Minimum Requirements for Bioequivalence Test

영문 생물학적동등성시험 기준

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머 리 말

2000년 7월 의약분업이 실시된 이래로 국내에서 생물학적동등성 시험이 활성화되고, 2001년 8월 약사법 개정에 따라 생물학적동등성이 인정된 품목에 한하여 대체조제가 가능하게 됨으로써 최근 생물학적동등성시험의 중요성이 한층 더 부각되고 있습니다.

의약분업 이래 국내의 생물학적동등성시험기준은 미국과 일본 등의 규정을 참고한 개정을 통하여 과학화를 거듭하여 왔으며, 현행 생물학적동등성시험기준은 국제적으로 통용되기에 손색이 없는 합리적인 규정으로 생각됩니다.

따라서, 생물학적동등성시험의 활성화가 의약분업의 성공여부를 가름한다고 해도 과언이 아닌 이 시기에 국립독성연구원에서 국내 생물학적동등성시험기준 영문판을 발간하는 것은 매우 의미있는 일이라 하겠습니다.

영문판 생물학적동등성시험기준의 활용으로 국내 생물학적동등성 시험 결과를 국제적으로도 인정받고 신뢰성을 확보하며, 국내의 기술력을 외국에 수출하여 국익에 기여하는 계기가 되기를 바랍니다.

끝으로 국내외 학계 및 연구소·제약업계의 생물학적동등성시험 관계자들께서 영문판 생물학적동등성시험 기준을 적극 활용하시기 바라며, 끊임없는 관심과 협조를 해 주실 것을 부탁드립니다.

2005년 12월 일

국립독성연구원장

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Korea Food & Drug Administration Notification # 2005-31

"Minimum Requirements for Bioequivalence Test (Korea Food & Drug Administration Notification #2002-60, November 22, 2002)" regulated in Article 23-2, Article 26 Clause 1 and 6, Article 34 Clause 1 of "Pharmaceutical Affairs Law", Article 23 Clause 1-1, Article 23-2, Article 24 Clause 2, Article 83 of the "Enforcement Regulations" of the same law and Article 57 of "Regulation of the Narcotics Control Law" has been amended, thus is notified as follows.

June 7, 2005

Commissioner
Korea Food & Drug Administration

Minimum Requirements for Bioequivalence Test

Chapter 1 General Provisions

Article 1 (Purpose) These minimum requirements are intended to assist appropriate performance of bioequivalence test for drugs by providing the procedures and methods of study, in accordance with Article 23-2, Article 26 Clause 1 and 6, Article 34 Clause 1 of "Pharmaceutical Affairs Law", Article 23 Clause 1-1, Article 23-2, Article 24 Clause 2, Article

83 of the "Enforcement Regulations" of the same law and Article 57 of "Regulation of the Narcotics Control Law".

Article 2 (Definitions of Terms) The following definitions of terms apply to this notification.

1. “Bioequivalence test" means an in vivo study to verify the statistical equivalence in bioavailability between two drug products with the same active ingredient and route of administration that are absorbed into the systemic circulation and become avaliable at the site of action.
2. “Bioavailability” means the rate and extent to which active ingredient or active metabolite is absorbed from a drug product into bloodstream.
3. “Drug product” means a final dosage form such as tablet, capsule, or suppository containing an active ingredient.
4. “Reference drug product” means a reference for test drug product. Reference drug product is an approved drug product which safety and efficacy were established, or is recognized as a reference drug product by KFDA.
5. “Test drug product” means a drug product being tested and should meet the criteria in Article 17 Clause 2. The active ingredient and administration route of test drug product are the same as that of reference drug product.
6. “Study subject” means an individual (hereinafter referred

to 'subject') or an animal who (that) participates in bioequivalence test, either as a recipient of a test drug product or a reference drug product.

7. “Test institution” means a facility unit including people, building, equipments where bioequivalence test is conducted, and should meet the criteria in this notification.
8. “Medical institution” means medical facility regulated in Article 3 of the "Medical Services Law" where medical checkup, administration, blood sampling, an adequate countermeasure against adverse event are conducted.
9. “Sponsor” means a pharmaceutical manufacturer·importer or an individual that requests bioequivalence test to test institution.
10. “Principal investigator” means an expert who is qualified by education, training, and experience to conduct the bioequivalence test, and is designated by director of test institution.
11. “Protocol” means a document that describes the objectives, design, and methodology of bioequivalence test.
12. “Inspection” means an action of conducting an official review on all facilities, documents and records of test institution, sponsor and medical institution according

to "Checklist" in Attachment 1, in order to check the compliance of study with this Notification.

13. “Drug substance with a narrow therapeutic dose range" means listed ingredients in Attachment 2.

Article 3 (Criteria for Waivers of Bioequivalence test) ① In principle, bioequivalence test can be waived for following categories.

1. An oral solution such as syrups, elixirs, tinctures (except emulsion and suspension) and topical solutions that contain an active ingredient in the same concentration and dosage form as a drug product that is the subject of an approved drug product, and that do not contain any excipient that affects drug absorption

1-2. Injections, ophthalmic solutions, and otic solutions that contain the same active and inactive ingredients in the same concentration as a drug product that is the subject of an approved drug product. It should be assured that following excipients do not affect the action of active ingredient

A. Injections : preservative, buffering agent, antioxidant

B. Ophthalmic solutions and otic solutions : preservative, buffering agent, isotonizing agent, viscosity adjustive

2. Topical drug product with non-systemic effect

3. Inhalation product as gas or vapor with local effect
4. Fluids, blood volume expanders, and artificial perfusion agents
5. Digestive enzyme preparation
6. Blood product
7. Herbal medicinal product
8. Vaccine
9. Lactobacillus preparation

② When the oral solid drug product is in the same dosage form and active ingredient, but in a different strength from the strength which bioequivalence test has been conducted, an in vivo bioequivalence demonstration of lower strengths can be waived based on dissolution tests according to the criteria in Attachment 3. For a higher strength in vivo bioequivalence test can be waived in case that is demonstrated linear elimination kinetics over the therapeutic dose range and established the clinical safety of the product based on characteristics of active ingredient.

③ If oral tablets or capsules are considered to meet the criteria in Attachment 4, in vivo bioequivalence test can be waived except for drug with narrow therapeutic range, specified dosage forms such as modified-release formulation, and dosage forms absorbed in buccal cavity such as sublingual and buccal products.

④ Commissioner of Korea Food and Drug Administration can notify the active ingredients with high solubility or high permeability according to criteria in Attachment 4.

Chapter 2. Study Request and Protocol

Article 4 (Study Request) ① Anyone intending to request a bioequivalence test can request a bioequivalence test to the test institution that meets the criteria in Article 6.

② According to Article 4 ①, anyone intending to request bioequivalence test should make a document contract for protocol and study-related responsibilities and duties provided in Article 5 with the test institution.

