MINISTRY OF HEALTH
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SOCIALIST REPUBLIC OF VIETNAM
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CIRCULARS

Regulations on drugs subject to bioequivalence testing and requirements for bioequivalence research data reporting documents in drug circulation registration in Vietnam

Pursuant to the Pharmacy Law dated April 6, 2016;

Pursuant to Decree No. 54 /2017/ND-CP dated May 8, 2017 of the Government detailing a number of articles and measures to implement the Pharmacy Law;

Pursuant to Decree No. 75/2017/ND-CP dated June 20, 2017 of the Government regulating the functions, tasks, powers and organizational structure of the Ministry of Health;

At the request of the Director of the Drug Administration of Vietnam,

The Minister of Health promulgates a Circular regulating drugs subject to bioequivalence testing and requirements for bioequivalence research data reporting documents in drug circulation registration in Vietnam.

Chapter I
General Provisions

Article 1. Scope

1. This Circular stipulates:

a) Generic drugs containing pharmaceutical ingredients or dosage forms must report bioequivalence research data when registering for circulation in Vietnam;

b) Documents on reporting data on bioequivalence studies of generic drugs.

2. This Circular applies to generic drugs that have systemic pharmacological effects after the drug substance is absorbed into the general circulation.

Article 2. Interpretation of terms

In this Circular, the following terms are understood as follows:

1. Test drug: A generic drug used to prove that it has the same therapeutic effect (in terms of both effectiveness and safety of the drug) when used on patients at the same dose level following the same route of administration. Specific conditions specified on the label (if any) compared to the control drug through bioequivalence test data (in vivo) or dissolution equivalence test (in vitro) compared to the control drug.

2. Comparator product/Reference product: A drug for which a generic drug will be used to replace it in treatment. Typically, reference drugs are invented drugs or drugs that have been granted marketing registration with complete data on effectiveness, safety and quality established.

3. Innovator pharmaceutical product: The first licensed drug in the world, based on complete data on quality, safety and effectiveness, including licensed drugs. licensed or not licensed for circulation in Vietnam.

4. Pharmaceutical equivalence: Are drugs that contain the same pharmaceutical ingredient (for single-ingredient drugs) or contain several types of pharmaceutical ingredients (for multi-ingredient drugs), pharmaceutical ingredients in drugs identical and have the same molar content, and at the same time these drugs have the same dosage form, the same drug release mechanism, have the same route of administration and have similar quality standards.

5. Pharmaceutical alternatives: These are drugs containing the same pharmaceutical ingredient but with different chemical and physical forms (salts, esters, ethers, isomers, mixtures of isomers). , complexes or derivatives) of each pharmaceutical substance or differ in drug content or dosage form.

6. Drug under consideration: Is a generic drug that has submitted an application for registration for circulation and in the application for circulation registration there is a report on bioequivalence research data.

7. Bioequivalence study (In vivo Bioequivalence study): A clinical study on volunteers designed to compare the bioavailability of a generic drug with a reference drug with the goal of proving its ability to replace drugs. control of generic drugs.

8. Equivalence dissolution test: Is a study comparing the dissolution diagrams between drugs in different dissolution environments. Solubility equivalence testing is also called in vitro equivalence study.

9. In vitro/in vivo correlation (In vitro - in vivo correlation): A mathematical model that describes the correlation between in vitro properties (dissolution properties or drug release properties) with in vitro response. vivo (drug concentration or total drug absorption achieved in the biological fluid) of a drug.

10. Research facility: is an organization participating in part or all of the process of bioequivalence testing or solubility testing of the drug under consideration.

11. Immediate release dosage form: A dosage form that uses excipients and classic preparation techniques, with no intention of changing the rate of drug release from the dosage form. Preparation - includes conventional dosage forms (Conventional dosage forms) such as tablets, capsules, suspensions, oral solutions, solutions, suspensions, emulsions for injection and non-standard dosage forms. Unconventional dosage form, also known as special dosage form (Specific dosage form) such as solid dispersion systems, lozenges, chewable tablets, oral dispersible tablets, sublingual tablets.

12. Modified release dosage form: A dosage form that uses a number of excipients and/or preparation techniques different from the immediate release dosage form to create speed and/ or the drug release site is different from the immediate-release dosage form when used by the same route of administration. Common modified release dosage forms include: enteric-coated dosage forms (delayed release), prolonged release dosage forms (prolonged release), multiphasic release dosage forms (multiphasic release), drugs intramuscular/subcutaneous injection to create a drug storage bag (intramuscular/subcutaneous depot), transdermal drug delivery system.

13. Fixed-dose combination finished pharmaceutical product: A drug in a formula that combines the doses of two or more pharmaceutical ingredients in a fixed ratio. Single-ingredient drugs packaged in combination in the same packaging unit for use at the same time do not fall into this category.

14. Biopharmaceutics classification system (abbreviated as BCS): A system for classifying pharmaceutical substances based on the solubility of the drug in water and the permeability of the drug through the gastrointestinal epithelium.

15. No requirement for bioequivalence testing (Bio-waiver): Approval of a generic drug that can replace a reference drug without requiring reporting of in vivo bioequivalence study data of the drug itself there.

16. Study when taking the drug in a fasting state: A bioequivalence study in which volunteers participating in the study take the drug in a fasting state and do not consume alcohol or xanthine for at least 8 hours.

