영주 교수



GUIDANCE DOCUMENT FOR BIOEQUIVALENCE STUDY

Enacted

National Institute of Safety Research Notification #1988-01 (October 28, 1988)

Revised

National Institute of Safety Research Notification #1990-02 (August 28, 1990)

National Institute of Safety Research Notification #1994-01 (February 07, 1994)

National Institute of Safety Research Notification #1995-03 (August 28, 1995)

Korea Food and Drug Safety Headquarter Notification #1996-06 (April 16, 1996)

Korea Food and Drug Safety Headquarter Notification #1996-16 (October 31, 1996)

Korea Food & Drug Administration Notification #1998-51 (April 29, 1998)

Korea Food & Drug Administration Notification #1998-86 (August 26, 1998)

Korea Food & Drug Administration Notification #2001-57 (September 05, 2001)

Korea Food & Drug Administration Notification #2002-60 (November 22, 2002)

Korea Food & Drug Administration Notification #2005-31 (June 07, 2005)

Korea Food & Drug Administration Notification #2007-65 (September 20, 2007)

Korea Food & Drug Administration Notification #2008-22 (May 07, 2008)

CONTENTS

Chapter 1. General Provisions	1
Article 1 (Purpose)	1
Article 2 (Terminology)	1
Article 3 (Criteria for BE Study Waivers)	5
Chapter 2. Request for and Protocol of the BE Study	7
Article 4 (The Sponsor)	7
Article 5 (The Protocol)	9
Chapter 3. The Test Institution and the Principal Investigator, etc.	12
Article 6 (The Test Institution)	12
Article 6-2 (Duties of the Director of a Test Institution)	13
Article 7 (Duties of the IRB)	16
Article 7-2 (Composition, Functions, and Management of the IRB)	18
Article 7-3 (Management of the IRB)	20
Article 7-4 (Common IRB)	21
Article 7-5 (The Person Responsible for Quality Assurance)	21
Article 7-6 (The SOP)	22
Article 8 (The Principal and Main Investigators)	23
Chapter 4. Selection and Safeguarding of the Study Population and Subjects ...	26
Article 9 (Selection of the Study Population)	26
Article 10 (Selection of Subjects)	27
Article 11 (Exclusion Criteria for Subjects)	27
Article 12 (Control of Subjects)	28
Article 13 (Number of subjects)	28
Article 14 (Informed Consent of Subjects)	29
Article 15 (Compensation of Subjects)	30
Article 15-2 (Securing of the Subjects' Personal Information)	30
Chapter 5. Method of Conduct of the BE Study	30
Article 16 (Method of Conduct of the BE Study)	30
Article 17 (The Reference and Test Drug Products)	31
Article 18 (Conduct of the BE Study or Other Tests)	32
Article 18-2 (Additional Trials)	37

Chapter 6. Evaluation and Final Report, Etc.	38
Article 19 (Evaluation)	38
Article 20 (Final Report)	40
Article 21 (Inspection of the Quality of the Results of the BE Study)	43
Article 22 (Keeping Data and Storing Analytical Samples)	44
Article 23 (Non-compliance of a BE Study to the Criteria)	44
Chapter 7. Supplementary Provisions	45
Article 24 (Others)	45
Attachment	47

Chapter 1. General Provisions

Article 1 (Purpose)

This guidance document provides information on how to comply with the policies and the governing status and regulations on conducting a bioequivalence study (BE study) for drug products, by providing procedures and methods, in accordance with Article 27, Clause 2; Article 31, Clauses 2 and 7; and Article 42, Clause 1 of the *Pharmaceutical Affairs Law* Article 24, Clause 1, Item 3; Article 25; Article 26, Clause 2; and Article 88 of the *Enforcement Regulations* of the same law; and Article 57 of the *Regulations of the Narcotics Control Law*.

Article 2 (Terminology)

① Some terms used in this guidance document are defined below.

1. A *bioequivalence* (hereinafter referred to as "BE") *study* is one of the *in vivo* studies that verify the BE of reference and test drug products. A BE study is conducted for two drug products that show systemic action after absorption of an active ingredient into the systemic circulation. The two drug products should have the same active ingredient and the same route of administration. The BE of the two drug products is verified by statistics (i.e., their BE must not significantly differ) using their bioavailability.
2. *Bioavailability* (hereinafter referred to "BA") is the rate and extent of the active ingredient or its active metabolite(s) that is absorbed into the systemic circulation.

3. A *preparation* is a final drug product administered to patients clinically, such as a tablet, capsule, or suppository, that contains an active ingredient.
4. A *reference* (or comparative) *drug product* is a drug product used as a reference for a test drug product. A reference drug product is an approved drug product (or an approved imported drug product) the safety and efficacy of which have been established or recognized by the Commissioner of the Korea Food & Drug Administration (hereinafter referred to as "KFDA").
5. A *test drug product* is a drug product that is being tested as mentioned in no. 1. The active ingredient and route of administration of a test drug product are the same as those of a reference drug product, as defined in the criteria in Article 17, Clause ②.
6. A *study population* refers to the persons or patients mentioned in Article 9. A *subject* is a person who participates in a BE study and takes both the test and reference drug products, as mentioned in Article 10.
7. A *test institution* is a facility, including the building and the persons and equipment therein, where a BE study is being conducted. A test institution should meet the criteria stipulated in this guidance document.
8. <Deleted>
9. A *sponsor* is a pharmaceutical manufacturer, an importer, or an

individual who requests for a BE study from a test institution.

10. The *principal investigator* is the person who has full responsibility for conducting a BE study in a test institution.
- 10-2. The *main investigator* is the person who performs tasks related to a BE study and determines necessary items as delegated to him/her by, and under the supervision of, the principal investigator. The *chief investigator*, who is one of the main investigators, is the representative of each test institution in cases when the BE study is being performed in various test institutions. The test institution that the chief investigator represents should be different from that of the principal investigator. The chief investigator is responsible for tasks delegated to him/her by the principal investigator and acts on behalf of the principal investigator.
- 10-3. A *management pharmacist*, who is designated by the director of a test institution, is a pharmacist who is responsible for receiving, storing, managing, and returning test and reference drug products used in a BE study.
- 10-4. An *administrator*, who is designated by the director of a test institution, is a person who performs some of the tasks of the director of a test institution with regard to a BE study, in accordance with Article 6.
11. A *protocol* is a planning document that describes the objective, study population, subjects, and design of a BE study.
- 11-2. The *final report on a BE study* (hereinafter referred to as "final

report") is an integrated document that presents the results of a BE study.

- 11-3. The *Institutional Review Board for a BE study* (hereinafter referred to as "IRB") is a regular committee that is independent from a test institution and that protects the rights, safety, and welfare of the subjects by inspecting and continuously confirming the protocol or the amended protocol and procedures related to obtaining the informed consent of the subjects, and the information supplied to the subjects.
- 11-4. The *Standard Operating Procedure* (hereinafter referred to as "SOP") is a detailed document on the methods and procedures of conducting specific tasks for a BE study according to the standard method.
- 11-5. *Quality assurance tasks* refer to inspection and other tasks that pertain to a BE study and facilities to ensure the reliability of the study results. Quality assurance tasks are performed by a person designated by the director of a test institution or the administrator.
12. An *inspection* is an action carried out by the KFDA Commissioner on all facilities, documents, and records of a test institution and a sponsor, etc., according to the *Checklist* in Attachment 1 of a BE study, to inspect whether or not the BE study has been adequately conducted according to the criteria in this guidance document.
13. A *drug component with a narrow therapeutic range* is a

component listed in Attachment 2 or its equivalent.

14. *Raw data* are the contents of an original document or the official copy of all documents, data, and records on methods of selection of subjects, blood or urine collection, reliability of the analytical method, sample analyses, calculations of the pharmacokinetic parameters, statistical analyses, etc. to reproduce or evaluate a BE study. Raw data include photographs, microfilms, micro PC copies, magnetic tapes, data on media readable by a computer, data recorded on an automatic inspection instrument, and other data stored in different media.

② The terms not defined in this guidance document follow the definitions in the *Korea Good Clinical Practices* (hereinafter referred to as "KGCP") and the *Korea Good Laboratory Practices* (hereinafter referred to as "KGLP").

Article 3 (Criteria for BE Study Waivers)

- ① In principle, a BE study can be waived for each of the following categories:
1. Oral solutions, such as syrups, elixirs, tinctures, etc. (except emulsions and suspensions) and topical solutions in case the active ingredient and its concentration are the same as those in the approved drug product and the excipient does not affect the absorption of the active ingredient;
 - 1-2. Injections, ophthalmics, and otics in case their raw drug material (excipient) is the same as that in the approved drug product. If the following excipients are different from those of the approved

drug product, then it should be verified that the excipients do not affect the action of the active ingredient:

- a. For injections: Preservatives, buffering agents, and anti-oxidants; and
 - b. For ophthalmics and otics: Preservatives, buffering agents, isotonicizing agents, and viscosity adjustives;
2. Topical preparations intended for local action, not systemic action;
 3. Preparations administered as inhalation preparations, in which the active ingredient (a gas or vapor) is inhaled;
 4. Preparations such as fluids, blood volume expanders, and artificial perfusion solutions;
 5. Digestive enzyme preparations;
 6. Blood preparations;
 7. Herbal medicine (or traditional Korean medicine) product
 8. Vaccine preparations; and
 9. Lactobacillus preparations.

- ② When a manufacturer applies for an oral solid preparation that has the same dosage form and the same active ingredient as an approved drug product but has a different strength, a dissolution test replaces the BE study, according to the criteria in Attachment 3. For drug preparations with higher strengths than that of an approved drug product, the BE study is waived if the active ingredient shows linear elimination kinetics that are over those of the approved therapeutic dose ranges

and if the safety of the drug preparation based on the characteristics of its active ingredient is established.

- ③ If it is proven that oral tablets or capsules meet the criteria in Attachment 4, the BE study is waived, except for preparations with drug components that have a narrow therapeutic range and recognized specific dosage forms such as controlled-release formulations, and preparations absorbed through the buccal cavity, such as sublinguals and buccals.
- ④ The KFDA Commissioner can issue a notice on drug components with high water solubility or high permeability after reviewing the criteria in Attachment 4.