Article 5 (Protocol) ① The principal investigator should prepare the protocol including following items through discussion with sponsor, and should get approval from IRB provided in Article 7.

1. Title and purpose of study
2. Name and amount of active ingredients, brand name, dosage form, strength and dosage regimen of the test drug product and reference drug product
3. Name, address and affiliation of sponsor
4. Name and address of test institution, and director

name of test institution

5. Initiation date and expected completion date of study
6. Name, affiliation, title, curriculum vitae and publications of principal investigator and investigator
7. Manufacturing and management of test drug product
8. Method of comparative dissolution test. However, for test drug product that is considered to be equivalent to reference drug product based on comparative dissolution results according to "Regulation for Management of Therapeutic Equivalence Test (KFDA Notification)", and that has never been changed in ingredients and amount, manufacturer and manufacturing process after comparative dissolution test, the submission of dissolution test method can be waived.
9. In case that requires the pilot bioequivalence test, general information such as subject number, administration dose, sample for analysis (blood, urine etc), target for analysis (parent compound, metabolites), analytical method and subject selection (in case of completed pilot study, the pilot study report including the certificate of medical checkup of subject, informed consent form)
10. Selection method of subject : subject inclusion criteria and exclusion criteria, advertisement for subject

recruitment, bioequivalence test-related information given to subject, informed consent form

11. Subject number and subject population
12. Medical checkup items (including clinical laboratory examination) selected by the medical doctor according to characteristics of drug
13. Dosing schedule including washout period
14. Agreement of subject compensation
15. Expected adverse events and precautions, and countermeasure against adverse events
16. Management of subject
17. Study method and dosing schedule : dose(s), the administration route, dosing method, dosing schedule(s), method of sampling (blood, etc.), sample amount, time points and interval of sampling (justification), storage condition of sample
18. In case of blood sample, the protection method from infection
19. Sample treatment and analytical methods
20. Analytical instruments, equipments, expandable supplies, and list of laboratory reagents
21. Statistical method, assessment parameters and criterion for judging
22. Quality assurance of study

23. Documents relative to composition and meeting minutes of IRB
24. Signatures of principal investigator, director, sponsor and investigator
25. Signed agreement between the test institution and the sponsor
26. Format for receipts and disbursements of drug products for bioequivalence test

② The principal investigator can amend the protocol through IRB review. However, when the principal investigator changes the items relevant to subject safeguard such as compensation, he/she should get the approval on protocol amendment from KFDA.

Chapter 3. Test Institution and Principal Investigator etc

Article 6 (Test Institution) ① The bioequivalence test institution should be equipped with facilities and equipments for study, and should have a person who can conduct bioequivalence test (except manufacturing company and its research institute). The manufacturing company and its research institute can participate only in analysis of blood sample, but medical checkup, administration, blood sampling, medical care of subject against adverse events

should be conducted at medical institution. The medical doctor who is in charge of above tasks should be an investigator provided in Article 8 ② and should comply with Article 8 ②. However, Article 6 ① is not applicable to the animal study.

② The principal investigator should accommodate subjects in appropriate place from 12 hours before administration to completion of blood sampling or 24 hours after administration. The process of administration and blood sampling should be performed at the medical institution.

③ The clinical laboratory examination in medical checkup should be performed at clinical laboratory that is member of "The Korean association of quality assurance of clinical laboratory" and is inspected regularly for quality assurance.

④ KFDA should inspect the facility of test institution that performs bioequivalence test for the first time, if requested from the director of test institution.

Article 7 (Institutional Review Board) ① A director of test institution should compose an institutional review board in the test institution, to serve the responsibilities provided in Article 7 ③. If the institutional review board already has been composed in accordance with "Minimum Requirements for Korea Good Clinical

Practice" inside the test institution, the director can use this institutional review board.

② The institutional review board should consist of at least 5 members, who have the qualifications and experience to review and evaluate the bioequivalence test. The institutional review board should include at least one member whose primary area of interest is in a non-scientific area such as a person from a bar association, a religious organization or an association of consumers, and at least one member who is independent of the test institution. A principal investigator or an investigator can not be a member of the institutional review board.

③ The responsibilities of institutional review board are as follow

1. Review the justification for selection of the principal investigator and investigator
2. Review and approve the protocol
3. Approve the significant amendments of protocol
4. Review the rights of subjects such as the safety and payments
5. Review the procedure related to subject selection and informed consent
6. Check the ongoing study and provide opinion on

matters relative to study

7. Review and evaluate the final report and raw data

④ Institutional review board should document and retain all records relevant to performance of duties provided in Article 7 ③. Institutional review board should transfer the records and documents to the principal investigator when institutional review board is informed the completion of study (including premature termination) from the principal investigator.

⑤ Other matters relevant to operation of institutional review board should follow "Minimum Requirements for Korea Good Clinical Practice".

Article 8 (Principal Investigator and Investigator) ① A director of test institution should designate a person as a principal investigator. The principal investigator should be qualified by education, training, and experience to conduct the bioequivalence test, and should provide evidence of such qualifications through curriculum vitae and other relevant documentation.

② The investigator group should include at least one pharmacist, a medical doctor and an investigator responsible for analysis of drug concentration in blood. The medical doctor who is in charge of medical checkup

on subjects in medical institution should be included as an investigator according to Article 6 ①. However, Article 8 ② is not applicable to animal study.

③ The responsibilities of principal investigator and compliance-relevant matters are as follow

1. Responsibilities

A. Manage the matters relative to operation of study such as the first aid, blood sampling and medical checkup

B. Prepare and amend the protocol

C. Designate the investigator. Guide and supervise the investigator. Assign the task

D. Prepare analytical instruments, equipments, expandable supplies, and laboratory reagents

E. Obtain and review clinical and non-clinical information

F. Observe and record any adverse events from subjects, or supervise the observation and recording of adverse events.

G. Supervise the administration and the care of subjects

H. Record the raw data and retain the documents of institutional review board

I. Storage and management of drug products for bioequivalence test

J. Prepare the final study report

2. Matters which principal investigator should comply with

A. The principal investigator should conduct bioequivalence test in compliance with the protocol.

B. The principal investigator should be aware of expected side effects of drug products and precautions described in protocol, and should consider a countermeasure against adverse events. The principal investigator should provide prompt and adequate medical care to a subject, and should report to the sponsor and the director of test institution with written document through institutional review board, in case of serious adverse events such as followings,

(1) In case of outbreak of death or life-threatening condition during test

(2) In condition that requires treatment in the hospital

(3) In case that causes permanent or significant handicap, dysfunction

C. If the principal investigator prepares or amends the protocol, he/she should provide its copies to institutional review board and to sponsor.

D. The principal investigator should closely communicate with sponsor and institutional review board, and should smoothly conduct the study. Upon completion of the study, the principal investigator prepares the final

report provided in Article 20 and should submit it to sponsor after review of institutional review board.