17. Study when taking the drug in a full state: A bioequivalence study in which volunteers participating in the study take the drug immediately after eating or according to the instructions on the time of taking the drug compared to meals stated in the Summary of drug properties.

18. Single-dose design study: A bioequivalence study in which biological samples used in analysis are collected after taking a single dose of the drug at each stage of the study.

19. Multi-dose design study: A bioequivalence study in which biological samples used in analysis are collected after taking multiple doses of a drug to achieve a stable drug concentration in the blood.

20. Polarized approach: Is the analysis and selection of 02 contents among many different contents of the same drug (with the same dosage form, produced by the same manufacturer) that are determined to be effective. maximum difference so that any difference between the remaining contents is within the difference between these two selected contents to conduct research and extrapolate the research results to the remaining contents. .

21. ASEAN: Is the abbreviation of the English phrase "Association of Southeast Asian Nations", translated into Vietnamese as Association of Southeast Asian Nations.

22. ICH: Is the abbreviation of the English phrase "International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use", translated into Vietnamese as International Conference on Harmonization of Pharmaceutical Registration Procedures for human use.

23. ASEAN bioequivalence research data reporting form: Is the reporting form specified in Appendix IV of the ASEAN Guidelines for Conducting Bioequivalence Research issued with Circular No. 32/2018 /TT-BYT dated November 12, 2018 of the Minister of Health Regulating the registration of circulation of drugs and medicinal ingredients (hereinafter abbreviated as Circular No. 32/2018/TT-BYT).

24. ICH bioequivalence study data reporting form: Is a reporting form according to ICH's guidelines on structure and content of clinical trial reports (Structure and Content of Clinical Study Reports - E3 Guideline). .

Chapter II

GENERIC DRUGS CONTAINING PHARMACEUTICAL SUBSTANCES AND DOSAGE FORMS MUST HAVE A REPORT ON BIOEQUIVALENCE STUDY DATA

Article 3. Generic drugs containing pharmaceutical ingredients must report bioequivalence research data when registering for circulation

1. Criteria for selecting pharmaceutical ingredients contained in generic drugs require bioequivalence research data to be reported when registering for circulation in the following order of priority:

a) Have a narrow treatment range;

b) Have low bioavailability and/or vary widely between individuals;

c) Found in prescription drugs, belonging to one of the pharmacological groups including cardiovascular drugs, hypoglycemic drugs, antibiotics, antipsychotic/epileptic drugs, antiviral drugs;

d) Included in drugs on the list of drugs used in national programs including: HIV-AIDS prevention project; Community mental health protection project; Tuberculosis prevention project; Malaria prevention project.

2. The list of pharmaceutical ingredients contained in generic drugs that must report bioequivalence research data when registering for drug circulation is specified in Appendix I issued with this Circular.

Article 4. Generic drugs according to dosage form must have a bioequivalence study data report when registering for circulation.
Generic drugs according to dosage form must have a bioequivalence study data report when registering for circulation. including:

1. The drug has a dosage form that releases the active substance immediately, has a systemic effect, contains the active ingredient specified in Clause 2, Article 3 of this Circular and does not fall into the cases specified in Article 5 of this Circular.

2. The drug has a modified pharmaceutical release dosage form, has systemic effects and does not fall into the cases specified in Article 5 of this Circular.

Article 5. Generic drugs are not tested for bioequivalence due to the availability of bioequivalence properties with the reference drug.
Generic drugs are not tested for bioequivalence due to the availability of bioequivalence properties with the reference drug including:

1. Generic drugs for intravenous use are solutions in water when injected, contain the same pharmaceutical ingredients at the same molar concentrations when used as control drugs and do not contain excipients that interact with the pharmaceutical ingredients. or has an effect on the distribution of the drug substance like the control drug. In case these excipients must be used in the formulation, the composition of these excipients must be similar to the composition of the excipients in the control drug in an amount equivalent to the amount used in the control drug or if there is a difference. differ in quantity, it must be proven that this difference does not affect the pharmacokinetics of the drug substance.

2. Generic drugs used by injection routes other than intravenous injection, in the form of solutions in water or in oil when injected, contain the same pharmaceutical substances at the same molar concentrations and contain the same excipients at similar concentrations when compared with control drugs. For injectable drugs that are solutions in water, the excipients in the formula may be different but must be of the same type (have the same function) with the same concentration as the excipients in the reference drug and the difference in excipients is the same. This medication must be demonstrated not to affect the viscosity of the solution.

3. Generic drugs are oral solutions when used (including drugs in solid form but with instructions for mixing into a solution before use) that are equivalent in preparation to the control drug and do not contain the same drugs. Excipients may affect the transport, absorption or stability in the body of the drug substance such as the reference drug. In cases where the formulation requires the use of excipients that may affect the transport, absorption or stability in the body of the drug substance, the type and amount of these excipients of the generic drug must be equivalent. similar to the control drug.