Chapter 2. Request for and Protocol of the BE Study

Article 4 (The Sponsor)

- ① A sponsor who intends to request for a BE study according to this guidance document should request for the BE study from an adequate test institution that meets the criteria in Article 6.
- ② According to ①, any sponsor who intends to request for a BE study should sign a contract with the director of a test institution for the preparation of a study plan and for the performance of the responsibilities and duties stipulated in Article 5.
- ③ A sponsor should have the protocol of his/her BE study approved by the KFDA Commissioner before conducting the BE study. In case one

of the following items must be changed in the approved protocol, the sponsor should have the amended protocol approved by the KFDA Commissioner:

1. Changes in the criteria for the inclusion and exclusion of subjects;
 2. Increase in the dosage and change in the method of administration;
 3. Changes in other items, such as those directly related to the subjects' safety; and
 4. Changes in the test institution (except for a change in the test institution to which some items of the BE study are consigned) or the principal investigator.
- ④ The sponsor should supply both the test and reference drug products to the test institution on time, in accordance with Article 17, and should keep the following records on both drug products: supplies to the test institution, receipts from the test institution, returns from the test institution, and disuse.
- ⑤ The sponsor should carry out audit whether or not the procedures of the BE study are being followed according to the SOP and relevant regulations, and should document the results of the study.
- ⑥ The sponsor should immediately report to the KFDA Commissioner, within the period defined for each of the following items, when considerable adverse drug reaction are produced on the subjects during the BE study:
1. In case the adverse drug reactions may cause death or are

life-threatening: Within seven days after the sponsor discovered such reaction

2. In case the subject must be hospitalized: Within 15 days after the sponsor discovered such need; and
 3. In case persistent or meaningful disabilities and induced malfunctions are observed in the subjects: Within 15 days after the sponsor discovered such disabilities or malfunctions.
- ⑦ The sponsor should report the results of the BE study to the KFDA Commissioner, according to the format of the accompanying document 1, within 20 days after the completion of the observation of the subjects.

Article 5 (The Protocol)

- ① The principal investigator should prepare the study protocol, which should include the following items, after discussing it with the sponsor, and should obtain the approval of the IRB in accordance with Article 7:
1. Title and purpose of the BE study;
 2. Generic name, brand name, dosage form, strength, and dosage regimen of both the test and reference drug products;
 3. Name and address of the sponsor, and name of the representative of the sponsor's company;
 4. Name, address, and name of the director of the test institution;
 5. Expected date of commencement and completion of the BE study;
 6. Name, affiliation, title, curriculum vitae, and achievements of the principal and main investigators;

7. Method of manufacture and management of the test drug product;
8. Method to be used for the comparative dissolution test (may be waived for test drug products that have been approved as equivalent to the reference drug product based on a comparative dissolution test, according to the *Regulation for the Management of the Therapeutic Equivalence Test (KFDA Notification)*, and if the raw material (excipient) and its amount, and the manufacturing process and the manufacturer, were not changed after the completion of the comparative dissolution test);
9. When a pilot BE study is required, general information, such as on the number of subjects, dosage, biological sample collected and analyzed, analytical component, analytical method, and criteria for the selection of the subjects (If a pilot study has been completed using an approved and marketed drug product, also the pilot study report, including the control of the subjects);
10. Criteria and method of selection of the subjects: Criteria for both the inclusion and exclusion of the subjects, advertising document for the recruitment of the subjects, document given to the subjects detailing information related to the BE study, and the informed consent forms of the subjects;
11. Number of subjects and method of classification of the subjects;
12. Items for physical examination(including clinical laboratory data) selected by a medical doctor (an main investigator) based on the characteristics of the drug product;
13. <Deleted>

14. Agreement on the subjects' compensation;
15. Expected adverse drug reactions and precautions after the administration of the drug product, and medical care in case of the development of adverse drug reactions;
16. Control of the subjects;
17. Method and design of the dosing regimen: dosage; route of administration; method of drug administration; schedule of drug administration(including the rationale for the determination of the wash-out period);method of collecting biological samples, blood, etc.; sample volume, sampling numbers, and time of the samplings (including the rationale for such); method of storage method of the biological samples; and nutritional specifications such as the menu, total calories, and nutrition consumption rate in case the BE study will be conducted after a meal (limited to controlled-release formulations);
18. Method of preventing infection of blood samples during their collection;
19. Method of treatment and analysis of the samples;
20. <Deleted>
21. Statistical method and evaluation parameters and criteria;
22. Establishment of quality assurance measures; and
23. <Deleted>
24. Signatures or seals of the principal investigator, the director of the test institution, the sponsor, and the chief investigator.
25. <Deleted>

26. <Deleted>

- ② Principal investigator can change the protocol through an IRB review, etc.

Chapter 3. The Test Institution and the Principal Investigator, etc.

Article 6 (The Test Institution)

- ① A test institution that conducts a BE study should have the following facilities, equipment, persons, and operating systems:
 1. Persons related to the BE study:
 - a. The principle investigator
 - b. The management pharmacist
 - c. The quality assurance person;
 - d. The person who will keep the data and
 - e. The main investigator
 2. Equipment, materials, and facilities for conducting the BE study (There should be a consignment contract if the handling and analysis of the samples will be conducted in another test institution);
 3. Composition and regulations of the IRB on BE studies;
 4. A certificate for a medical institution [There should be a consignment contract if the physical examination of the subjects, the administration of the drug products, the blood sampling, and

the prevention and management of drug-induced adverse effects will be conducted in another test institution (i.e., in a medical institution)]; and

5. The SOP related to the conduct of BE studies.

- ② All procedures for the administration of drug products and blood sampling should be conducted in a medical institution.
- ③ The clinical laboratory examinations for the physical examination of the subjects should be conducted at a clinical laboratory that is registered as a member of the Korean Association of Quality Assurance of Clinical Laboratories and is inspected regularly for quality assurance.
- ④ The director of the test institution can request the KFDA Commissioner to inspect whether or not the test institution meets the required conditions listed in ①. The KFDA Commissioner should request the relevant public officers to inspect the test institution and to decide whether or not the test institution can adequately conduct the BE study. The inspection could be waived if the test institution's facilities and staff have previously been inspected.

Article 6-2 (Duties of the Director of a Test Institution)

- ① The director of a test institution should organize an IRB for the test institution, in accordance with Article 7, Clause ②. The IRB shall perform the duties stipulated in Article 7, such as to review the performance of the BE study, etc. The director of the test institution should then appoint the members of the IRB. If a clinical IRB, according to KGCP, has already been composed, then the clinical IRB

could replace the IRB.

- ② The director of a test institution should make the management of the IRB independent.
- ③ The director of a test institution should appoint a partner medical institution (another test institution). The medical institution should conduct physical examinations, administration of drug products, blood sampling, and prevention and management of adverse drug reactions on the subjects of a BE study.
- ④ The director of a test institution should ensure that an appropriate and technically reasonable SOP is prepared and followed according to the notification; should approve the preparation, amendment, change, and withdrawal of the SOP; and should keep a file of the SOP.
- ⑤ The director of a test institution should appoint a person who shall be responsible for quality assurance, and should ensure that quality assurance measures are performed according to the preset criteria.
- ⑥ The director of a test institution should perfectly prepare for the conduct of a BE study by facilitating the availability of the laboratories, facilities, and professionals required to conduct the BE study and managing first –aid requirements, etc.
- ⑦ The director of a test institution should cooperate when a BE study sponsor or the KFDA Commissioner requests for an inspection of the test institution’s SOP or for the documents that state the names of the members of the test institution’s IRB and their credentials.
- ⑧ The director of a test institution should make sure the principal investigator will cooperate well when there are requests for inspection

or informed inspection by the KFDA Commissioner, in accordance with Article 4, Clause ⑤ and Article 21, or when IRB requests for an inspection of the data on the performance of the duties of the IRB, as stipulated in Article 7.

- ⑨ The director of a test institution should appoint a management pharmacist from another test institution for adequate management of drug products.
- ⑩ The director of a test institution should appoint a person who shall be responsible for keeping the records and data from the IRB and the principal investigator. Such records and data should be kept for five years from the date of approval (in case an approval condition exists, from the date of deletion of the condition; and in the case of approved and marketed drug products, from the approval date on the final report) or from the date of discontinuation, in case the development of the corresponding drug product is discontinued. The director of a test institution should devise a method of protecting such records and data from early damage or loss by accident.
- ⑪ The director of a test institution should educate or train each of its main investigators so as to make them clearly understand their responsibilities and respect research ethics, and should keep relevant records.
- ⑫ The director of a test institution may ask an administrator to perform the responsibilities stipulated in Clauses ④ ⑤ ⑦ ⑧ and ⑪

Article 7 (Duties of the IRB)

- ① The duties of the IRB are as follows:
 1. Review of the selection and changes of the principal and main investigators;
 2. Review and approval of study protocols;
 3. Approval of amended protocols;
 4. Review of the rights of subjects, such as to safety and compensation (including review of poor circumstances of subjects while participating in a BE study); and
 5. Review of procedures related to the selection of subjects and of the method of obtaining the informed consent of the subjects.
- ② The IRB should require a copy of each of the following documents for its proper management and discussion of a BE study:
 1. Protocol of the BE study (original or amended);
 2. Informed consent form of the subjects
 3. Information document given to the subjects (including explanations of the BE study to the subjects)
 4. Information on safety
 5. Information on compensation of the subjects;
 6. Recent curriculum vitae and other credentials of the principal investigator; and
 7. Documents necessary for the IRB's performance of its duties, such as the SOP, etc.
- ③ The IRB should review the BE study documents submitted by the principal investigator within the designated period, and should document

the name of the BE study, the documents it reviewed, the date of its review/s, and the following:

1. Approval of the original or amended protocol;
 2. Compliments;
 3. Turndowns; and
 4. Cessation or reservation of an approved BE study.
- ④ The IRB should check whether or not the principal investigator has the qualifications needed to properly conduct the BE study, based on the principal investigator's most recent curriculum vitae and other credentials.
- ⑤ The IRB should review whether or not the amount and method of compensation of the subjects adversely affect their participation in the BE study. In this case, the amount of the compensation should be adjusted based on the extent and period of the subject's participation in the BE study. The monetary compensation should not force the subjects to finish the BE study.
- ⑥ The IRB should check whether or not information on the subjects' monetary compensation (when they are supposed to be given monetary compensation for participation in the BE study), such as the amount, method of payment, and time of payment of such compensation, are mentioned in the explanation document on the BE study that was given to the subjects before the start of the BE study. The IRB should also review the compensation method for subjects who do not wish to finish the BE study.
- ⑦ The IRB should also quickly review the following:

1. The treatment of the reported adverse drug reactions
 2. The management of the last observation document on the subjects in the BE study;
 3. The management of the request for changes in the protocol (including the amended protocol) approved by the KFDA Commissioner
 4. Changes in administrative procedures, such as in the main investigator (but not in the chief investigator), emergency telephone numbers, and minor changes in the protocol that do not affect the determination of the BE;
 5. Changes in the protocol as requested by the IRB; and
 6. Items related to the BE study that need to be rapidly reviewed according to the SOP of the IRB.
- ⑧ The IRB should submit its SOP document related to its management or documents stating the names of its members and their qualifications when these are requested by the sponsor or the KFDA Commissioner.
- ⑨ The IRB should keep relevant data or documents on the names of its members, its reviewed documents, and others, and should protect these from early damage or accidental loss. When the observation of the subjects in a BE study has been completed, the IRB should hand in the relevant data or documents to the person who is responsible for keeping them, according to Article 6, Clause ⑩.