④ The principal investigator should designate a person who is qualified by training and experience for conducting the bioequivalence test as an investigator. The designated investigator should be under the supervision of principal investigator. The doctor should be in charge of medical care such as medical checkup, administration, and blood sampling. The pharmacist should be in charge of receipt, custody, inventory and return of drug products.

Chapter 4. Selection and Safeguard of Study Subject

Article 9 (Selection of Study Subject) ① In principle, study subject should be a healthy adult volunteer. However in case that meets the following criteria and is approved by KFDA, a patient or an alternative animal can be study subject. In this case, the rationale and the scientific evidence for selection of the patient or the animal should be provided.

1. In case that it may be more reasonable to admit patients into bioequivalence test
2. In case that there is proper animal model and a definite correlation between animal result and human result

3. In case that there are concerns for subject in ethical aspect or in safety aspect such as oncology product

Article 10 (Selection of Subject) ① Among subjects recruited through advertisement of bioequivalence test, the subject should be a healthy adult who meets the following criteria. Taking into account the purpose of study, age and condition of health, the medical doctor should select subjects.

1. 19 years ~ 55 years at the time of medical checkup
2. A person who is free from inherent or chronic disease, and also illness symptoms from internal examination (if necessary, electroencephalogram, electrocardiogram, endoscopy and autoradiography)
3. A person who is selected by the medical doctor, taking into account results from clinical laboratory tests such as hematology, blood chemistry, urinalysis
4. In case of a woman, a woman who is not pregnant at medical checkup

② Only the certificate of medical checkup issued within 1 month before study initiation is valid for bioequivalence test. The opinion document from medical doctor with test title and sponsor name that the selected subject meets the criteria in Article 10 ① should be provided.

③ A subject who has been previously involved in another bioequivalence test or clinical trial should provide previous records within 3 months before test initiation. In this case, the medical doctor should judge suitability for subject.

Article 11 (Subject Exclusion Criteria) A person who meets the following criteria should be excluded.

1. A person who has taken the metabolic enzyme inducer or inhibitor such as barbiturates within 1 month prior to study initiation, or who drinks to excess
2. A person who has taken medicines that can influence bioequivalence test within 10 days prior to study initiation
3. A person who is judged to be incongruent by the medical doctor

Article 12 (Subject Management) The subject should be restricted of exercise, meal, smoking, xanthine drinks, and alcohol from 12 hours before study initiation to completion of blood sampling.

Article 13 (Subject Number) The total number of subjects in the test should provide adequate power for bioequivalence

demonstration. The subject number can be determined based on the drug characteristics.

Article 14 (Informed Consent of Subject) ① The principal investigator should fully explain this study to subject and receive the informed consent form voluntarily from the subject, according to "Minimum Requirements for Korea Good Clinical Practice" Article 17.

② In case of a patient, the principal investigator should obtain approval from subject's primary physician.

Article 15 (Subject Compensation) In order to safeguard the right of subject, the sponsor should provide proper compensation to subject. It is recommended to provide the insurance for subject.

Chapter 5. Study Method and Operation

Article 16 (Study Method) In principle, in vivo study is recommended for bioequivalence test that estimates the bioavailability on the basis of blood concentration of active ingredient or active metabolites. The recommended study design for bioequivalence is a single dose study under fasting condition in the same day, two-treatment,

two-period (2×2) crossover with adequate washout period according to Article 18-②-4. In case of bioequivalence test using excreted amount in urine or other study designs, the rationale of the study design should be provided.

Article 17 (Reference Drug Product and Test Drug Product) ① Reference drug product should meet the criteria in Article 2-4.

② Test drug product should be a final dosage form and meet the following criteria. In case that bioequivalence test is waived based on result of comparative dissolution test according to Article 3 ②, the test drug product should meet the following provisions 1 and 4.

1. The test drug product should be manufactured with the same raw materials and formulation in the same condition as that of the final product for marketing. The quality and content of the test drug product should meet its "In house specification and test method"
2. The test drug product should be a drug product that is approved by KFDA according to Article 26 in "Pharmaceutical Affairs Law" or meets criteria in Article 36 of "Minimum Requirements for Korea Good Clinical Practice". The "In house specification and test method" and its result should be submitted.

3. The batch size of the test drug product should be at least 100,000 units. If the commercial batch size of the test drug product is smaller than 100,000 units, the batch size of final product can be acceptable.
4. Test drug product should be that either the total content/potency of the active drug substance according to "In house specification and test method" is within 5% of labeled content (100%) of reference, or the difference in content/potency between test and reference drug product is within 5%.

Article 18 (Study Conduct) ① The batches of test and reference drug product for comparative dissolution test should be the same production batches for bioequivalence test. The dissolution test method can be selected according to characteristics of drug products. If the test drug product meets criteria in Article 5-①-8, the comparative dissolution test can be waived.

② Bioequivalence test

1. Dose

A. In principle, the single-dose study with clinical dosage is recommended. If the measurement of drug concentration is difficult in single-dose study because of high detection limit of analytical method,

then multiple-dose can be acceptable within the range of maximum daily dose.

B. In the following cases, multiple-dose, steady-state study may be performed.

(1) In case that there is a difference in the rate of absorption, but no difference in extent of absorption

(2) In case that there is a significant difference in individual bioavailability

(3) In case of the modified-release formulation

2. Administration method

A. Single-dose

(1) The subject should be in the fasting state at least 10 hours before drug administration and should continue to fast for up to 4 hours after dosing. The drug can be administered after meal under condition of scientific reasons or certain purposes. In this case, all subject should be provided the same meal if possible, and the drug should be administered 30 minutes after the meal.

(2) The test or reference drug product should be administered with 240 mL of water.

B. In the multiple-dose study, the first dose is given to the subject under fasting condition. The subsequent

administration should be carried out between meals at the same interval to demonstrate attainment of steady state.

3. Blood or urine sampling should be performed at appropriate intervals to obtain an adequate description of the drug concentration-time profile and to estimate the parameters for bioavailability assessment. The sampling should be performed at the same interval and time between test and reference drug product. In case of drug products with particular absorption pattern such as fast acting product or modified-release product, the exact timing and interval for sample collection should be determined on the scientific basis such as pharmacokinetic profile of reference drug product.

A. Blood sampling

(1) Blood sampling should continue for three or more terminal half lives of the drug, or until AUCt reaches at least to the 80% of AUC_{∞}.

(2) In principle, 12 samples should be collected per subject per drug. At least two quantifiable samples should be collected before the expected peak time. Total number of samples can be determined based on the Tmax and the period of sampling.

(3) For multiple-dose study, sufficient numbers of blood sample should be collected to assess the $C_{ss,max}$ and $C_{ss,min}$.