4. Generic drugs in gas form when used are equivalent in preparation to control drugs.

Chapter III
REGULATIONS ON COMPARATIVE MEDICINES AND REQUIREMENTS FOR BIOEQUIVALENCE TESTING

Article 6. Control drugs used in bioequivalence testing

1. Criteria for selecting reference drugs used in bioequivalence testing for circulation registration are specified in the following order of priority:

a) Drugs on the list of original brand-name drugs announced by the Ministry of Health or drugs that have been granted circulation registration by the Ministry of Health with complete quality, safety and clinical effectiveness data;

b) Reference drugs are invented drugs that have not been granted a Certificate of registration for circulation in Vietnam but have been approved by one of the strict pharmaceutical management agencies specified in Clause 10, Article 2 of Circular No. 32/2018/TT-BYT . approved and being circulated in the markets of these countries;

c) In case it is not possible to identify a reference drug that meets the provisions of Points a and b of this Clause, priority shall be given to selecting a reference drug as follows:
- The drug has been strictly controlled by one of the pharmaceutical management agencies. stipulated in Clause 10, Article 2 of Circular No. 32/2018/TT-BYT approved and being circulated in the markets of these countries.
- The drug has been prequalified by the World Health Organization.
Among drugs that meet these conditions, priority is given to selecting drugs with a valid circulation registration certificate issued by the Ministry of Health of Vietnam.

2. In addition to meeting the regulations in Clause 1 of this Article, control drugs used in bioequivalence testing are drugs with immediate drug release dosage forms, drugs with modified drug release dosage forms, and combination drugs. Fixed dose cases must also meet the following regulations:

a) In case the drug under consideration is a single-ingredient drug with a dosage form that releases the drug immediately, the reference drug is a single-ingredient drug with a dosage form that releases the drug immediately;

b) In case the drug under consideration is a drug with a modified drug release dosage form, the reference drug is a drug with a modified drug release dosage form with the same drug release mechanism;

c) For fixed-dose combination drugs:
- In case the drug under consideration is intended to replace an approved fixed-dose combination drug with complete clinical safety and effectiveness data (it is a specialized drug). generic drug or patent drug), select this fixed-dose combination drug as the control drug.
- In cases where the drug under consideration is developed with the purpose of replacing a dose combination regimen of single-component drugs and this dose combination regimen has complete clinical safety and effectiveness data. , control drugs are corresponding single-ingredient drugs.

3. Control drugs used in bioequivalence testing must have clear origin. Documents proving the source and origin of reference drugs are specified in Point c, Clause 1, Article 8 of this Circular.

4. Based on the criteria for selecting reference drugs specified in Clause 1 of this Article, based on other regulations for reference drugs specified in Clauses 2 and 3 of this Article and based on the practical situation, the Department The Pharmacy Manager prepares a list of reference drugs, consults with the Advisory Council for granting registration certificates for drugs and medicinal ingredients to issue a Decision promulgating the List of reference drugs used in bioequivalence testing. The list of reference drugs used in bioequivalence testing is published by the Drug Administration of Vietnam - Ministry of Health on the Department's website at https://dav.gov.vn/.

Article 7. Regulations for bioequivalence research in bioequivalence research data reporting dossiers

1. Research must meet the following requirements:

a) Must be designed and implemented according to the provisions of the ASEAN Bioequivalence Testing Guidelines or reference guidelines of other organizations specified in Appendix VI issued with this Circular;

b) For drugs in dosage forms that release modified pharmaceutical ingredients, are administered orally and have systemic effects, research must be conducted when using the drug in an empty state and research when using the drug in a fed state;

c) For drugs in dosage forms that release active ingredients immediately, have systemic effects, and do not fall into the cases specified in Article 5 of this Circular, research must be carried out when using the drug in the fasting state. In cases where the pharmacokinetic properties of the reference drug are known to mean that food affects bioavailability or the reference drug has instructions for use after meals, the study can be performed when the drug is administered in a fed state instead. Research when taking the drug in a fasting state;

d) For fixed-dose combination drugs, the bioequivalence of all pharmaceutical ingredients in the drug must be researched and evaluated;

d) Apply bioequivalence test design for each drug as recommended by the US Food and Drug Administration (US FDA) or the European Medicines Agency (EMA).

2. Research must be conducted at testing units that have been evaluated and recognized by competent authorities in the host country and must be carried out in compliance with the principles of good clinical drug testing practice (GCP) stipulated in Clause 1, Article 4 of Circular No. 29/2018/TT-BYT dated October 29, 2018 of the Minister of Health regulating clinical drug testing and good laboratory practices (GLP) according to stipulated in Clause 1, Article 3 of Circular No. 04/2018/TT-BYT dated February 9, 2018 of the Minister of Health regulating Good Laboratory Practices.

3. In case the bioequivalence study of the drug under consideration uses a reference drug that is a patented drug but is not produced at the same production facility as the patented drug that is granted a circulation registration certificate in Vietnam, The registration facility needs to demonstrate the interchangeability between the reference drug used in research and the patent drug granted registration for circulation in Vietnam according to the ASEAN Bioavailability/Bioequivalence Research Guidelines.

4. Sample report on drug bioequivalence research data specified in Point a, Clause 1, Article 8 of this Circular. Specific requirements for reporting bioequivalence study data of the drug under consideration are specified in Appendix III issued with this Circular.