Article 7-2 (Composition, Functions, and Management of the IRB)

- ① The IRB should have at least five members, who have the

qualifications and experience to review and evaluate BE studies. Among them, at least one member should be a non-specialist in the field of BE study, such as a member of a bar association, a religious organization, or an association of consumers whose primary area of interest is not medicine, dentistry, herbal medicine, pharmacy, or nursing; and at least one member should be independent from the test institution.

- ② The director of the IRB is elected from the votes of the members of the IRB. Persons who are related to the investigators and the sponsor should not participate in decision-making or express their opinions on the corresponding BE study.
- ③ The IRB should keep and manage well the documents on the names and qualifications of its members.
- ④ The IRB members should perform their duties according to their documented SOP, keep activity reports and records of meetings, and follow preset criteria and relevant regulations.
- ⑤ All decisions should be made in an IRB meeting. The meeting should be announced in advance. The required number of members for valid decisions should follow the SOP.
- ⑥ Only IRB members in attendance can make decisions and express their opinions on a BE study.
- ⑦ The principal investigator can provide the IRB all the information it needs on a BE study, but should not influence the IRB members nor participate in the decision-making process related to the BE study performed by the principal investigator.

- ⑧ The IRB may ask for advice from persons who are not IRB members but experts in the field of BE study for appropriate discussion.

Article 7-3 (Management of the IRB)

The IRB should follow its SOP regarding the following:

1. Composition and duties of the IRB, including the names and qualifications of its members
2. Methods of calling for, scheduling, and processing IRB meetings;
3. Rapid reviews in accordance with Article 7, Clause ⑦, and approval of minor changes in BE studies being processed;
4. Prohibition of the participation of subjects in a BE study before the approval of the study protocol, etc.
5. Prohibition of the conduct of BE studies that divert from their original protocol before the approval of their amended protocol, except when immediate removal of risk factors developed in subjects is necessary or the changes are related to administrative processes, such as changes in the main investigator (but not changes in the chief investigator) and the emergency telephone numbers
6. Quick notification of the principal investigator of the following in a document:
 - a. Procedures on making decisions, sharing opinions, formulating rationales, and issuing notices related to BE studies; and
 - b. Procedure on making formal objections when decisions are not accepted; and

7. Other items on the management of the IRB.

Article 7-4 (Common IRB)

- ① In case a BE study is being conducted by more than one test institution, the IRB could be jointly formed (hereinafter referred to as "common IRB") after discussion with the director of each test institution.
- ② The duties, composition, management, etc. of the common IRB could follow the provisions in Article 7 or Article 7-3. The duties of the common IRB shall be common the test institutions, and duties related to other items shall be duties of the IRB of each test institution.
- ③ According to Clause ① a decision made by the common IRB after a joint discussion shall be considered the decision of the IRB of each test institution.

Article 7-5 (The Person Responsible for Quality Assurance)

- ① The person responsible for quality assurance should keep all copies of the protocol and the SOP approved by the corresponding test institution.
- ② The person responsible for quality assurance should inspect whether or not essential items as stipulated in the pertinent criteria are included in the protocol, the SOP, etc., and should document them.
- ③ The person responsible for quality assurance should carry out audit whether or not all processes stipulated in the pertinent criteria are being followed, and should judge and record whether or not the investigators are following the protocol and the SOP.

- ④ The person responsible for quality assurance should make a final report to ensure that the observation methods, procedures, and results are accurately and completely documented, and that the reported results accurately and completely reflect the raw experimental data.
- ⑤ The person responsible for quality assurance should report in writing his/her audit results as quickly as possible to the director of the test institution or to the administrator and principal investigator.
- ⑥ The person responsible for quality assurance should prepare and sign a certificate of quality assurance. The certificate of quality assurance should reflect the date and contents of the inspection and the date when the inspection results were reported to the director of the test institution or to the principal investigator, and should be included in the final report.
- ⑦ The person responsible for quality assurance should not participate in the BE study that he/she is inspecting.

Article 7-6 (The SOP)

- ① ① The SOP should list the following items among the duties of a test institution:
 - 1. Management of the IRB, in accordance with Article 7-3;
 - 2. Receipt, storage, inventory control, administration to each subject, and return of the test and reference drug products;
 - 3. Recruitment of subjects, receipt of their consent form, and selection of subjects
 - 4. Control of subjects, such as methods of drug administration and

blood sampling, and medical care of subjects in case of development of drug-induced adverse effects

5. Receipt, discernment, handling, and storage of samples for analysis
 6. Handling and analysis of samples
 7. Usage and management of instruments
 8. Repair, maintenance, and management of the computer system
 9. Preparation and discernment of chemicals, instruments, reagents, and solutions;
 10. Preparation, reporting, storage, and retrieval of documents
 11. Activities of the person responsible for quality assurance; and
 12. Other necessary items.
- ② The test institution should keep its SOPs related to its performance of its activities available anytime.
- ③ Items on the BE study that are not followed based on the SOP should be recorded, and the principal investigator should be aware of them.
- ④ In case the SOP is amended, its contents and the date of its amendment should be recorded and kept.

Article 8 (The Principal and Main Investigators)

- ① The principal and main investigators should be qualified based on professional education and training, should have sufficient experience to adequately conduct a BE study, and should provide evidence of such qualifications via a curriculum vitae and other relevant documents when requested by the sponsor, the IRB, and the KFDA Commissioner.

② <Deleted>

③ The responsibilities and observances of the principal investigator are as follows:

1. Responsibilities

- a. Manage all procedures, such as for first aid, blood sampling, and physical examination of subjects;
- b. Prepare and amend the protocol as needed;
- c. Designate the main investigators and brief them on their duties, and guide and supervise them;
- d. Prepare the analytical instruments, main equipment, expandable supplies, and laboratory reagents needed for the BE study;
- e. Collect and review non-clinical and clinical information;
- f. Observe and record symptoms and any adverse drug reaction that occurs in the subjects, and supervise them
- g. Control subjects and supervise the administration of drug products to them;
- h. Record raw data; and
- i. <Deleted>
- j. Prepare a final report.

2. Observances

- a. The BE study should be conducted in compliance with the protocol that was set with the sponsor and approved by the IRB and the KFDA Commissioner. If the BE study was conducted differently from the approved protocol, it should be documented with acceptable reasons for each item where a deviation occurred.
- b. The principal investigator should be aware of expected

drug-induced unwanted reactions and precautions mentioned in the protocol in advance, and should prepare for such reactions. Prompt and adequate medical care should be given in case of the development of serious adverse drug reaction, as stipulated in Article 4, Clause ⑥ the events should be reported to the director of the test institution in writing as approved by the IRB; and the sponsor and the main investigator should be notified.

- c. Principal investigator should provide copies of the IRB-approved original or amended protocol to the sponsor.
- d. The BE study should be adequately conducted with close communication with the sponsor and the IRB. As stipulated in Article 20, a final report should be prepared and submitted to the sponsor after the completion of the BE study.
- e. The protocol and changes therein should be sent to the person responsible for quality assurance. The principal investigator should effectively communicate with the person responsible for quality assurance during the conduct of the BE study, if necessary.
- f. When the observations of the subjects are completed, the completion of the observation with a summary of the results should be reported to the IRB, and the sponsor should likewise be informed.
- g. Records and reports should conform to the relevant provisions of Article 18 of KGCP.

④ Medical care, such as physical examinations, administration of drug products, blood sampling, and prevention and treatment of adverse drug reaction should be controlled by a medical doctor (an main investigator).

- ⑤ A management pharmacist should perform the receiving, inventory control, administration of drug products to each subject, and return of the drug products used in the BE study, and should record the dates of administration of the drug products, the inventories of the drug products, the drug manufacturing numbers or lot numbers, the drug expiration dates (if necessary), etc., and should keep the drug products as requested by the sponsor and according to relevant criteria.
- ⑥ All main investigators should conform to the criteria stipulated in Article 8, Clause ③, Item 2, a and g.

Chapter 4. Selection and Safeguarding of the Study Population and Subjects

Article 9 (Selection of the Study Population)

- ① In principle, the study population should be composed of healthy adult volunteers. Patients could replace healthy adult volunteers as the study population if each of the following criteria is approved by the KFDA Commissioner, in which case the rationale and scientific evidence for the selection of the patients should be submitted:
 1. In case it may be more reasonable to select patients for the BE study; and
 2. <Deleted>
 3. In case there are concerns about selecting healthy adult volunteers due to ethical or safety problems, such as with regard to drug

products for malignant tumors.

Article 10 (Selection of Subjects)

① The subjects recruited through advertisements on BE studies should be healthy adults who meet each of the following criteria [A medical doctor (an main investigator) should consider the age and health condition of the subjects and select subjects suitable to the purpose of the BE study, and the doctor's medical opinion on each subject should be included in the case report]:

1. 19–55 years old at the time when the physical examination will be made;
2. Subjects who are free from inherent or chronic diseases, and illness symptoms based on internal examination (if necessary, based on an electroencephalogram, electrocardiogram, chest and stomach endoscopy, or gastrointestinal x-ray test);
3. Subjects who were selected by a medical doctor (an investigator) based on the results of clinical laboratory tests that took into account the specificities of the drug products to be administered, such as via hematology, blood chemistry, and urinalysis; and
4. In the case of women, those who are not pregnant at the time of the performance of the physical examination.

Article 11 (Exclusion Criteria for Subjects)

Subjects who meet one of the following criteria should be excluded:

1. Subjects who have taken drug products that are enzyme inducers, such as barbiturates, or inhibitors; or who drank excessive alcohol

within one month prior to the initiation of the BE study;

2. Subjects who have taken drug products that could influence the results of the BE study within 10 days before the initiation of the BE study;
3. Subjects who are judged by a medical doctor (an main investigator) as unsuitable for the BE study; or
4. Subjects who have participated in a BE study or any other clinical study within three months before the start of the BE study.

Article 12 (Control of Subjects)

- ① Subjects' intake of food and drinks should be carefully controlled, and they should fast for 10 h before the administration of drug products.
- ② Drinking water 1 h before and after the administration of drug products is not allowed.
- ③ Subjects should not be in a supine position at least 2 h after the administration of drug products, and should maintain a posture and do only activities that would minimize the effects on their gastrointestinal blood flow rate and motility.