B. Urine sampling

(1) Urine sampling follows blood sampling.

(2) For urine collection, it is recommended that subjects entirely empty their bladders. When blood sampling and urine sampling are performed simultaneously, the timing for blood collection occurs in the middle of urine sampling.

(3) When cumulative excreted amount in urine-time profiles at steady-state between test and reference are compared in multiple-dose study, sufficient numbers of urine sample should be collected to estimate the amount of drug excreted and excretion rate in urine.

4. A washout period should be determined based on the sufficient time to eliminate pre-administered drug from body. The washout period should be more than at least 5 half lives of active ingredient after administration.

5. Analytical Objects and Methods

A. The objects for analysis are an active ingredient or

its active metabolite(s) in blood or urine sample that are considered to be in proportion to parent drug. For combination drug products, in principle all active ingredients are measured.

B. The analytical method should demonstrate specificity, lineality, accuracy, precision, and sufficient sensitivity to measure the actual concentration of the active ingredient and metabolite(s).

Chapter 6. Evaluation and Report, etc.

Article 19 (Evaluation) ① In case of blood sample, the comparative parameters for evaluation include AUC_t and Cmax for single-dose study, and AUCτ and Css,max for multiple-dose study. The supplementary parameters for evaluation include Tmax and comparative dissolution profile. For rapid acting products such as nitroglycerine sublingual formulation, Tmax can be included in comparative evaluation parameters. In this case, Cmax and Tmax are actual measured values and AUC is calculated using trapezoidal rule based on blood concentration. In case of urine sample, the comparative parameters for evaluation include Aet, Aeτ, Umax, instead of AUC_t, AUCτ, Cmax.

Glossary)

AUC : Area under the plasma concentration-time curve

AUC_t : Area under the plasma concentration-time curve from time zero to last measurable plasma drug concentration at time t

AUC_∞ : Area under the plasma concentration-time curve from time zero to time infinite ($AUC_\infty = AUC_t + C_t/\lambda_Z$)

C_t : Plasma drug concentration at time t

λ_Z : Terminal elimination rate constant

AUC_t/AUC_∞ : Ratio AUCt to AUC_∞

$t_{1/2\beta}$: Terminal half life

$AUC\tau$: Area under the plasma concentration-time curve during dosing interval τ at steady state

Cmax : Maximum concentration of drug in the blood

$C_{ss,max}$: Maximum concentration of drug in the blood at steady state

$C_{ss,min}$: Minimum concentration of drug in the blood at steady state

Tmax : Time of occurrence for maximum drug concentration

Umax : Maximum rate of drug excretion in urine

Aet : Cumulative amount of drug excreted in urine from time zero to last collection time t

$Ae\tau$: Cumulative amount of drug excreted in urine during dosing interval τ at steady state

② When log transformation and statistical evaluation on comparative parameters except Tmax are performed, the 90% confidence intervals for the difference in mean values between the test and reference should be within log 0.8~log 1.25. The case that meets the following conditions is considered to be equivalent.

1. The case that the difference in log-transformed mean values of comparative parameters between test and reference drug product is within log 0.9~log 1.11
2. The case that dissolution between test and reference drug product is equivalent under all test conditions, according to "Regulation for Management of Therapeutic Equivalence Test (KFDA Notification)". However, this provision is not applicable to solid oral dosage form (except modified-release form) and enteric coated form, unless the average dissolution from reference drug product reaches 85% within specified time. For modified-release form, this corresponds to the case that the average dissolution from test drug product reaches within ±10% of average dissolution from reference drug product at the point which the reference drug product dissolves around 30%, 50%, 80%.
3. The case that total subject numbers are more than 20 (10 per group)

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

Article 20 (Final study report) The principal investigator should submit the final study report including the following items to KFDA after completion of study in accordance with approved protocol.

1. Title, purpose of study and summary of result
2. Ingredients and brand name of reference and test drugs, dosage form and manufacturing date, batch number, result of quality control test
3. Manufacturer and manufacturing site of active ingredient of test drug product (in case of subdivision and repacking, manufacturing site of bulk material, and subdivision and repacking site), batch number, certificate of analysis. Import licence, etc in the case of imported raw material
4. Manufacturing process of test drug product in detail (manufacturing date, amount of raw materials, standard amount, etc)
5. Name, address and affiliation of sponsor
6. Name and address of test institution. Name of director of test institution
7. Name, affiliation, title of principal investigator and

investigator

8. Period of study
9. Result of comparative dissolution test (in case that meets criteria in Article 5-①-8, submission of the result is waived)
10. Result of pilot study (including records relevant to subject management such as the certificate of medical checkup, informed consent form, in case of human subject)
11. Selection method of subject : subject inclusion criteria and exclusion criteria, advertisement for subject recruitment, bioequivalence test-related information given to subject, informed consent form
12. Certificate of medical checkup issued by medical institution (including clinical laboratory examination data and opinion of medical doctor)
13. Dropouts of subject and reason
14. Case report form (including blood sampling schedule)

14-2. Subject management records : from 12 hours before study initiation to completion of blood sampling

15. Study design : dose(s), administration route, administration method, administration date, sampling method, sample amount, sample numbers and sampling schedule, the storage condition of sample,

washout period

16. In case of blood sampling, the protection method from infection
17. Sample treatment and analytical methods (validation data : specificity, lineality, accuracy, precision, and sensitivity, etc)
18. Study result : blood concentration-time data per subjects (with diskette) and log-transformed values, pharmacokinetic parameters such as AUC_t ($AUC\tau$), Cmax ($C_{ss,max}$), Tmax, AUC_∞, AUC_t/AUC_∞, $t_{1/2\beta}$, analysis data, statistical process and evaluation (including raw data)
19. Assessment criteria and principal investigator's opinion on result
20. In case of animal study, species, strain, number, age, sex, body weight, supplier, purchase date and condition for breed
21. Records of institutional review board
22. Receipt and disbursement of drug products for bioequivalence test
23. Signatures of principal investigator, director, sponsor and investigator
24. The bioequivalence test protocol approved by institutional review board

Article 21 (Inspection) The commissioner of KFDA can direct KFDA's official and experts designated by commissioner to inspect matters relevant to bioequivalence test for confirmation on reliance of study result, if necessary.

Article 22 (Custody of Archives and Samples) The sponsor and principal investigator should retain the documents relevant to study such as protocol and final study report for 5 years after approval.

Article 23 (Noncompliance) ① If the principal investigator's noncompliance with this notification is found during study, the sponsor corrects a mistake and takes proper action to prevent from recurrence. If the significant and continuous noncompliance is found, the sponsor should stop the study and report to KFDA.

Chapter 7. Supplementary Provisions

Article 24 (Others) ① Any matters not provided in this notification comply with "Minimum Requirements for Korea Good Clinical Practice".