5. Bioequivalence testing of the drug under consideration is not required in the following cases:

a) The drug under consideration has a formulation in proportion to the reagent in the bioequivalence study and meets the regulations in Section I, Appendix II issued with this Circular;

b) The drug under consideration has the same dosage form, formulation, and manufacturing process but has a different pharmaceutical content than the drugs tested in the bioequivalence study and meets the regulations in Section II, Appendix Appendix II issued together with this Circular;

c) The drug being considered to be prepared in solid form with immediate release of active ingredients for oral use is equivalent in preparation to the control drug and the active ingredient belongs to the group of fast-dissolving, fast-absorbing substances according to the classification table of the biopharmaceutical system and meets the requirements. Meet the regulations in Section III, Appendix II issued with this Circular;

d) The drug under consideration is produced at a production location other than the production location of the reagents in the bioequivalence study and meets the conditions specified in Section IV, Appendix II issued with this Circular.

Chapter IV
DOSSIER REPORTING DATA OF BIOEQUIVALENCE STUDY

Article 8. Documents reporting bioequivalence research data in case the drug under consideration is tested for bioequivalence with a control drug.

1. The components of the dossier include the following documents:

a) Report bioequivalence research data (in vivo) of the drug according to the current version of the ASEAN bioequivalence research data report form or the ICH bioequivalence research data report form, in which a commitment on the similarity between the reagent used in research and the drug under consideration must be prepared according to Form 01/BE specified in Appendix VII issued with this Circular;

b) Documents and information of research facilities specified in Article 12 of this Circular;

c) Documents proving the origin of the reference drug used in the study include:
- Copy of the invoice for purchasing the reference drug from the supplier clearly showing the supplier's name and address;
- A copy of the drug label certified by the registration facility/manufacturing facility fully and clearly showing the following information: drug name, name and address of the drug manufacturer, production batch number, expiry date;
- A commitment signed by the director of the registration facility/manufacturer on the authenticity of the documents provided above, committing that the reference drug has been purchased from the correct market of the country where the drug is licensed to be stored. and stored according to the drug storage conditions stated on the label from the time of purchase to the time the study begins.

2. In case the drug is being considered for bioequivalence testing and volunteers use the drug in different states (full, hungry, single, multiple doses), the dossier reporting bioequivalence research data includes Multiple bioequivalence research reports and each research report corresponding to each state of drug use must contain or explain all the documents specified in Clause 1 of this Article.

Article 9. Documents reporting bioequivalence research data for drugs under consideration specified in Points a and b, Clause 5, Article 7 of this Circular.

Documents reporting bioequivalence research data for drugs under consideration. The drugs under consideration specified in Points a and b, Clause 5, Article 7 of this Circular include the following documents:

1. Application for not performing bioequivalence testing (Biowaiver) for the drug under consideration according to form 02/BE specified in Appendix VII issued with this Circular.

2. Bioequivalence profile of the content or concentrations selected for bioequivalence testing with the reference drug meets the regulations in Article 8 of this Circular.

3. Explanation on the selection of contents to report bioequivalence research data and use of bioequivalence test results of these contents to recommend not performing bioequivalence tests for the products. remaining content, including the content of the drug under consideration.

4. Comparison table of the dosage formula of the contents for which bioequivalence testing is not recommended, including the content of the drug under consideration with the dosage formula of the contents with equivalent research data reported. biology.

5. Table comparing the production process of the contents for which bioequivalence testing is not recommended, including the content of the drug under consideration, with the production process of the contents for which equivalent research data are reported. biology.

6. Report on solubility equivalence test between concentrations, it is recommended that bioequivalence testing is not performed, including the content of the drug under consideration and the concentrations for which bioequivalence research data have been reported. Requirements for solubility equivalence test reports are specified in Appendix IV issued with this Circular.

7. A commitment on the similarity between the drug under consideration and the reagent used in the solubility equivalence test according to form 01/BE specified in Appendix VII issued with this Circular.

8. Information on the linear pharmacokinetics of the drug under consideration (if applicable).

Article 10. Documents reporting bioequivalence research data for drugs under consideration specified in Point c, Clause 5, Article 7 of this Circular
Documents reporting bioequivalence research data for drugs under consideration Consider the provisions at Point c, Clause 5, Article 7 of this Circular, including the following documents:

1. Application for not performing bioequivalence testing (Biowaiver) for the drug under consideration according to form 02/BE specified in Appendix VII issued with this Circular.

2. Documents of the research facility specified in Article 12 of this Circular.

3. Documents proving that the drug substance/drug substances contained in the drug under consideration have good solubility and permeability properties according to the instructions in Appendix III. Exemption from biological testing based on condoms of the ASEAN Guidelines for Conducting Bioequivalence Studies issued with Circular No. 32/2018/TT-BYT .

4. Data proving that the drug under consideration has excipients that meet the regulations to be considered for not performing bioequivalence testing, including:

a) Comparison table of excipient ingredients in the formula between the drug under consideration and the reference drug or a drug that is not the reference drug but has equivalent formulation to the drug under consideration and has been approved by one of the regulatory agencies. Strict regulations prescribed in Clause 10, Article 2 of Circular No. 32/2018/TT-BYT are taken as reference drugs along with information on the source of ingredients of excipients in this reference drug or reference drug formula. .
Some accepted official search sources include: Instructions for drug use approved by the Drug Administration of Vietnam, summaries of approved drug characteristics, or Drug evaluation reports posted on the agency's website. European Medicines Agency (EMA) and Strict Drug Administration (SRA) prescribed in Clause 10, Article 2 of Circular No. 32/2018/TT-BYT or on official drug information sites such as eMC (electronic Medicines Compendium). In case information about the ingredients of excipients in the control drug formula or reference drug cannot be looked up, qualitative results of the excipient ingredients in the formula of the control drug or reference drug must be provided to verify the results. demonstrate that the drug under consideration has the same excipients in its formulation as one of these drugs;

b) In case the drug formula contains excipients that affect the bioavailability of the drug: Qualitative and quantitative results of these excipients in the drug formula under consideration and the control drug formula to prove that the drug under consideration and the reference drug have the same content of these excipients;

c) Report on validation of qualitative and quantitative analysis procedures used in the above tests.