Article 13 (Number of Subjects)

The number of subjects should meet the requirements for statistical validity. The number of subjects can be determined based on the characteristics of the active component of the pertinent drug products. The minimum number of subjects is 12.

Article 14 (Informed Consent of Subjects)

- ① ① The principal investigator should fully explain the BE study to the subjects and should have the voluntary informed consent of each subject, according to Article 17 of the *Minimum Requirements for KGCP*.
- ② In case patients are selected as subjects, the principal investigator should obtain the consent of each of the patients' primary physician in addition to each patient's informed consent, both in writing.
- ③ If the subject's consent was obtained before his/her participation in the BE study, the principal investigator (or the person designated by the principal investigator) should sign on the informed consent form according to Clause 1, and should write the date when he/she signed it in his/her own handwriting.
- ④ Each subject who signed the consent form and wrote thereon the date when he/she signed it in his/her own handwriting, as stipulated in ③, may obtain copies of the signed document or other documents given to him/her before he/she participated in the BE study. In case the form for the informed consent was changed during the conduct of the BE study, each subject should obtain a copy of the changed consent form that reflects his/her signature and the date when he/she signed the form. If the information document that was given to each subject is changed, each subject should be given a copy of the changed document.

Article 15 (Compensation of Subjects)

To safeguard the rights of the subjects, they should be given rapid and appropriate compensation. It is recommended that an insurance policy be bought for each subject.

Article 15-2 (Securing of the Subjects' Personal Information)

All the persons related to the BE study, such as the sponsor, the principal investigator, the main investigator (including the chief investigator), the management pharmacist, the administrator, the IRB members, the persons responsible for quality assurance, etc., should handle all the subjects' records with utmost confidentiality.

Chapter 5. Method of Conduct of the BE Study

Article 16 (Method of Conduct of the BE Study)

① In principle, a BE study is conducted *in vivo* to calculate the BA by measuring the plasma concentrations of the active ingredients or their active metabolites. The subjects are randomly distributed and in principle, a single dose of the reference and test drug products is administered to them on the same day while they are in a fasting state via a two treatment and two-period (2 x 2) cross-over design with an adequate wash-out period, according to Article 18-②-4. In the case of the measurement of the total amount excreted in the urine or in another design, its rationale should be provided.

- ② For controlled-release formulations, studies after meals should be performed in addition to studies under a fasting state, as stipulated in the ① In principle, for studies after meals, the subjects are randomly distributed, and a single dose of the reference and test drug products is administered to them via a two-period (2 x 2) cross-over study with a high-fat diet (over 900 kcal, with more than 35% fat).

Article 17 (The Reference and Test Drug Products)

- ① The reference drug product should meet the criteria in Article 2-①-4.
- ② The test drug product should be the final product and should meet the following criteria [In case the BE study is waived based on the results of a comparative dissolution test (see the attached Table 3) according to Article 3, Clause 2, the test drug product should meet provisions 1, 3, and 4 below]:
1. The test drug product should be manufactured with the same raw materials (excipients), the same formulation, and the same conditions as those of a final product for marketing, and the quality and content of the test drug product should meet the "in-house specifications and test method"
 2. The test drug product should be a drug product that has been approved by the KFDA according to Article 26 of the Pharmaceutical Affairs Law or should meet the criteria set in Article 36 of the Minimum Requirements for KGCP, and the "in-house specifications and test method" and its results should be attached;

3. The batch size of the test drug product should be at least 100,000 units (In case the commercial batch size of the test drug product is smaller than 100,000 units, the batch size of the final drug product would be acceptable); and
4. The test drug product should be either totally composed of have the full potency of its active drug substance according to the "in-house specifications and test method," and should have 5% of the labeled content (100%) of the reference drug product; or the difference between the content or potency of the test and reference drug products should be within 5%.

Article 18 (Conduct of the BE Study or Other Tests)

① The batches of the test and reference drug products for the comparative dissolution test should be the same as the batches used for the BE study. The method of the dissolution test can be selected according to the characteristics of the drug products. In case the test drug product meets the criteria in Article 5-①-8, the comparative dissolution test can be waived.

② BE study

1. Dose

- a. In principle, a single dose must be administered to patients. In case determining the drug concentrations is difficult in a single-dose study because of the high detection limit in the analytical method, then in principle, a single maximum daily dose can be administered to patients.

- b. In the following cases, the BE study can be conducted at a steady state after the administration of multiple-dose drug products:
 - (1) In case there is a difference in the rate of absorption, but no difference in the extent of absorption;
 - (2) In case there are large intersubject variations in the BA; and
 - (3) In cases of controlled-release formulations.
- 2. Method of administration of drug products
 - a. Single-dose administration
 - (1) The drug product should be administered to subjects who fasted for at least 10 hours before and up to 4 hours after the drug administration. Drug products could be administered to subjects after meals, however, in case the scientific reasons or specific purposes are reasonable. In this case, the same meal should be provided to all the subjects just before the administration of the drug products, if possible, and the drug products should be administered 30 minutes after the meal starts.
 - (2) For studies of controlled-release formulations after meals, the same high-fat diet should be taken within 20 minutes in at least a 10-hour fasting state. The drug products should be administered 30 minutes after the meal starts.
 - (3) Drug products should be administered with 240 mL of water.

- b. In multiple-dose studies, the first dose is generally given under a fasting state. The subsequent doses should be administered between meals with the same intervals to achieve a steady state in the plasma concentrations.
3. Blood or urine sampling to analyze the active ingredients or their active metabolites should be performed with sufficient number of samples and at adequate time points to estimate all the parameters for the BA assessment. The sampling should be performed with the same number of samples and at the same time point for the test and reference drug products. In the case of preparations with particular absorption patterns, such as controlled-release preparations and preparations that require the fast onset of action, the frequency of sampling and the sampling time point should be determined scientifically, such as based on pharmacokinetic data on a reference drug product.
 - a. Blood sampling
 - (1) Blood samples should be collected within a sufficient period, as, for example, for three or more times of the terminal half-life, or until the AUC for the last measured time (AUC_t) reaches at least 80% of the AUC from time zero to infinity (AUC_∞). In case the terminal half-life is long and intersubject variations in the apparent volume of distribution and clearance are small, blood samples may be collected for up to 72 h.
 - (2) In principle, the number of blood samples should be more

than 12 points. At least two samples should be collected before the peak time. The total number of samples can be determined based on the duration of the sampling time and the time when the maximum concentration is reached.

- (3) In case the test and reference drug products will be compared based on the blood concentration–time curve at a steady state after multiple-dose administration, a sufficient number of blood samples should be collected to ensure the maximum concentration ($C_{ss,max}$) and the minimum concentration ($C_{ss,min}$) at the steady state.

b. Urine sampling

- (1) The method of urine sampling should follow that of the blood sampling.
 - (2) The subjects should be notified that they should empty their urinary bladder to ensure complete urine collection. When blood sampling and urine sampling are simultaneously performed, it is better to collect blood samples in the middle of urine sampling time intervals.
 - (3) When the test and reference products will be compared based on the cumulative amount excreted in the urine–time profiles at a steady state after multiple-dose administration, a sufficient number of urine samples should be collected to estimate the amount and the excretion rate of the urine.
4. The wash-out period should be determined based on the time required to eliminate the active components of the

pre-administered (first-period) drug product from the body. The wash-out period should be more than five times the half-life of the active ingredients after the pre-administration of the drug product.

5. Component and method of analysis
 - a. The component to be analyzed should be an active ingredient or its active metabolite in the blood (serum or plasma) or the urine sample. For the analysis of the active metabolite, the formation of the metabolite should be proportional to the doses of the parent drug. In principle, for combination drug products, all active ingredients should be measured.
 - b. The analytical method should ensure specificity, linearity, accuracy, precision, and sufficient sensitivity to accurately determine the actual concentrations of the analytical component.
6. Instruments, chemicals, reagents, and solutions
 - a. The instruments to be used in the BE study should have a control system so that complete records on the operation can be maintained and preserved.
 - b. The instruments, chemicals, reagents, and solutions should be so managed as to be easy to discern.
7. Management of the samples for analysis
 - a. The date and total number of samples received, and the number of samples used in the analysis, should be recorded, and the said documents should be kept.
 - b. Procedures for the handling and storage of the samples for

analysis should be established.

- c. Containers should be labeled with relevant information for easy discernment.

Article 18-2 (Additional Trials)

If the test drug product has not been proven to be BE to the reference drug product for the number of subjects stipulated in Article 13, additional trials can be conducted only once. The results of the additional trials should be analyzed using statistics combined with the results of the preceding BE study. To use the results of the additional trials in the evaluation, according to Article 19, all of the following should be satisfied:

1. The same protocol employed in the preceding BE study;
2. At least 12 subjects per group;
3. To prove consistency using statistics (α . 0.05, significance level below 0.05), each of the following items should be satisfied, and the consistency can be proven using other statistics, if reasonable:
 - a. The ratio of the mean square error (MSE) of the preceding BE study and the additional trials (the smaller of the two values should be the denominator) should be smaller than the top 5-percent value of the F-distribution that has a corresponding degree of freedom; and
 - b. There should be no interaction between the formulation effects of the preceding BE study and the additional trials when the significance level is below 0.05; and

4. It should be clearly mentioned in the protocol whether or not additional trials were conducted.

Chapter 6. Evaluation and Final Report, Etc.

Article 19 (Evaluation)

- ① In the case of blood samples, comparative parameters for evaluation include the AUC_t and C_{max} for a single-dose study, and the AUC_τ and $C_{ss,max}$ for a multiple-dose study. The supplementary parameters for evaluation include the time when the maximum concentration (T_{max}) is reached, and the comparative dissolution profile. For preparations that show rapid onset of action, such as the nitroglycerine sublingual tablet, the T_{max} can be included as a comparative evaluation parameter. In this case, the C_{max} and T_{max} are directly read from the experimental data and the AUC is calculated using the trapezoidal rule method. In the case of urine samples, comparative parameters for evaluation include the A_{et} , $A_{e\tau}$, and U_{max} , instead of the AUC_t , AUC_τ , and C_{max} , respectively.