② If the final report of bioequivalence test is submitted

to KFDA for approval of drug product (including postapproval changes), the study report should be signed by the director of test institution provided in Article 6.

Additional Provisions

① (Date of enforcement) This Notification shall enter into force from the date of notification.

② (Temporary Measures) In case of any bioequivalence test protocol that is approved by KFDA or submitted for review to KFDA before the date of enforcement of this notification, the former notification shall be applicable thereto.

Attachment

[Attachment 1]

Checklist for Inspection of Bioequivalence Test

Test Institution and Its Director	
Medical Institution and Its Director	
Sponsor and Its Representative	
Test Drug Product	
Reference Drug Product	
Remarks	

Ⅰ. Test Institution

No.	Checklist	○/×	Remarks
Ⅰ-1	**Qualification of Test Institution**		
Ⅰ-1-1	Is the test institution qualified for bioequivalence test? ○ Medical facilities (a medical practitioner's office or hospital) ○ National institution of health research ○ Institute under medical college or college of pharmacy ○ Institute of health research supported by government ○ Other		
Ⅰ-2	**Compliance with Protocol**		
Ⅰ-2-1	Is administration or manufacturing (import) of test drug product performed after approval(including approval on amendment) of protocol?		
Ⅰ-2-2	Is cross over and washout period processed in accordance with protocol?		
Ⅰ-3	**Selection and Management of Subject**		
Ⅰ-3-1	Does the principal investigator explain information of test fully to subjects and obtain informed consent form from subjects voluntarily?		
Ⅰ-3-2	Does the principal investigator comply with compensation agreement?		

No.	Checklist	○/×	Remarks
I -3-3	Does the principal investigator have countermeasures against expected side effects and precautions, and comply with them?		
I -3-4	Does the principal investigator accommodate subjects in appropriate place from 12 hours before administration?		
I -3-5	Are management and education for subjects properly conducted during blood sampling?		
I -3-6	Is administration to subjects performed according to protocol?		
I -3-7	Are subjects in the fasting state at least from 10 hours before drug administration to 4 hours after dosing according to approved protocol?		
I -3-8	Are subjects controlled properly up to completion of blood sampling?		
I -4	**Management of Drug Product**		
I -4-1	Does the pharmacist properly store and manage the drug products used in test?		
I -4-2	Does the pharmacist perform receipt and disbursement of drug products used in test, and maintain its records?		
I -4-3	Are drug products stored under proper storage condition, and in separate place according to regulation?		

No.	Checklist	○/×	Remarks
Ⅰ-5	**Sample Analysis**		
Ⅰ-5-1	Does the institute for analysis prepare instruments, reagents and equipments for test?		
Ⅰ-5-2	Are samples for analysis stored properly?		
Ⅰ-5-3	Is validation on analytical method performed? Are validation data maintained?		
Ⅰ-6	**Institutional Review Board**		
Ⅰ-6-1	Is IRB composed in accordance with regulation?		
Ⅰ-6-2	Are the review, records and retainment of IRB reasonable?		
Ⅰ-7	**Retainment and Management of Data**		
Ⅰ-7-1	Are documents relative to bioequivalence test (including IRB records) retained and maintained properly?		

Conformer	Signature

Ⅱ. Medical Institution

No.	Checklist	○/×	Remarks
Ⅱ-1	**Qualification of Medical Institution**		
Ⅱ-1-1	Are medical checkup and medical care conducted at proper medical institution?		
Ⅱ-1-2	Is clinical laboratory a member of "The Korean association of quality assurance of clinical laboratory" and inspected regularly for quality assessment for recent 2 years?		
Ⅱ-1-3	Does clinical laboratory prepare 'Standard Operating Procedure' describing the each step of examination?		
Ⅱ-2	**Management of Subject**		
Ⅱ-2-1	Are drug products administered to subjects according to dosage regimen under supervision of medical doctor?		
Ⅱ-2-2	Is blood sampling performed properly according to protocol?		
Ⅱ-2-3	Is adequate medical care to subject such as prevention from adverse reaction and treatment provided after blood sampling?		
Ⅱ-3	**Medical Checkup for Subject**		
Ⅱ-3-1	Are the internal examination and the clinical chemistry for selected subjects performed properly?		

No.	Checklist	○/×	Remarks
Ⅱ-4 Ⅱ-4-1	**Retainment and Management of Data** Are documents relative to bioequivalence test retained and maintained properly?		

Conformer	Signature

Ⅲ. Sponsor

No.	Checklist	○/×	Remarks
Ⅲ-1	**Manufacturing and Control of Test Drug Product**		
Ⅲ-1-1	Do initiation and completion of test correspond to the final report of bioequivalence test?		
Ⅲ-1-2	Are documents relative to manufacturer, manufacturing site, supplier, batch number of raw material, and in case of imported raw material, source, specification and import licence retained?		
Ⅲ-1-3	Are manufacturing and quality control of test drug product conducted properly?		
Ⅲ-1-4	Is quality control of reference drug product conducted properly?		
Ⅲ-2	**Retainment and Management of Data**		
Ⅲ-2-1	Is agreement document between test institution and sponsor retained?		
Ⅲ-2-2	Are records relative to receipt and disbursement of test and reference drug products retained?		
Ⅲ-2-3	Are documents relative to bioequivalence test retained and maintained properly?		

Conformer	Signature

※ Review Opinion

Judgement	Accept		Nonacceptance	
Comment or Reasons in case of Nonacceptance				

[Attachment 2]

Narrow Therapeutic Range Drugs

(Related to Articles 2-13)

Number	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, Glyclopyramide, Tolazamide, Tolbutamide

2) Aminophylline, Oxtriphylline = Choline theophylline, Diprophylline = Dyphylline, Proxyphylline, Theophylline

[Attachment 3]

Minimum Requirements for Comparative Dissolution Test for Level of Formulation Change of Different Strengths of Solid Oral Dosage Forms

(Related to Articles 3-2)

1. Level of formulation changes

When the test drug product is in the same dosage form, active ingredient and ratio of composition as reference drug product but in different strengths from reference, the formulation change is level A. If the ratio of composition is not the same between test and reference drug product, the level of changes in formulation should be determined according to Table 1 and Table 2. If the change is equal to or less than the range of level B, it is B. If the change is more than the ranges of level B and equal to or less than the ranges of level C, it is level C. Similarly, the change in excipients in the range between C and D is level D. All cases of change exceeding the level D are level E. Any change in coloring or flavoring agents is level A. Among the changes, the highest level of change is defined as the level of formulation change.