5. Report evaluating the dissolution properties of the drug (for drugs with very fast dissolution properties) or Report on testing the solubility equivalence between the drug under consideration and the reference drug (in case the drug has the property of dissolving very quickly). dissolves quickly). Requirements for solubility equivalence test reports are specified in Appendix IV issued with this Circular.

6. A commitment on the similarity between the drug under consideration and the reagent used in the dissolution or dissolution equivalence test according to form 01/BE specified in Appendix VII issued with this Circular.

7. Documents related to reference drugs as prescribed in Point c, Clause 1, Article 8 of this Circular.

Article 11. Documents reporting bioequivalence research data for drugs under consideration specified in Point d, Clause 5, Article 7 of this Circular
Documents reporting bioequivalence research data for drugs under consideration Consider the provisions at Point d, Clause 5, Article 7 of this Circular, including the following documents:

1. Application for not performing bioequivalence testing (Biowaiver) for the drug under consideration according to form 02/BE specified in Appendix VII issued with this Circular.

2. In case of change in production location due to a change from the manufacturer of the drug owner to a manufacturer under contract with the drug owner or a change between manufacturers under contract with the drug owner : The drug owner's document designates the drug manufacturer under consideration as a contract manufacturer with the drug owner and the contract manufacturer's written acceptance of participation in the contract drug manufacturing is accepted. point. In case the difference in production location is due to a change from one contract manufacturer to another by the owner, add a written explanation from the drug owner about the reason for this change.

3. In case of change in drug production location due to change between different manufacturers of the same drug owner or change between different production locations of the same manufacturer: Document of the owner The drug or the registration facility explains the reason for changing the production location.

4. Quality records of reagents in bioequivalence studies include:
- Part S. Pharmaceutical substances: Summary of the pharmaceutical substance synthesis process with a process diagram; Solvents used in the process; Pharmaceutical properties; Impurity characteristics; Pharmaceutical quality standards; Pharmaceutical batch analysis data;
- Part P. Finished products: Preparation formula; Production process; Excipient quality standards; Quality standards and finished product analysis procedures; Finished product batch analysis data of at least 03 batches, at least the pilot batch size specified in Appendix V of this Circular - including batches used in bioequivalence testing; Finished product stability (in case there is not enough long-term stability data of the drug under consideration until the registration expiration date); Bioequivalence dossier meets the regulations in Article 8 of this Circular.

5. Documents specified in Clauses 3, 4, 5, 6, 7 and 8, Article 9 of this Circular in the case of drugs manufactured at the old location have been implemented according to the provisions of Point a or Point b, Clause 5 Article 7 of this Circular.

6. List of changes related to the dosage formula, batch size, manufacturing process, and drug substance manufacturer during circulation (if any) of drugs manufactured at the old manufacturing location .

7. Document approving these changes from the host country's pharmaceutical management agency.

8. Documents of changes and additions for each listed change meet the regulations in Appendix II issued with Circular No. 32/2018/TT-BYT , except administrative documents.

9. Explanation of scientific bases and experimental data proving that the reagents in the bioequivalence study are still representative of the drug under consideration. The explanation of scientific bases must have the following minimum contents:

a) The similarity of the manufacturing formula between the drug under consideration and the reagent in the bioequivalence study or the correlation in the dosage formula between the drug under consideration and the reagent in the bioequivalence study. Meet the conditions specified in Sections I, II - Appendix II issued with this Circular in case the drug manufactured at the old location is approved in a form that does not require bioequivalence testing according to regulations. at Point a or Point b, Clause 5, Article 7 of this Circular;

b) Similarity in drug substance quality standards including drug properties known to affect the bioavailability of the finished drug, quality standards of excipients, manufacturing processes, and regulatory requirements. Standard operating procedures, equipment used in production, environmental control during the production process, finished product quality standards;

c) Characteristics of excipients that affect the bioavailability of the drug in the formulation;

d) Compare batch analysis data of at least 03 batches, at least at the pilot batch size specified in Appendix V of this Circular between batches of reagents used in bioequivalence studies and batches of drugs under consideration. .

10. The solubility equivalence test report between the drug produced at the old production site and the drug under consideration demonstrates the similarity in the solubility diagram between the two drugs. Requirements for solubility equivalence test reports are specified in Appendix IV issued with this Circular. This document is not required if the change in production location involves only one or several steps including primary packaging without dosing, quality control, batch release and secondary packaging.

11. Report research data demonstrating established in vitro- in vivo correlations in the case of drugs with modified release dosage forms. In case the change in production location only involves one or several stages including primary packaging after the drug has been dosed, quality control, batch release and secondary packaging, no documents are required. This.