Definition of Each Parameter

AUC: The total area under the blood (serum or plasma) concentration–time curve

AUC_t : The AUC from time zero to the last measured time, t , in the blood (serum or plasma)

AUC_{∞} : The AUC from time zero to time infinity ($AUC_{\infty} = AUC_t + C_t/\lambda_z$)

C_t : The plasma concentration at time t

λ_z : The terminal-phase elimination-rate constant

AUC_t/AUC_{∞} : The ratio of AUC_t to AUC_{∞}

$t_{1/2\beta}$: The terminal-phase half-life

AUC_{τ} : The AUC during the dosing interval, τ , at a steady state

C_{max} : The maximum concentration in the blood (serum or plasma)

$C_{ss,max}$: The maximum concentration in the blood (serum or plasma) at a steady state

$C_{ss,min}$: The minimum concentration in the blood (serum or plasma) at a steady state

T_{max} : The time when C_{max} was reached

U_{max} : The maximum rate of drug excreted into the urine

A_{et} : The cumulative amount excreted in the urine from time zero to the last collection time, t

$A_{e\tau}$: The cumulative amount excreted in the urine during the dosing interval, τ , at a steady state

- ② After the log transformation of the parameters, except for T_{max} , and the statistical evaluation of the comparative parameters are performed, the 90% confidence intervals for the differences in the mean values of the test and reference drug products should be within $\log 0.8$ – $\log 1.25$. If the values are not between $\log 0.8$ – $\log 1.25$, then the test drug product is considered BE, if all the following are met:

1. In case the difference between the log-transformed mean values of

comparative parameters of the test and reference drug products is within $\log 0.9$ – $\log 1.11$;

2. In case the results of the dissolution test between the test and reference drug products are equivalent under all test conditions, according to the Regulation for the Management of the Therapeutic Equivalence Test (KFDA Notification), although this provision is not applicable to solid oral preparations (except for controlled-release preparations) and enteric coated preparations, unless the average dissolution rate from the reference drug product reaches 85% within the specified time point (For controlled-release preparations, the average dissolution rate from the test drug product reaches within $\pm 10\%$ of the average dissolution from the reference drug product at the time point at which the reference drug product dissolves at around 30, 50, and 80%); and
3. The total number of subjects should be more than 24 (12 per group).

③ In principle, an analysis of variance(ANOVA) is performed at (probability) = 0.05.

Article 20 (Final Report)

The principal investigator should submit a final report, which should include all the following items, to the sponsor, and the sponsor should submit the final report to the KFDA Commissioner:

1. The title, purpose, and summary of the BE study;

2. The generic and brand names, dosage form, manufacturing date, batch number, and results of the quality control test of the reference and test drug products;
3. The manufacturer, the place of manufacture (in case of subdivision and repacking, the place of manufacture of bulk materials, and the subdivision and repacking site), the batch number of the active ingredient, and a certificate of analysis of the raw material (excipient) used for the preparation of the test drug product;
4. The detailed manufacturing process for the test drug product (the manufacturing date, the amount of raw materials used, the standard amount, etc.);
5. The name and address of the sponsor, and the name of the director of the company where the sponsor works
6. The name and address of the director of the test institution;
7. The name, affiliation, and title of the principal and main investigators;
8. The duration of the BE study;
9. The results of the comparative dissolution test (in case the criteria in Article 5-①-8 are met, the submission of the results is waived);
10. The results of the pilot study (for humans, the document on the control of the subjects);
11. The criteria for and method of selecting the subjects (the inclusion and exclusion criteria for selecting the subjects, the

advertisement for the recruitment of subjects, and the information given to the subjects);

12. <Deleted>
13. Dropouts among the subjects and the reasons for such;
14. The case report form (including the schedule of the blood sampling time points);
- 14-2. The document on the control of the subjects;
15. The design of the BE study (the dose, route of administration, method of administration, administration date, method of collecting the samples to be analyzed, sampling volume, sample numbers and sampling time points, storage condition of the samples to be analyzed, wash-out period, and nutrition specifications, such as the menu, total calories, and nutrition consumption rate for a BE study that will be conducted after a meal (only for the controlled-release formulations)
16. In the case of blood sampling, the method of infection prevention;
17. The handling of the samples to be analyzed and the analytical methods (validation data: specificity, linearity, accuracy, precision, sensitivity, etc.);
18. The results of the BE study [the actual analytical data, such as the blood concentration data at each time point per subject (the data storage material, such as a diskette, should be submitted); the log-transformed values; the pharmacokinetic parameters such as the AUC_t (AUC_τ), C_{max} ($C_{ss,max}$), T_{max} , AUC_∞ , AUC_t/AUC_∞ , $t_{1/2}$

- β, etc.; the analytical results, including the validation of the analytical method (including the computer-readable storage materials that contain the raw data and the method of integration); and the statistical process (raw data);
19. The evaluation criteria and the principal investigator's opinion on the results;
 20. <Deleted>
 21. The records of the IRB;
 22. The records of receipts and disbursements of the drug products for the BE study;
 23. The signatures or seals of the principal investigator, the director of the test institution, the sponsor, and the chief investigator;
 24. The final protocol approved by the IRB; and
 25. The certificate of quality assurance.

Article 21 (Inspection of the Quality of the Results of the BE Study)

- ① If necessary, the KFDA Commissioner can direct KFDA officials and experts to inspect all the procedures relevant to the BE study. The officials and experts can inspect whether or not the BE test was conducted according to the criteria for the confirmation of the reliance of the BE study results, if necessary.
- ② If necessary, the KFDA Commissioner can direct KFDA officials and experts to inspect the BE study procedures without notifying the test institution, and to inspect whether or not the BE study is being conducted and recorded according to its protocol, SOP, criteria, and related relevant regulations.

Article 22 (Keeping Data and Storing Analytical Samples)

① The sponsor or the person responsible for keeping data, as assigned by the director of the test institution according to Article 6, Clause ⑩, should keep the data on the following items for five years after the date of approval of the BE study results (in case there is an approval condition, after the date of deletion of the condition); and the analytical samples must be stored until the date of approval of the BE study results (if there is an approval condition, until the date of deletion of the condition):

1. The protocol and the final report;
2. The raw data
3. All the quality inspection records
4. Records on the qualifications, training, experience, and duties of the main investigator
5. Records of and reports on the use and management of instruments;
6. Past records on all SOPs; and
7. The test and reference drug products with the same lot number, as used in the BE study (in amounts sufficient to reproduce the BE study twice).

② A label should be attached to the data container, which should be kept in the data storage room for easy storage and location.

Article 23 (Non-compliance of a BE Study to the Criteria)

If the principal investigator does not follow this guidance document during

the conduct of a BE study, the sponsor should correct him/her and take proper action to prevent the recurrence of such non-compliance. In case the sponsor discovers significant and continuous non-compliance, he/she should stop the BE study and report the case to the KFDA Commissioner.

Chapter 7. Supplementary Provisions

Article 24 (Others)

- ① For any matter not provided in this guidance document, the minimum Requirements for KGCP shall be upheld.
- ② If the final report on a BE study will be submitted to KFDA for the latter's approval of a test drug product (including the post-approval changes), the final report should be issued by the director of the test institution, as stipulated in Article 6.

Additional Provisions (#2007-65 and 2007.9.20)

Article 1 (Date of Enforcement)

This guidance document will be in force starting July 1, 2008.

Article 2 (Temporary Measures)

In the case of any BE study protocol that was approved by the KFDA Commissioner or that was submitted to the KFDA before the date of

enforcement of this guidance document, the former guidance document shall be applicable thereto.

Article 3 (Preparation for Inspection of the Suitability of a Test Institution)

The director of a test institution and the KFDA Commissioner can request for an inspection of whether or not the test institution can adequately conduct a BE study, as provided in Article 6, Clause 4, and perform the tasks necessary for the judgment of the suitability of the test institution before the enforcement of this guidance document.

Additional Provisions (#2008-22 and 2008.5.7)

Article 1 (Date of Enforcement)

This guidance document shall be in force starting July 1, 2008.

Article 2 (Temporary Measures)

In the case of any BE study protocol that was approved by the KFDA Commissioner or submitted to the KFDA before the date of enforcement of this guidance document, the former guidance document shall be applicable thereto.

Attachment

[Annexed Paper Item 1 Form]

Final Report on the Subjects' Observation				
Reporter	Name			
	Name and Address of the Test Institution			
Drug Product (Component)			Approval Date of the Protocol	
Test Institution	Name		Tel.	
	Address			
First Date of the Selection of the Subjects				
Date of Observation of the Final Subject				
Number of the Participating Subjects				
Summary of the Considerable Adverse Drug Reactions				
Remarks				
<p>I report herein the completion of my observations on the subjects according to Article* Clause* of the guide document for bioequivalence studies.</p> <p style="text-align: center;">year month day</p> <p style="text-align: right;">Reporter (Signature or Seal) Investigator Tel.</p> <p>To the KFDA Commissioner</p>				

210 mm × 297 mm

[Attachment 1]

Checklists for the Inspection of the Bioequivalence Study

Test Institution and One of Its Directors		
When Some Items were Consigned to Another Test Institution	Items Consigned	
	Name of the Consigned Test Institution and of One of Its Directors	
A Sponsor and Director of the Company		
Test Drug Product		
Reference Drug Product		
Remarks		

I. Test Institution for the Bioequivalence Study (General Items)

Classification No.	Checklist	Propriety (O/X)	Remarks
I-1	Compliance with the protocol		
I-1-1	1. Were the subjects recruited after the approval (amendment) of the protocol?		
I-1-2	2. Did the principal and main investigators agree with the sponsor and conduct the BE study according to the protocol approved by the KFDA and IRB commissioners, and did they follow the SOP?		
I-1-3	3. Were justifiable reasons documented on all the items when the BE study was conducted differently from the approved protocol?		
I-1-4	4. Was a final report on the subjects' observation, with a summary of the results, reported to IRB, and was the sponsor notified when the observations of the subjects had been completed?		
I-2	Selection of the Subjects and Management of the BE Study		
I-2-1	1. Did the principal investigator fully explain the information regarding the BE study to the subjects, and did he/she obtain the voluntary informed consent of the subjects?		

Classification No.	Checklist	Propriety (O/X)	Remarks
I-2-2	2. Did the principal investigator (or a person delegated by him/her) agree with the subjects before their participation in the BE study, and did he/she sign the consent form and write the date by his/her own handwriting?		
I-2-3	3. Did the principal investigator fully explain the schedule and specifications of the drug products that were used in the BE study?		
I-2-4	4. Was the agreement of providing compensation for the subjects complied with?		
I-2-5	5. Was the administration of the drug products adequately conducted according to the protocol, and was the schedule, such as the wash-out period, conducted according to the protocol?		
I-2-6	6. Were the measures to avoid the expected adverse drug reactions, drug product precautions, and medical care in case drug-induced adverse effects occurred prepared according to the criteria, and were these complied with?		

Classification No.	Checklist	Propriety (O/X)	Remarks
I-2-7	7. Were the medical treatment, such as the physical examination of the subjects, the administration of the drug products, the blood sampling, and the prevention and treatment in case the drug-induced adverse effects occurred controlled under the supervision of a medical doctor (an investigator)?		
I-2-8	8. Were the samples analyzed according to the SOP of the test institution (or of the consigned test institution)?		
I-3	Management of the Drug Products		
I-3-1	1. Did a management pharmacist adequately store and manage the drug products that were used in the BE study in an adequate place, according to the relevant criteria?		
I-3-2	2. Did a management pharmacist receive and disburse the drug products (receipt, inventory control, administration, and return of the drug products) that were used in the BE study, and did he/she retain their records?		