Table 1. Level of change in excipients for uncoated product

Excipient category and component	Percent excipient (w/w) compared to total dosage form weight (%)		
	B	C	D
Disintegrant Starch Other	3.0 1.0	6.0 2.0	9.0 3.0
Binder	0.50	1.0	1.5
Lubricant·Polisher Stearate and its salt Other	0.25 1.0	0.50 2.0	0.75 3.0
Glidant	5.0	10	15
Other (except coloring and flavoring agents)	1.0	2.0	3.0
The total additive effect of all excipient changes	5.0	10	15

Table 2. Level of change in excipients for coated product

Core /coated layer	Excipient category and component	Percent excipient (w/w) compared to total dosage form weight (%)		
		B	C	D
Core	Disintegrant			
	Starch	3.0	6.0	9.0
	Other	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
	Other	1.0	2.0	3.0
	Glidant	5.0	10	15
	Other (except coloring and flavoring agents)	1.0	2.0	3.0
	The total additive effect of all excipient changes in core	5.0	10	15
Film-coated layer[1)]	The total additive effect of all excipient changes in film-coated layer	5.0	10	15
Sugar-coated layer	The total additive effect of all excipient changes in sugar-coated layer	5.0	10	15

1) All film-coated layer including water-proofing, undercoating, enteric coating and controlled release, except sugar-coated layer

2. Comparative dissolution test according to level of change in formulation

The types of therapeutic equivalence test according to level of change in formulation are described in Table 3.

Table 3. Comparative dissolution test according to level of change in formulation

level	Immediate release product/ Enteric coated product/ Controlled-release product	Therapeutic range of active ingredient[1)]	Solubility[2)]	Dissolution profile[3)]	Dissolution test/ Bioequivalence test[4)]
A					Dissolution test
B					Dissolution test
C	Immediate release/ Enteric coated product	Wide	High solubility		Dissolution test
			Low solubility		Bioequivalence test
		Narrow	High solubility	≧85%/30min	Dissolution test
				<85%/30min	Bioequivalence test
			Low solubility		Bioequivalence test
	Controlled release product	Wide			Dissolution test
		Narrow			Bioequivalence test
D	Immediate release product	Wide	High solubility	≧85%/30min	Dissolution test
				<85%/30min	Bioequivalence test
			Low solubility		Bioequivalence test
		Narrow			Bioequivalence test
	Enteric coated product/ Controlled release product				Bioequivalence test
E					Bioequivalence test

1) The ingredients in Attachment 2 are in narrow therapeutic range group. The other ingredients are considered to be in wide therapeutic range.
2) If less than 85% of drug from drug product is dissolved up to 6 hours under conditions specified in Article 8 Table 1.1-(4) of "Regulation for Management of Therapeutic Equivalence Test (KFDA Notification)", the reference drug product is considered as a low solubility drug. The other cases are high solubility drug.
3) If more than 85% of drug from drug product is dissolved within 30 minutes under all conditions specified in Article 8 of "Regulation for Management of Therapeutic Equivalence Test (KFDA Notification)", this is expressed as "≧85%/30min". The other cases are expressed as " ‹85%/30min"
4) The comparative dissolution test should be performed in accordance with Article 8 of "Regulation for Management of Therapeutic Equivalence Test (KFDA Notification)", and its result is evaluated according to Article 10-3 of the same regulation. If comparative dissolution profile fails to demonstrate the equivalence, bioequivalence test should be conducted.

[Attachment 4]

Waivers of in vivo bioequivalence test for solid oral tablet or capsule

(Relative to Articles 3-3)

1. Definitions of terms

The following definitions of terms apply to this notification.

A. "Biopharmaceutics Classification System (BCS)" is a scientific framework for classifying drug substances based on their aqueous solubility and intestinal permeability.

B. "Solubility test" is a test described in Attachment 4-1 for classifying the solubility of drug substances according to BCS,

C. "Permeability test" is a test described in Attachment 4-2 for classifying the permeability of drug substances according to BCS. This test directly or indirectly measures the rate or extent of absorption of a drug substance across human intestinal membrane using human/animal system or cell line.

D. "Dissolution test" is a test described in Attachment

4-3 for measuring the dissolved amount of drug substance from solid oral dosage form.

2. Biopharmaceutics Classification System

The drug substances are classified as the follows based on their solubility and permeability. The BCS approach can be used to justify biowaivers.

A. Class 1 : High Solubility - High Permeability

B. Class 2 : Low Solubility - High Permeability

C. Class 3 : High Solubility - Low Permeability

D. Class 4 : Low Solubility - Low Permeability

3. Biowaivers

A. General matters

As the oral tablet or capsule containing Class 1 drug substances according to BCS, both test and reference drug product should dissolve rapidly and the inactive ingredients used in the dosage form must not significantly affect absorption of the active ingredient.

B. Solubility

It should be demonstrated through "Solubility test" in Attachment 4-1 that the highest dose strength of solid oral dosage form is soluble in 250 mL or less of aqueous media over the pH range of 1~7.5.

C. Permeability

In human or nonhuman systems capable of predicting the extent of drug absorption in human, the extent of absorption of active ingredient or transfer rate across human intestinal membrane is measured. It should be demonstrated that the extent of absorption in human is determined to be 90% or more of an administered dose through "Permeability test" in Attachment 4-2, in the absence of evidence suggesting instability in the gastrointestinal tract.

D. Dissolution

The result from "Dissolution test" in Attachment 4-3 should meet the following.

(1) Both test and reference drug product dissolve 85% of the labeled amount of the drug substance within 15 minutes, or

(2) Both test and reference drug product dissolve 85% of the labeled amount of the drug substance within 30 minutes and the dissolution profiles between test and reference are similar.

4. Data to support a request for biowaivers

A. Data on origin or discovery and details of development

Data describing characteristics of drug product, details of

development, and summary of submitted documents to demonstrate the biowaiver of subject drug

B. Data on structural determination and physicochemical properties

Data describing composition, amount of active and inactive ingredient, specifications of raw material and manufacturing method (including "In house Specification and Test method)

C. Solubility Data

Data supporting high solubility of the test drug substance should be developed. The following information should be included in the application.

(1) A description of test methods, including information on analytical method and composition of the buffer solutions

(2) Information on chemical structure, molecular weight, nature of the drug substance (acid, base, amphoteric, or neutral), and dissociation constants (pKa)

(3) Test results (mean, standard deviation, and coefficient of variation) summarized in a table under solution pH, drug solubility (e.g., mg/mL), and volume of media required to dissolve the highest dose strength

(4) A graphic representation of mean pH-solubility profile

If the drug substance is considered to have high solubility by KFDA, the above data can be exempted.

D. Permeability data

Data supporting high permeability of the test drug substance in human, animal or cell system should be developed, and should be one of the followings.