12. In case of change of production location due to change of manufacturer and the drug produced at the old production location has been granted registration for circulation in Vietnam according to the ASEAN common technical dossier (ACTD) but has not yet been approved. To be declared a drug with proven bioequivalence, the dossier reporting bioequivalence research data for the drug produced at the old production site must meet the provisions in Article 8 and the reporting dossier No. Bioequivalence research data for the drug under consideration must meet the regulations in Clauses 1, 2, 3, 5, 6, 7, 8, 9, 10 and 11 of this Article.

13. In case the production location is changed due to a change in manufacturer and the drug produced at the old production location has been declared a drug with proven bioequivalence in Vietnam, the dossier reports research data. Bioequivalence research for the drug under consideration must meet the regulations in Clauses 1, 2, 3, 5, 6, 7, 8, 9, 10 and 11 of this Article.

14. In case of change between different production locations of the same manufacturer and the drug produced at the old production location has been granted a certificate of registration for circulation in Vietnam: Apply in the form of change or addition. supplement for pharmaceutical drugs that have been registered for circulation as prescribed in Appendix II issued with Circular No. 32/2018/TT-BYT .

Article 12. Documents and information of research facilities

1. No documents from research facilities are required for bioequivalence testing facilities in Vietnam that have been evaluated and published by the Ministry of Health of Vietnam in the list of facilities that meet the conditions for conducting testing. bioequivalence of drugs on the electronic information portal of the Ministry of Health and the website of the Drug Administration of Vietnam or a facility authorized in writing by the Ministry of Health to conduct bioequivalence testing of drugs.

2. Documents for research facilities certified by the World Health Organization and published in the list of reference laboratories (prequalified laboratories) with bioequivalence testing scope or facilities approved by one of the reference laboratories. The drug management agency stipulates in Clause 10, Article 2 of Circular 32/2018/TT-BYT evaluates and certifies the scope of bioequivalence testing or the facility is certified by a competent management agency of one of the ICH countries for bioequivalence testing or facilities listed on the list of bioequivalence research facilities recognized under the ASEAN mutual recognition agreement for bioequivalence research data reporting of medicine (posted on the ASEAN website) and other facilities in countries with which Vietnam has an agreement to recognize and recognize one of the following two types of documents:

a) Original or copy of Certificate of facility meeting GCP and GLP principles or ISO/IEC 17025 or License/certificate/confirmation/notification issued by the competent authority of the host country facility with bioequivalence testing function or Certificate/confirmation/notification issued by the competent authority of the host country with content agreeing for the facility to perform bioequivalence testing;

b) Results of self-searching of legal documents specified in Point a of this Clause from the English website of the agency issuing legal documents, accompanied by a document providing information on the search link to the Department of Administration. Pharmacy in cases where the issued legal documents are electronic copies, including cases where there is not enough signature, signer's name and confirmation stamp of the competent state management agency of the country issuing the legal documents. physical.

3. Documents that must be submitted to research facilities other than those specified in Clauses 1 and 2 of this Article are one of the following types of documents:

a) Original or copy of License/certificate/confirmation/notification issued by the competent authority of the host country to the facility with bioequivalence testing function or Certificate/certification/ Notification issued by the competent authority of the host country with the content of consent for the testing facility to conduct bioequivalence testing of the drug under consideration;

b) Original or copy of GLP Certificate or ISO/IEC 17025 certificate with the scope of biological fluid analysis issued by the host country's management agency for the facility participating in the analysis phase and the Certificate receive GCP issued by the host country's management agency for facilities participating in the clinical phase;

c) In case the facility cannot provide the documents specified in Point a or b of this Clause because the host country's law does not provide for these documents to be issued to the facility conducting the research, request the registration unit. The drug registration company under consideration provides documents to demonstrate compliance with GCP and/or GLP as follows:
- Documents proving compliance with GLP:
+ Quality manual or master records of the research facility Similar student. These documents must demonstrate the capacity and scope of testing;
+ Original or copy of the contract between the bioequivalence research facility and the sponsor and subcontracts of the bioequivalence research facility;
+ List of inspections by the management agency or accreditation agency in the past 3 years and the most recent inspection report of the local management agency.
- Documents proving compliance with GCP:
+ Overall profile of the clinical bioequivalence research facility demonstrating full testing capacity for drug bioequivalence testing;
+ Original or copy of the contract between the bioequivalence research facility and the sponsor and subcontracts of the bioequivalence research facility;
+ Original or copy of the inspection report of the national drug management agency or WHO conducted within no more than 3 years;
+ Original or copy of research monitoring report by the sponsor or research organization for the research under consideration.

4. Documents specified in Clause 2 and Points a and b Clause 3 of this Article must meet the following regulations:

a) Must remain valid during the research period. In case the documents do not clearly state the validity period, they will be considered valid for 3 years from the date of issue;

b) In case the GLP Certificate or GCP Certificate does not meet the provisions of Point a of this Clause, accept the GLP/GCP assessment conclusion in the inspection minutes/report of the competent management agency for the first time. within 03 years after the date of assessment.

5. The documents specified in this Article must be stamped and certified by the registration facility. The registration establishment must be responsible before the law for its self-search results at Point b, Clause 2 of this Article and the legality and accuracy of the documents and information specified in this Article.