Classification No.	Checklist	Propriety (O/X)	Remarks
I-4	IRB		
I-4-1	1. Was IRB composed and managed according to the guide document for BE studies (or KGCP) and the SOP?		
I-4-2	2. Did IRB perform the review, recording, and retention of the document according to the SOP?		
I-5	Retention and Management of the Raw Data, etc.		
I-5-1	1. Were the following items related to the BE study adequately retained and managed?		
	A. the protocol and the final report		
	B. the raw data		
	C. all the records of the inspection according to the quality assurance works		
	D. the records on the qualifications, training, experiences, and distributed duties of the main investigator		
	E. the records and reports on the usage and management of the instruments		
	F. the files of the past records of all the SOPs		

Classification No.	Checklist	Propriety (O/X)	Remarks
	<p>G. the test and reference drug products that have the same lot number used in the BE study (sufficient numbers to allow the BE study to be reproduced two times)</p> <p>H. analysis samples</p> <p>I. a service contract with a sponsor of the BE study</p>		
I-5-2	2. Were the documents retained, reported, stored, and inspected according to the SOP?		
I-6	Quality Assurance		
I-6-1	1. Were copies of the approved protocol and SOP kept?		
I-6-2	2. Did the protocol, SOP, etc. contain the items that are necessary for compliance with the guide document for BE studies, and were they documented?		
I-6-3	3. Was an inspection performed to assure that the BE study was conducted according to the criteria for BE studies, and was whether the main investigator followed the protocol and SOP based on the results of the inspection recorded?		

Classification No.	Checklist	Propriety (O/X)	Remarks
I-6-4	4. Was the final report inspected in terms of whether the method, procedure, and result of the observation were accurately and completely described, and whether the reported results accurately and completely reflect the raw data?		
I-6-5	5. Were the results of the inspection rapidly reported in a document to a director of the test institution or to the administrator and the principal investigator?		
I-6-6	6. Was a quality assurance certificate (reflecting the date and contents of the inspection and the date of reporting to a director of the test institution or the principal investigator) prepared and signed, and was this attached to the final report?		

<p style="text-align: center;">Confirmer</p>	<p style="text-align: center;">Signature</p>
--	--

II. Test Institution for the BE Study (Medical Institution)

Classification No.	Checklist	Propriety (O/X)	Remarks
II-1	Selection of the Subjects		
II-1-1	1. Were the internal examinations and the physical examination of subjects, etc. well conducted, and were the related records well managed?		
II-1-2	2. Did a medical doctor (an investigator) choose the subjects based on the criteria of inclusion and exclusion according to the guide document for BE studies and the protocol?		
II-2	Control of the Subjects		
II-2-1	1. Did a medical doctor (an investigator) adequately control the subjects, such as controlling their food intake before the administration of the drug products, up to the last blood sampling, according to the approved protocol?		

Classification No.	Checklist	Propriety (O/X)	Remarks
II-2-2	2. Did a medical doctor (an investigator) supervise the method of administration of the drug products, and the dose administered, as indicated in the approved protocol?		
II-2-3	3. Were adequate blood samples collected, as indicated in the approved protocol?		
II-2-4	4. Were the subjects adequately managed (e.g., prevention and medical care in case adverse drug reaction/s emerged after the administration of the drug products), and were the related records reported and managed according to the SOP?		
II-3	Management of the Analytical Samples		
II-3-1	1. Were the storage and handling of the samples after the blood sampling, and the transport of the analysis samples, correctly performed according to the SOP?		

Classification No.	Checklist	Propriety (O/X)	Remarks
II-4	Management of the Drug Products		
II-4-1	1. Did a management pharmacist store and manage the drug products that were used in the BE study at an appropriate place, according to the relevant criteria?		
II-4-2	2. Did a management pharmacist receive and disburse the drug products that were used in the BE study, and did he/she retain the relevant records?		
II-5	Retention and Management of the Data, etc.		
II-5-1	1. Were the documents related to the BE study adequately stored and retained?		
II-5-2	2. Were the retention, report, storage, and inspection of the records followed according to the SOP?		

Confirmer	Signature
-----------	-----------

III. Test Institution for the BE Study (Test Institution for the Analysis of the Samples)

Classification No.	Checklist	Propriety (O/X)	Remarks
III-1	Management of the Samples		
III-1-1	1. Were the analysis samples received, discerned, handled, and stored according to the SOP?		
III-1-2	2. Were the samples handled and analyzed according to the SOP?		
III-1-3	3. Were the chemicals, instruments, reagents, and solutions prepared and discerned according to the SOP?		
III-1-4	4. Was the analytical method validated, and were their relevant data retained?		
III-2	Storage and Retention of the Data, etc.		
III-2-1	1. Were the data related to the BE study kept and retained well?		
III-2-2	2. Were the records retained, reported, stored, and inspected according to the SOP?		

Confirmer	Signature
-----------	-----------

IV. A Sponsor

Classification No.	Checklist	Propriety (O/X)	Remarks
IV-1	Manufacturing and Management of the Test and Reference Drug Products		
IV-1-1	1. Was the test drug product manufactured or imported after the approval of the drug item?		
IV-1-2	2. Were the data on the source of the active ingredient used in the manufacturing of the test product and its specifications, such as its manufacturer, manufacturing site, supplier, batch number, records of its imported active ingredient, and import license (in case there is an imported active ingredient), retained?		
IV-1-3	3. Were the manufacturing and quality control of the test drug product properly performed according to the approved protocol and the master formulation?		
IV-1-4	4. Was the quality control of the reference drug product adequately conducted?		
IV-1-5	5. Was a comparable dissolution test adequately performed on the test and reference drug products?		

Classification No.	Checklist	Propriety (O/X)	Remarks
IV-2	Inspection, etc. of the BE Study		
IV-2-1	1 Do the starting and final dates of the BE study coincide with those indicated in the final report?		
IV-2-2	2. Did the test institution check whether the procedures of the BE study were conducted according to the SOP and the relevant criteria, and were the results of such inspection documented?		
IV-2-3	3. Were the significant drug-induced adverse effects that emerged during the BE study reported to the KFDA Commissioner within the time indicated in the guide document for BE studies?		
IV-2-4	4. Was a report on the observations of the subjects submitted to the KFDA Commissioner within 20 days after the completion of such observations?		

✳Comments

Judgment	Accept		Reject	
Comment(s) and reason(s) in case of rejection				

[Attachment 2]

Active Ingredient Having a Narrow Therapeutic Range

(Related to the Article 2 Clause 13)

Number	Active ingredient
1	Aprindine
2	Carbamazepine
3	Clindamycin
4	Clonazepam
5	Clonidine
6	Cyclosporine
7	Digitoxin
8	Digoxin
9	Disopyramide
10	Ethinyl Estradiol
11	Ethosuximide
12	Glybuzole
13	Guanethidine
14	Isoetharine
15	Isoprenaline
16	Isoproterenol
17	Lithium
18	Metaproterenol
19	Methotrexate
20	Minoxidil

Number	Ingredient
21	Phenobarbital
22	Phenytoin
23	Prazosin
24	Primidone
25	Procainamide
26	Quinidine
27	Sulfonylurea compounds ¹⁾
28	Tacrolimus
29	Theophylline compounds ²⁾
30	Valproic acid
31	Warfarin
32	Zonisamide

1) Acetohexamide, Glibenclamide, Gliclazide, Glyclopamide, Tolazamide, Tolbutamide

2) Aminophylline, Oxitriphylline (Choline Theophylline), Diprophylline (Dyphylline), Proxyphylline, Theophylline

[Attachment 3]

Criteria for the Comparative Dissolution Test of Solid Oral Preparations with Different Strengths according to the Level of Changes in Raw Materials and Their Amounts

(Related to Article 3, Clause 2)

1. Level of Changes in Raw Materials (Excipients) and Their Amounts

When the same manufacturer applies for a BE study of a new test drug product that has the same dosage form and the same active ingredient as a new test drug product that has the same ratio of active ingredients and all excipients compared to an approved test drug product, but the active ingredient of which has a different strength, the level of changes in the excipients and their amounts follow level A. If the ratios of a new product and an approved test product are not the same, the level of changes for each excipient is determined according to Tables 1 and 2. If the change is equal to or less than the range of level B, it follows B. If the change is between level B and level C, it follows level C. Similarly, if the change in the excipient is between level C and level D, it follows level D. In all cases of changes that exceed level D, they follow level E. Any change in the coloring or flavoring agents follows level A. Among the changes, the highest level of changes is defined as the level of changes in the excipient.

Table 1. Level of Changes in the Excipients for the Uncoated Preparations

Purpose of Mixing and Components of the Excipients	Percent Difference of the Excipient (w/w) Compared with the Total Weight of the Unit Dosage Form		
	B	C	D
Disintegrant			
Starch	3.0	6.0	9.0
Others	1.0	2.0	3.0
Binder	0.50	1.0	1.5
Lubricant · Polisher			
Stearate and its salt	0.25	0.50	0.75
Others	1.0	2.0	3.0
Glidant	5.0	10	15
Others (except coloring and flavoring agents)	1.0	2.0	3.0
Absolute additive value of the differences in the contents of each changed excipient	5.0	10	15

Table 2. Level of Changes in the Excipients for Coated Preparations

Classification	Purpose of Mixing and Components of the Excipients	Percent Difference of Each Excipient (w/w) Compared with the Total Weight of the Unit Dosage Form		
		B	C	D
Core	Disintegrant			
	Starch	3.0	6.0	9.0
	Others	1.0	2.0	3.0
	Binder	0.50	1.0	1.5
	Lubricant·Polisher			
	Stearate and its salt	0.25	0.50	0.75
	Others	1.0	2.0	3.0
	Glidant	5.0	10	15
Others (except coloring and flavoring agents)	1.0	2.0	3.0	
	Absolute additive value of the differences in the contents of each excipient whose core was changed	5.0	10	15
Film-coated layer ¹⁾	Absolute additive value of the differences in the contents of each excipient whose film-coated layer was changed	5.0	10	15
Sugar-coated layer	Absolute additive value of the differences in the contents of each excipient whose sugar-coated layer was changed	5.0	10	15

¹⁾ All the coated layers, such as the waterproof, undercoated, enteric-coated, and controlled-release layers, except the sugar-coated layer

2. Criteria for the Comparative Dissolution Test on the Changes in the Level of the Excipient

The types of BE studies that should be conducted on the changes in the level of the excipient are listed in Table 3.