(1) Human pharmacokinetic studies

(A) Information on study design and methods

(B) Pharmacokinetic data

(2) Permeability test across intestinal membrane

(A) Information supporting the suitability of a selected method

1) Description of the test method

2) Criteria for selection of human subjects (human, animal or epithelial cell line)

3) Drug concentrations and analytical method in the donor fluid

4) Method used to calculate extent of absorption or permeability

5) Information on efflux potential such as bidirectional transport data (if appropriate)

(B) Information of model drugs

1) Data on extent of absorption in humans (mean, standard deviation, coefficient of variation) used to establish suitability of a method
2) Permeability values for each model drug (mean, standard deviation, coefficient of variation) and permeability class
3) Extent of absorption as a function of permeability (mean ± standard deviation or 95% confidence interval)
4) Data on identification of the low/high permeability class (low/high) and selected internal standard

(C) Results

1) Permeability data on test drug substance and internal standard (mean, standard deviation, coefficient of variation)
2) Stability information in gastrointestinal tract
3) Data supporting passive transport mechanism
4) Methods used to establish high permeability of the test drug substance

If the drug substance is considered to have high permeability by KFDA, the above data can be exempted.

E. Dissolution data

Data supporting rapid dissolution attributes of the test

and reference products should be developed. The following information should be included in the application.

(1) A brief description of the test product used for dissolution testing (batch or lot number, expiry date, strength, weight, dimensions)

(2) Dissolution data

(A) The percentage of labeled claim dissolved at each specified testing interval in each individual dosage unit

(B) The mean percent dissolved, range (highest and lowest) of dissolution, and coefficient of variation (relative standard deviation)

(C) A graphic representation of the mean dissolution profiles for the test and reference products in each media

(3) Data supporting similarity in dissolution profiles between the test and reference products in each media, using the f_2

F. Data on Excipients

When new excipients are included in an immediate-release solid dosage form or atypically large amounts of commonly used excipients (e.g., surfactants such as polysorbate 80, sweeteners such as mannitol,

sorbitol) are included, the information documenting the absence of an impact on bioavailability of the drug should be provided.

G. The prodrug means the drug substance that has no physiological effect itself, but converse to active moiety through enzymatic or non-enzymatic reaction in the body. When the prodrug-to-drug conversion is shown to occur predominantly after intestinal membrane permeation, the permeability of the prodrug should be measured. When this conversion occurs prior to intestinal permeation, the permeability of the drug should be determined. It is recommended that solubility data and dissolution data on both prodrug and active moiety are submitted.

[Attachment 4-1]

Solubility Test

Ⅰ. Selection of test substance

The test substance should be identical to active ingredient of drug product for biowaiver.

Ⅱ. Test method

The equilibrium solubility and pH-solubility profile of the drug substance should be determined using acid·base titration or validated method in aqueous media with physiological pH (pH 1.0 ~ 7.5). The method should be an assay that can distinguish the drug substance from its degradation products. If degradation of the drug substance is observed as buffer composition and/or pH, it should be reported along with stability data in gastrointestinal tract recommended in Attachment 4-2 III.

1. Test condition

A. Amount of drug substance : the highest dose strength of approved immediate-release oral dosage form

B. Buffers : In principle, standard buffer solution described in the Korean Pharmacopoeia. If these buffers

are not suitable for physical or chemical reasons, other buffer solutions can be used.

C. Temperature of buffer : 37 ± 1℃

D. pH of buffer : The number of pH conditions for a solubility determination can be based on the ionization characteristics of the test drug substance. A sufficient number of pH conditions should be evaluated to accurately define the pH-solubility profile.

For example) When the pKa of a drug is in the range of 3~5, solubility should be determined at 1, pKa-1, pKa, pKa+1 and 7.5. The pH should be determined after addition of drug substance to buffer.

E. Number of test : A minimum of three replicate determinations is recommended. Depending on studies, additional replication may be necessary.

[Attachment 4-2]

Permeability Test

Ⅰ. Selection of test substance

The test substance should be identical to active ingredient of drug product for biowaiver.

Ⅱ. Test method

The permeability class of a drug substance can be determined in human subjects using mass balance, absolute bioavailability, or intestinal perfusion approaches. The other methods include in vivo or in situ intestinal perfusion in a suitable animal model (e.g., rats), and/or in vitro permeability methods using excised intestinal tissues, or monolayers of suitable epithelial cells. In many cases, for example, when the absolute bioavailability is 90% or more, or when 90% or more of the administered drug is recovered in urine, a single method may be sufficient. When a single method fails to conclusively demonstrate a permeability classification, two different methods may be advisable.

1. Pharmacokinetic Studies in Humans

A. Mass Balance Studies

Pharmacokinetic mass balance studies using unlabeled, stable isotopes or a radiolabeled drug substance can be used to document the extent of absorption of a drug. Depending on the variability of the studies, a sufficient number of subjects should be enrolled in the study to provide a reliable estimate of the extent of absorption. Because this method can provide highly variable estimates of drug absorption for many drugs, other methods described below may be preferable.

B. Absolute Bioavailability Studies

Oral bioavailability determination using intravenous administration as a reference can be used. Depending on the variability of the studies, a sufficient number of subjects should be enrolled in a study to provide a reliable estimate of the extent of absorption. When the absolute bioavailability of a drug is shown to be 90% or more, additional data to document drug stability in the gastrointestinal fluid is not necessary.

2. Intestinal Permeability Methods

The following methods can be used to determine the permeability of a drug substance from the gastrointestinal tract

A. In vivo intestinal perfusion studies in humans

B. In vivo or in situ intestinal perfusion studies using suitable animal models

C. In vitro permeability studies using excised human or animal intestinal tissues

D. In vitro permeability studies across a monolayer of cultured epithelial cells.

Except in vivo intestinal perfusion studies in humans, other test methods are considered appropriate for passively transported drugs. The observed low permeability of some drug substances in humans could be caused by efflux of drugs via membrane transporters such as P-glycoprotein (P-gp). When the efflux transporters are absent in these models, or their degree of expression is low compared to that in humans, there may be a greater likelihood of misclassification of permeability class for a drug subject to efflux compared to a drug transported passively. Expression of known transporters in selected study systems should be characterized. Functional expression of efflux systems (e.g., P-gp) can be demonstrated with techniques such as bidirectional transport studies, demonstrating a higher rate of transport in the basolateral-to-apical direction as compared to apical-to-basolateral direction using selected model drugs or chemicals at concentrations that do not saturate

the efflux system (e.g., cyclosporin A, vinblastine, rhodamine 123). An acceptance criterion for intestinal efflux that should be present in a test system cannot be set at this time. The nonhuman permeability test methods are recommended only for drug substances that are transported by passive mechanisms. Pharmacokinetic studies on dose linearity or proportionality may provide useful information for evaluating the relevance observed in vitro efflux of a drug. For example, there may be fewer concerns associated with the use of in vitro methods for a drug that has a higher rate of transport in the basolateral-to-apical direction at low drug concentrations but exhibits linear pharmacokinetics in humans.