Chapter V
IMPLEMENTATION PROVISIONS

Article 13. Effectiveness of implementation

1. This Circular takes effect from November 1, 2022.

2. Circular No. 08/2010/TT-BYT dated April 26, 2010 of the Minister of Health Guidance on reporting bioavailability/bioequivalence research data in drug registration expires from the date This Circular takes effect.

Article 14. Application roadmap

1. From the effective date of this Circular, establishments registering the following drugs must submit bioequivalence research data reports when submitting applications for drug circulation registration, As follows:

a) Generic drugs are prepared in immediate-release form and enteric-coated modified-release form, single ingredient or fixed-dose combination formula, containing pharmaceutical ingredients on the List of required pharmaceutical ingredients. Requires reporting of bioequivalence research data when registering for drug circulation;

b) Generic drugs prepared in modified release form, except for enteric-coated drugs that do not fall into the cases specified in Point a of this Clause;

2. After 36 months from the effective date of this Circular, drug registration establishments must submit bioequivalence testing dossiers when submitting applications for circulation registration for all drugs. generic prepared in enteric-coated modified release form, except for drugs that must comply with the provisions of Clause 1 of this Article.

3. After 48 months from the effective date of this Circular, the drug registration facility has been granted a circulation registration certificate for drugs containing pharmaceutical ingredients or dosage forms subject to bioequivalence testing according to regulations. In this Circular, drugs must be declared with documents proving bioequivalence. The order and procedures for declaring drugs with documents proving bioequivalence are specified in the Circular regulating the registration for circulation of drugs and medicinal ingredients.

Article 15. Transitional provisions

1. Reporting bioequivalence research data in dossiers requesting issuance, change, or supplementation of marketing registration documents submitted before the effective date of this Circular will continue to be implemented according to the provisions of this Circular. Circular No. 08/2010/TT-BYT dated April 26, 2010 of the Minister of Health guiding the reporting of bioavailability/bioequivalence research data in drug registration, except in cases where the facility registers itself. voluntarily comply with the provisions of this Circular.

2. For drugs that have submitted registration dossiers for circulation before the effective date of this Circular: No additional bioequivalence research data report is required before granting circulation registration; The registration facility must comply with the provisions in Clause 3, Article 14 after the drug is granted a circulation registration certificate.

3. For bioequivalence studies and solubility equivalence tests conducted before the effective date of this Circular, accept the enterprise's commitment on the origin of the reference drug used in the drug. research according to form 03/BE specified in Appendix VII issued with this Circular if documents proving the origin of the reference drug cannot be provided as prescribed in Point c, Clause 1, Article 8 of this Circular. This circular.

4. For bioequivalence studies conducted before the effective date of this Circular, research facilities, control drugs, and research designs are accepted in cases where the drug under consideration has been approved by one of the following: Strict pharmaceutical management agencies stipulated in Clause 10, Article 2 of Circular No. 32/2018/TT-BYT approved and are being circulated in the markets of these countries.

5. For bioequivalence studies conducted before the effective date of this Circular, except for the cases specified in Clause 3 of this Article, the control drug selected in the study is accepted if it belongs to one of the following: following cases:

a) Belongs to the list of original brand-name drugs issued by the Ministry of Health at the time of conducting the research;

b) Has been approved in writing by the Drug Administration of Vietnam - Ministry of Health;

c) Has been approved and saved by one of the European pharmaceutical management agencies (EMA) and strict drug regulatory agencies (SRA) specified in Clause 10, Article 2 of Circular No. 32/2018/TT-BYT. operating in this national market.

Article 16. Terms of reference

In case legal documents and regulations cited in this Circular are changed, supplemented or replaced, the legal documents or regulations shall apply. new citation.

The reference technical instructions specified in Appendix VI issued with this Circular are applied as a basis for reviewing and evaluating bioequivalence test dossiers. In case these instructions are changed or updated, establishments are allowed to apply the new versions.

Article 17. Responsibility for implementation

1. The Drug Administration of Vietnam is responsible for:

a) Organize guidance and implementation of the provisions of this Circular;

b) Update and publish the List of reference drugs used in bioequivalence testing issued by the Ministry of Health;

c) Update and publish the list of bioequivalence testing facilities evaluated and recognized by the Ministry of Health of Vietnam.

2. Chief of the Ministry Office; Director of the Drug Administration of Vietnam; Chief Inspector of the Ministry; Heads of units under and under the Ministry of Health; Directors of Departments of Health of provinces and centrally run cities; Heads of sectoral health facilities; Directors of drug bioequivalence testing facilities; Organizations and individuals operating in the field of drug registration are responsible for implementing this Circular.

3. During the implementation process, if there are any difficulties or problems, agencies, organizations and individuals are requested to report them to the Ministry of Health (Drug Administration) for consideration and resolution./.

Recipients:
- Social Committee of the National Assembly;
- Office of the Government (Government Gazette Office, Government e-information portal);
- Q. Minister of Health (to report);
- Deputy Ministers of Health (for discussion);
- Ministry of Justice (Department of Inspection of Legal Documents);
- Science and technology;
- Ministry of National Defense (Military Medical Department);
- Ministry of Public Security (Department of Health);
- Ministry of Transport (Department of Health and Transport);
- The financial;
- Departments, Bureaus, General Departments, Ministry Offices, Ministry Inspectorates;
- Department of Health of provinces and centrally run cities;

Vietnam Pharmaceutical Corporation;
- Pharmaceutical business associations Vietnam;
- Vietnam Pharmaceutical Association;
- Electronic information portal of MOH, Website of Department of Management;
- Domestic and foreign drug production and trading enterprises;
- Save: VT, PC, QLD (5).