Table 3. Criteria for the Comparative Dissolution Test on the Changes in the Level of the Excipient

Level	Preparation Type	Therapeutic Range of the Active Ingredient ¹	Solubility in Water ²	Dissolution Rate ³	Comparative Dissolution Test or BE Study ⁴
A					Comparative dissolution test
B					Comparative dissolution test
C	Immediate-release preparations/enteric-coated preparations	Wide	Soluble		Comparative dissolution test
			Hardly soluble		BE study
		Narrow	Soluble	≥85%/30 min	Comparative dissolution test
			Hardly soluble	<85%/30 min	BE study
	Controlled-release preparations	Wide			Comparative dissolution test
		Narrow			BE study

D	Immediate-release preparations	Wide	Soluble	≥85%/30 min	Comparative dissolution test
				<85%/30 min	BE study
		Hardly soluble		BE study	
		Narrow			BE study
	Enteric-coated preparations/controlled-release preparations				BE study
E					BE study

- a. Ingredients listed in Attachment 2 and their equivalents are classified as a narrow-therapeutic-range group. Others are classified as a wide -therapeutic -range group.
- b. If less than 85% of the active ingredient is dissolved for up to 6 hours under conditions specified in Article 8, Table 1.1-4 of the *Regulation for the Management of the Therapeutic Equivalence Test (KFDA Notification)*, it is not considered a water-soluble drug. Others are considered water-soluble drugs.
- c. If more than 85% of the active ingredient from the test and reference drug products are dissolved within 30 minutes under all conditions specified in Article 8 of the *Regulation for the Management of the Therapeutic Equivalence Test (KFDA Notification)*, it is expressed as "≥ 85% / 30 min." Others are expressed as "< 85% / 30 min."
- d. A comparative dissolution test should be performed in accordance with Article 8 of the *Regulation for the Management of the Therapeutic Equivalence Test (KFDA Notification)*, and the BE must be evaluated according to Article 10-3 of the same regulation. In the case of level A, if the dissolution test is established in the criteria and the test method of the

reference drug product, a comparable dissolution test should be performed according to the corresponding test method, and the BE must be evaluated according to Article 10, Clause 3. If a comparative dissolution profile fails to demonstrate equivalence, a BE study should be conducted.

[Attachment 4]

**Criteria for *In Vivo* Bioequivalence Test Waivers
for Oral Solid Tablets or Capsules**
(Relative to Article 3, Clause 3)

1. The following terms were defined in this attachment.
 - a. The *Biopharmaceutics Classification System* (hereinafter referred to as "BCS") is a scientific classification system for classifying drug substances based on their aqueous solubility and intestinal permeability.
 - b. A *solubility test* is the test described in Attachment 4-1 for classifying the solubility in water (hereinafter referred to as "solubility") of drug substances according to the BCS.
 - c. A *permeability test* is the test described in Attachment 4-2 for classifying the permeability of drug substances according to the BCS. This test directly or indirectly measures the rate or extent of absorption of a drug substance across human intestinal membranes using humans, animals, or cell lines.
 - d. A *dissolution test* is the test described in Attachment 4-3 for measuring the dissolution rate of active ingredients from oral solid preparations.
2. BCS

Drug substances are classified as follows based on their solubility and permeability (a waiver for an *in vivo* BE study could be required based on the BCS):

 - a. Class 1: High solubility -High permeability;
 - b. Class 2: Low solubility - High permeability;
 - c. Class 3: High solubility - Low permeability; and
 - d. Class 4: Low solubility - Low permeability.

3. Criteria for Biowaivers of BE Studies

a. General Matters

Oral tablets or capsules that contain an active ingredient are classified in Class I, according to the BCS. The active ingredients from both test and reference drug products should be rapidly dissolved, and the excipients should not affect the absorption of the active ingredients.

b. Criteria Based on the Solubility of the Active Ingredients

The solubility test in Attachment 4-1 should demonstrate that the highest strength of the approved solid oral dosage form with the same active ingredient is soluble in 250 mL or less of water over a pH range of 1–7.5.

c. Criteria Based on the Permeability of the Active Ingredients

Based on human or non-human systems capable of predicting the extent of the active ingredient in humans or based on the measurement of the transfer rate across the human intestinal membrane, the permeability test in Attachment 4-2 should demonstrate that the extent of absorption of humans of an administered dose is 90% or more. There should be no evidence, however, that the active ingredient is unstable in the gastrointestinal tract.

d. Criteria Based on the Dissolution of the Preparations

The results of the dissolution test in Attachment 4-3 should meet the following criteria:

(1) The active ingredients of the test and reference drug products should dissolve at an amount equal to or more than 85% of the labeled amount of the active ingredient within 15 minutes; and

(2) The active ingredient of both the test and reference drug products should dissolve at an amount equal to or more than 85% of the labeled amount of the active ingredient within 30 minutes, and the dissolution

profiles of the test and reference drug products should be similar.

4. Documents to Support a Request for Biowaivers

a. Documents on Origin and Developmental Procedures

A summary of the documents, characteristics, and developmental procedures of a drug product should be submitted to determine whether or not a test drug product could be given a biowaiver.

b. Documents on the Determination of the Chemical Structure and Physicochemical Properties

Documents that describe the composition, amount of raw components, final specifications of the raw components, and manufacturing method of a test drug product (including the "in-house" specifications and the test method) should be submitted.

c. Documents on the Solubility of the Active Ingredient

Documents that support the high solubility of the active ingredient should be verified. All the following information should be included:

- (1) Documents that describe the test methods, including information on the analytical method and the composition of the buffer solutions;
- (2) Documents that describe the chemical structure, molecular weight, characteristics (acid, base, amphoteric, or neutral), and dissociation constants (pKa) of the active ingredient;
- (3) Summary of the table that lists the test results of the solubilities of the active ingredient in various pH solutions (e.g., mg/mL), and volume of media required to dissolve the highest strength; and
- (4) A graph that shows the pH-mean solubility profile.

In case the active ingredient is considered to have high solubility after the KFDA review, submission of the above data can be waived.

d. Documents on the Permeability of the Active Ingredient

Documents that confirm the high permeability of the active ingredient in humans, animals, or cell lines should be submitted, and should belong to one of the following:

(1) A pharmacokinetic study of humans:

- (a) Information on the study design and methods and
- (b) Pharmacokinetic data

(2) A permeability test across the intestinal membrane:

(a) Information that confirms the suitability of the selected test method:

- 1) Description of the test method
- 2) Criteria for the selection of the study population (humans, animals, or epithelial cell lines)
- 3) The drug concentration and the analytical method used for the donor fluid
- 4) Method of calculating the extent of absorption or permeability of the drug; and
- 5) Information on the drug's efflux potential, such as bidirectional transport data (only if possible)

(b) Information on model drugs:

- 1) A list of each model drug used to verify the suitability of a method and data on the extent of its absorption by humans (mean, standard deviation, and coefficient of variation);
- 2) Permeability value of each model drug (mean, standard deviation, and coefficient of variation) and classification of each model drug based on the permeability test;
- 3) Extent of absorption of the drug (mean \pm standard deviation or 95% confidence interval) based on its permeability values; and

- 4) Data on the selected internal standard and verified classification of the drug's permeability (low/high) based on its permeability values; and

(c) Data on the test results:

- 1) Permeability values (mean, standard deviation, and coefficient of variation) of the internal standard and the test drug substance;
- 2) Data on the stability of the test drug substance in the gastrointestinal tract;
- 3) Adequate data to verify the passive transport mechanism of the test drug substance; and
- 4) The test method used to verify the high permeability of the test drug substance.

If the active ingredient in the test drug product is considered to have high permeability after the KFDA review, submission of the above data can be waived.

e. Data on the Dissolution Test

Data that confirms the rapid dissolution of both the test and reference drug products should be submitted. The following information should be included:

- (1) A brief description of the test product used in the dissolution test (the batch or lot number, expiration date, strength, weight, size, etc.);
- (2) The dissolution data:
 - (a) Percentage of the labeled amount dissolved at each specified time point for each strength;
 - (b) A table that lists the mean dissolution rate, dissolution range (highest and lowest), and coefficient of variation (relative standard deviation); and

- (c) A graph that shows the mean dissolution profiles of the test and reference drug products in each medium; and
- (3) Data that confirms the similarity of the dissolution profiles of the test and reference drug products in each medium, using the f_2 value.
- f. Data on the Excipients
- In case new excipients that were not included in the approved immediate-release oral solid preparations are used, or atypically large amounts of commonly used excipients (especially surfactants, such as polysorbate 80, and sweeteners, such as mannitol and sorbitol) are included, data should be submitted to verify that the excipients do not affect the BA and
- g. In case the drug substance does not have biological activity by itself, but is converted to a bioactive substance through an enzymatic or non-enzymatic reaction in the body (hereinafter referred to as "prodrug"), permeability data on prodrug should be submitted when the conversion predominantly occurs after the permeation through the intestinal membrane, or the permeability data on the bioactive substance should be submitted when the conversion occurs before the permeation through the intestinal membrane. It is recommended that solubility and dissolution data on both prodrug and its bioactive substance be submitted.

Attachment 4-1

Solubility Test

I. Selection of the Test Substance

In principle, the test substance should be identical to the active ingredient of the test drug product for which an application for the waiver of the BE study is being filed.

II. Method

In principle, the solubility in an equilibrium state and the pH-solubility profile of a drug substance are determined using the acid-base titration method or other adequately validated methods in aqueous media in the physiological pH range (pH 1.0–7.5). The method should distinguish between a drug substance and its degradation product(s). If the drug substance is degraded due to its component(s) or the pH of the buffer, data on the stability of the test substance in the gastrointestinal tract based on Attachment 4-2 III should be submitted.

A. Conditions

1. Amount of the test drug substance: The highest strength of the approved immediate-release oral solid preparations
2. Media: In principle, the standard buffer solutions described in *Korean Pharmacopoeia* are used. If these buffer solutions are not suitable on a test drug substance for physical or chemical reasons, other buffer solutions can be used.
3. Temperature of the media: $37 \pm 1^\circ\text{C}$
4. pH of the media: The solubility test should determine various

numbers of pH media based on the ionization characteristics of the test drug substance to accurately define its pH–solubility profile.

e.g., When the pKa of a drug is in the range of 3–5, a solubility test should be performed at pHs 1, pKa –1, pKa, pKa +1, and 7.5. The pH should be determined after the addition of the drug substance to the media.

5. Number of tests: At least three test repetitions are recommended. An additional test may be needed depending on the characteristics of the test substance.

Attachment 4-2

Permeability Test

I. Selection of the Test Substance

In principle, the test substance is identical to the active ingredient of a drug product for which the waiver of the BE study has been approved.