For application of the BCS, an apparent passive transport mechanism can be assumed when one of the following conditions is satisfied:

A. A linear (pharmacokinetic) relationship between the dose (e.g., relevant clinical dose range) and measures of bioavailability (area under the concentration-time curve) of a drug is demonstrated in humans

B. Lack of dependence of the measured in vivo or in situ permeability is demonstrated in an animal model on initial drug concentration (e.g., 0.01, 0.1, and 1 times the highest dose strength dissolved in 250 mL)

in the perfusion fluid

C. Lack of dependence of the measured in vitro permeability on initial drug concentration (e.g., 0.01, 0.1, and 1 times the highest dose strength dissolved in 250 mL) is demonstrated in donor fluid and transport direction (e.g., no statistically significant difference in the rate of transport between the apical-to-basolateral and basolateral-to-apical direction for the drug concentrations selected) using a suitable in vitro cell culture method that has been shown to express known efflux transporters (e.g., P-gp)

To demonstrate suitability of a permeability method intended for application of the BCS, a rank-order relationship between test permeability values and the extent of drug absorption data in human subjects should be established using a sufficient number of model drugs. For in vivo intestinal perfusion studies in humans, six model drugs are recommended. For in vivo or in situ intestinal perfusion studies in animals and for in vitro cell culture methods, twenty model drugs are recommended. Depending on study variability, a sufficient number of subjects, animals, excised tissue samples, or cell monolayers should be used in the study to provide a reliable estimate of drug permeability. This relationship should allow precise differentiation

between drug substances of low and high intestinal permeability attributes.

For demonstration of suitability of a method, model drugs should represent a range of low (e.g., < 50%), moderate (e.g., 50 − 89%), and high (≥ 90%) absorption. Sponsors may select compounds from the list of drugs and/or chemicals provided in Table 1 or they may choose to select other drugs for which there is information available on mechanism of absorption and reliable estimates of the extent of drug absorption in humans.

After demonstrating suitability of a method and maintaining the same study protocol, it is not necessary to retest all selected model drugs for subsequent studies intended to classify a drug substance. Instead, a low and a high permeability model drug should be used as internal standards (i.e., included in the perfusion fluid or donor fluid along with the test drug substance). These two internal standards are in addition to the fluid volume marker (or a zero permeability compound such as PEG 4000) that is included in certain types of perfusion techniques (e.g., closed loop techniques). The choice of internal standards should be based on compatibility with the test drug substance (i.e., they should not exhibit any significant physical, chemical, or permeation interactions).

When it is not feasible to follow this protocol, the permeability of internal standards should be determined in the same subjects, animals, tissues, or monolayers, following evaluation of the test drug substance. The permeability values of the two internal standards should not differ significantly between different tests, including those conducted to demonstrate suitability of the method. At the end of an in situ or in vitro test, the amount of drug in the membrane should be determined.

For a given test method with set conditions, selection of a high permeability internal standard with permeability in close proximity to the low/high permeability class boundary may facilitate classification of a test drug substance. For instance, a test drug substance may be determined to be highly permeable when its permeability value is equal to or greater than that of the selected internal standard with high permeability.

3. Instability in the Gastrointestinal Tract

Determining the extent of absorption in humans based on mass balance studies using total radioactivity in urine does not take into consideration the extent of degradation of a drug in the gastrointestinal fluid prior to intestinal membrane permeation. In addition, some

methods for determining permeability could be based on loss or clearance of a drug from fluids perfused into the human and/or animal gastrointestinal tract either in vivo or in situ. Documenting the fact that drug loss from the gastrointestinal tract arises from intestinal membrane permeation, rather than a degradation process, will help establish permeability. Stability in the gastrointestinal tract may be documented using gastric and intestinal fluids obtained from human subjects. Drug solutions in these fluids should be incubated at 37℃ for a period that is representative of in vivo drug contact with these fluids; for example, 1 hour in gastric fluid and 3 hours in intestinal fluid. Drug concentrations should then be determined using a validated stability-indicating assay method. Significant degradation (>5%) of a drug in this protocol could suggest potential instability. Obtaining gastrointestinal fluids from human subjects requires intubation and may be difficult in some cases. Use of gastrointestinal fluids from suitable animal models and/or simulated fluids such as Gastric and Intestinal Fluids Korean Pharmacopoeia or other Pharmacopoeia designated by KFDA can be substituted when properly justified.

Table 1. Model drugs for intestinal permeability test

Model Compound	Permeability Classification
Antipyrine	High (Potential internal standard candidate)
Caffeine	High
Carbamazepine	High
Fluvastatin	High
Ketoprofen	High
Metoprolol	High (Potential internal standard candidate)
Naproxen	High
Propranolol	High
Theophylline	High
Verapamil	High (Potential efflux pump substrate candidate)
Amoxicillin	Low
Atenolol	Low
Furosemide	Low
Hydrochlorthiazide	Low
Mannitol	Low (Potential internal standard candidate)
Methyldopa	Low
Polyethylene glycol 400	Low
Polyethylene glycol 1000	Low
Polyethylene glycol 4000	Low (Zero permeability marker)
Ranitidine	Low

[Attachment 4-3]

Dissolution Test

Ⅰ. Selection of test drug product

Test drug product should be that either the total content/potency of the active drug substance according to "In house specification and test method" is within 5% of labeled content (100%) of reference, or the difference in content/potency between test and reference drug product is within 5%.

Ⅱ. Test method

Dissolution test should be conducted with at least 12 dosage units under the conditions specified, and should be measured using validated analysis method. If dissolution tests in all buffer system are considered to be unnecessary on the basis of characteristics of product, the scientific evidence should be provided.

1. Apparatus : Dissolution test are conducted with Apparatus 1 (100rpm) or Apparatus 2 (50rpm) of dissolution test in 8th Edition of Korean

Pharmacopoeia, according to characteristics of product.

2. Volume of buffer : In principle, 900 mL

3. Temperature of buffer : 37 ± 0.5℃

4. Buffer

A. pH 1.2 solution : "Buffer 1" for "Disintegration test" in 8th Edition of Korean Pharmacopoeia

B. pH 4.0 solution : Acetate buffered solution adjusted pH 4.0 [0.05mol/L acetic acid : 0.05mol/L sodium acetate (41 : 9)]

C. pH 6.8 solution : "Buffer 2" for "Disintegration test" in 8th Edition of Korean Pharmacopoeia

For capsules and tablets with gelatin coating, Simulated Gastric and Intestinal Fluids (its specification should meet Korean Pharmacopoeia or other Pharmacopoeia designated by KFDA) with enzymes can be used.

5. Sampling schedule : 10min, 15min, 20min, 30min

Ⅲ. Assessment of similarity

When comparing the test and reference products, dissolution profiles should be compared using a similarity factor (f_2). The similarity factor is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in

the percent (%) of dissolution between the two curves.

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

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

Minimum Requirements for Bioequivalence Test

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발 행 일 2005 12 ㅣ

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