II. Test Method

The permeability of a drug substance can be determined by mass balance and absolute BA tests on humans, or intestinal perfusion tests. Other tests using a suitable animal model (e.g., rats), such as an *in vivo* or *in situ* intestinal perfusion test or an *in vitro* permeability test using excised intestinal tissues or monolayers of suitable epithelial cells, could be used to measure the permeability of a drug substance. In many cases, as, for example, when the absolute BA is not less than 90% or when it has been confirmed that no less than 90% of the administered dose was recovered in the urine, such test may be sufficient. In case a single test fails to clearly classify the permeability, the use of two other different methods is recommended.

A. Pharmacokinetic Test on Humans

1. Mass Balance Test

The pharmacokinetic mass balance test is a test that measures the extent of absorption of a drug using unlabeled stable isotopes or a radiolabeled drug substance. Due to the variability associated with the test, a sufficient number of subjects should participate in the test to obtain a reliable estimate of the extent of absorption. Because

this test could result in highly variable estimates of the absorption of many drugs, the absolute BA test is preferred.

2. Absolute BA Test

The absolute BA test is a test that determines the oral BA of a drug based on the data obtained from its intravenous administration. Due to the intersubject variability associated with this test, a sufficient number of subjects should participate in it to provide a reliable estimate of the absolute BA. When the absolute BA of a drug is 90% or more, no additional data on the drug's stability in the gastrointestinal fluid are needed.

B. Gastrointestinal Tract Permeability Test

The following tests can be used to determine the permeability of a drug substance across the gastrointestinal tract:

1. An *in vivo* intestinal perfusion test on humans;
2. An *in vivo* or *in situ* intestinal perfusion test using suitable animal models;
3. An *in vitro* permeability test using excised human or animal intestinal tissues; and
4. An *in vitro* permeability test across a monolayer of cultured epithelial cells.

In vivo intestinal perfusion test on humans, permeability tests are considered applicable only to passively transported drugs. In case the permeability of a given drug is found to be low in humans, the efflux of the drug via a membrane transporter such as P-glycoprotein (hereinafter referred to as "P-gp") may be involved. As permeability

tests have no efflux transporter or the expression level of the efflux transporter is lower than that found in the human gastrointestinal tract, such tests are likely to result in misclassification of the permeability of drug substances. Thus, the expression of known transporters in a given test should be adequately characterized. The functional expression of efflux systems (e.g., P-gp) may be confirmed using a bi-directional transport study that involves model drugs (e.g., cyclosporin A, vinblastine, and rhodamine 123) in sub-saturated concentrations of the efflux transporter to demonstrate the faster rate of basolateral to apical (hereinafter referred to as "B→") transport than the rate of the apical to basolateral (hereinafter referred to as "A→") transport. A non-human permeability test is recommended when a drug substance is transported via a passive mechanism. Pharmacokinetic studies on dose-linearity or dose-proportionality may provide useful information on the validity of the efflux data for a given drug substance obtained from *in vitro* tests. For example, there may be little concern on the use of an *in vitro* permeability test for a drug that shows linear pharmacokinetics in humans, despite the high *in vitro* B→ transport rate of the drug in a low concentration. To apply the BCS, a clear passive transport mechanism can be assumed when one of the following conditions is satisfied:

1. A linear pharmacokinetic relationship between the dose (e.g., relevant clinical dose ranges) and the measured BA (AUC) of a drug is demonstrated in humans
2. A lack of dependence of the measured *in vivo* or *in situ* permeability on the initial drug concentrations (e.g., 0.01, 0.1, and 1 times the highest strength dissolves in 250 mL) is demonstrated in an animal model or

3. A suitable *in vitro* cell culture method that has been shown to express known efflux transporters (e.g., P-gp) is used, and lack of dependence of the measured *in vitro* permeability on the initial drug concentrations (e.g., 0.01, 0.1, and 1 times the highest strength dissolves in 250 mL) of both the donor fluids and on the transport direction is demonstrated (e.g., there is no statistically significant difference in the rate of transport between A→ and B→ for the drug concentrations tested).

To demonstrate the suitability of a permeability test intended for the application of the BCS, a rank-order relationship between the test permeability values and the extent of the drug absorption data for humans should be established using a sufficient number of model drugs. For an *in vivo* intestinal perfusion test on humans, six model drugs are recommended. For an *in vivo* or *in situ* intestinal perfusion test on animals and for an *in vitro* cell culture test, 20 model drugs are recommended. Depending on the test variability, a sufficient number of subjects, animals, excised tissue samples, or cell monolayers should be used in the test to provide a reliable estimate of drug permeability. The relationship could ensure the differentiation of the attributes of intestinal permeability of drug substances.

To demonstrate the suitability of a test, model drugs that represent low (e.g., < 50%), moderate (e.g., 50-89%), and high (> 90%) ranges of the extent of absorption should be provided. The compounds listed in Table 1 may be selected, although other drugs could also be used for which there is available information on the mechanism of their absorption and reliable estimates of the extent of their absorption by humans.

After the suitability of a test is demonstrated, it is not necessary to include all model drugs to classify a drug substance when the same test protocol is used. Instead, low- and high-permeability model drugs should be used as internal standards. These internal standards should be included in the perfusion or donor medium, together with the test drug substance. In addition to the internal standards, an appropriate fluid volume marker (or an impermeable marker such as PEG 400), which is typically included in certain types of perfusion studies (e.g., closed-loop studies), should be added to the medium. These internal standards should have no interaction, such as physical, chemical, or permeation interaction, with the test drug substance. When it is not feasible to follow this protocol, the permeability of the internal standard should be determined in the same subjects, animals, tissues, or monolayers used in the evaluation of the permeability of the test drug substance. The permeability values of the internal standards should not significantly differ from those in other tests, including in the test conducted to test the suitability. At the end of an *in situ* or *in vitro* test, the amount of drug remaining in the membrane should also be determined.

In an established test method, the permeability of the test drug substance is readily assessed when the test employs an internal standard with permeability close to the limit set for the low- or high-permeability class. For example, a test drug substance may be classified as a highly permeable drug when its permeability is equal to or greater than the high-permeability internal standard.

C. Instability of the Drug Substance in the Gastrointestinal Tract

When the extent of absorption of a drug by humans is assessed by

measuring the total radioactivity in the urine based on the mass balance test, the extent of degradation of a drug product in the gastrointestinal fluid before the drug's permeation across the intestinal membrane is not considered. In certain tests, however, the permeability measurement from the *in vivo* or *in situ* perfusate may reflect the loss or elimination of the drug substance in the gastrointestinal tract of humans or animals. Thus, the verification of the origin of the drug loss in the test medium as the permeation across the intestinal membrane, rather than the degradation of the drug in the gastrointestinal tract, will help in the assessment of the permeability.

The stability test in the gastrointestinal tract is performed in the gastric and intestinal fluids of humans. The drug dissolved in these fluids should be incubated at 37°C for the period in which the drug is in contact with the fluid *in vivo*, as, for example, 1 hour in the gastric fluid and 3 hours in the intestinal fluid. The drug concentrations should then be determined using a standard stability-indicating analysis. Significant degradation (> 5%) of a drug substance may indicate instability. Gastrointestinal fluids from humans could be collected via intubation. If this method is not feasible, gastrointestinal fluids from suitable animal models or the simulated gastric and intestinal fluids described in *Korean Pharmacopoeia* or in other official documents and in the pharmacopoeia designated by the KFDA Commissioner may be substituted.

Table 1. Model drugs for intestinal permeability test

Model drug	Permeability classification
Antipyrine	High (potential candidate as internal standard)
Caffeine	High
Carbamazepine	High
Fluvastatin	High
Ketoprofen	High
Metoprolol	High (potential candidate as internal standard)
Naproxen	High
Propranolol	High
Theophylline	High
Verapamil	High ((potential candidate as internal standard)
Amoxicillin	High
Atenolol	High
Furosemide	High
Hydrochlorthiazide	High
Mannitol	High (potential candidate as internal standard)
Methyldopa	High
Polyethylene glycol 400	High
Polyethylene glycol 1000	High
Polyethylene glycol 4000	High (potential candidate as internal standard)
Ranitidine	High

Attachment 4-3

Dissolution Test

I. Selection of the Test Drug Product

The test drug product should either be fully made up of the active substance or the potency of its active substance content should be within 5% of that of the labeled content (100%) of the reference drug product, according to the "in-house" specifications and the test method, or the difference in the content or potency of the test and reference drug products should be within 5%.

II. The Test Method

The dissolution test should be conducted with at least 12 dosage units of both the test and reference drug products under specific conditions, and the active ingredient should be measured using a validated analytical method. If a dissolution test in each medium is considered unnecessary based on the characteristics of a drug product, a scientific justification should be provided.

- A. Apparatus: The dissolution test should be conducted using Apparatus 1 (100 rpm) or Apparatus 2 (50 rpm) of the dissolution test in the 9th Edition of *Korean Pharmacopoeia*, according to the characteristics of the preparations.
- B. The volume of the media should, in principle, be 900 mL.
- C. The temperature of the media should be $37 \pm 0.5^{\circ}\text{C}$.
- D. The media
 1. pH 1.2 solution: "Buffer 1," as specified in the dissolution test in the 9th Edition of *Korean Pharmacopoeia*
 2. pH 4.0 solution: Acetate-buffered solution [0.05 mol/L acetic acid : 0.05mol/L sodium acetate (41:9)] adjusted to pH 4.0

3. pH 6.8 solution: "Buffer 2," as specified in the dissolution test in the 9th Edition of Korean Pharmacopoeia [For gelatin-coated capsules and tablets, refer to Simulated Gastric and Intestinal Fluids (The specifications should meet the requirement in Korean Pharmacopoeia or in other official documents, and the pharmacopoeia designated by the KFDA Commissioner) with the addition of enzymes can be used.)]
4. Sampling time: 10, 15, 20, and 30 min

III. Assessment of Similarity

To compare the dissolution profiles of the test and reference drug products, a similarity factor (f_2) should be used. The similarity factor is calculated using the percent (%) difference in dissolution between the profiles of the two drug products, via the following equation:

$$f_2 = 50 \cdot \log \left[1 + (1/n) \sum_{t=1}^n (R_t - T_t)^2 \right]^{-0.5} \cdot 100$$

Two dissolution profiles are considered similar if the f_2 value is > 50 . To use the mean data in the calculation, the coefficient of variation should not be more than 20% at the 10-minute point, and should not be more than 10% at any other time point. Note that when both the test and reference drug products dissolve 85% or more of the label amount of the drug within the 15-minute point using all three dissolution media recommended above, the comparison with the f_2 value is unnecessary.