KT. MINISTER
DEPUTY

Do Xuan Tuyen

Appendix I

D LIST OF PHARMACEUTICAL SUBSTANCES CONTAINED IN GENERIC DRUGS THAT MUST REPORT BIOEQUIVALENCE STUDY DATA WHEN REGISTERING FOR CIRCULATION OF THE DRUG

(Issued together with Circular No. 07 /2022/TT-BYT dated September 5 , 2022 of the Ministry of Health)

No	Drug substance name
first	Amlodipine
2	Azithromycin
3	Carbamazepine
4	Cefixime
5	Cefuroxime Axetil

6	Clarithromycin
7	Glibenclamide
8	Gliclazide
9	Metformin
ten	Metoprolol
11	Nifedipine
twelfth	Rifampicin
13	Amoxicillin + clavulanic acid
14	Carvedilol
15	Cefpodoxime
16	Ezetimibe
17	Irbesartan
18	Itraconazole
19	Risperidon
20	Rosuvastatin
21	Simvastatin
22	Sulpiride
23	Sultamicillin
24	Telmisartan
25	Valproate sodium
26	Fenofibrate

Appendix II

CONDITIONS TO BE APPLICABLE TO DRUGS THAT DO NOT REQUIRE *IN VIVO* BIOEQUIVALENCE TESTING

(Issued together with Circular No. 07 /2022/TT-BYT dated September 5 , 2022 of the Ministry of Health)

I. The drug under consideration has a formulation in the same ratio as the reagent in the bioequivalence study:

1. Proportional formulations are formulations of different concentrations of the same drug (with the same dosage form, produced by the same manufacturer) that meet the following conditions:

a) For drugs in immediate-release dosage form: Preparation formulas of different strengths with the same active ingredients and excipients (not including coating excipients, capsule shells, coloring excipients, flavoring, preservatives are ingredients that do not have the ability to change the bioavailability of the drug) with the same combination ratio between the pharmaceutical ingredients and these excipients or when a pharmaceutical ingredient accounts for an equal or equal ratio. lower than 5% by weight in the formula, the total amount of excipients in the formula of different concentrations is the same or only the amount of filler excipients changes according to the change in drug content, while the total amount of excipients The rest in the formula of different concentrations is the same. If the medicine is a coated tablet, the weight in the formula is calculated according to the weight of the filled tablet. If the medicine is a capsule, the volume in the formula is calculated according to the volume of medicine packed in the capsule.

b) For drugs in enteric-coated dosage form:

- When the drug is an enteric-coated tablet: The formulation of these different strengths has the same pharmaceutical ingredients and excipients (not including excipients that create color, flavor, and preservatives). ingredients that are not likely to change the bioavailability of the drug) with the same combination ratio between the drug substance and these excipients or when a drug substance accounts for a proportion equal to or less than 5% of the weight in the formula. formula, the total amount of excipients in the tablet formula multiplied by different concentrations is the same or only the amount of filler excipients changes according to the change in drug content, while the total amount of excipients remaining in the formula The different contents are the same and the ratio of acid-resistant coating weight/tablet surface area between tablets with different contents (mg/cm2) must be the same).

- When the medicine is a capsule containing enteric-coated particles: Different strengths use the same type of enteric-coated particles (produced from the same manufacturing process) and differences in drug content in the capsule is achieved by adjusting the number (or mass) of seeds packed into the capsule.

c) For drugs in extended-release dosage form:

- Different concentrations have the same drug release mechanism and the dosage formula of different concentrations has the same pharmaceutical ingredients and excipients with the same combination ratio between these pharmaceutical ingredients and excipients. or when a drug substance accounts for a proportion equal to or less than 5% of the weight in the formula, the total amount of remaining excipients in the formula of different concentrations is the same or only the amount of filler excipients changes accordingly. The change in drug content and the total amount of remaining excipients in the formula of different concentrations are the same. If the medicine is a coated tablet, the weight in the formula is calculated according to the weight of the filled tablet. If the medicine is a capsule, the volume in the formula is calculated according to the volume of medicine packed in the capsule.

- When the drug is a capsule containing extended-release granules: Different strengths using the same extended-release granules (manufactured from the same manufacturing process) and differences in drug content in the capsule is achieved by adjusting the number (or mass) of seeds packed into the capsule.

d) For drugs in transdermal dosage form: Different concentrations have the same pharmaceutical ingredients and excipients, the difference in content is proportional to the difference in active surface area. application of the patch, whereby the lower concentrations are smaller areas of the highest concentration.

d) For drugs with fixed-dose combination formulas: The conditions for different concentrations of the drug to be considered proportional formulation must be satisfied with all active ingredients in the drug. Accordingly, when considering each pharmaceutical ingredient, the remaining

pharmaceutical ingredients are considered excipients in the formula, unless scientific evidence is provided to prove that differences in proportions are acceptable. combination with these remaining pharmaceutical substances. For two-layer tablets, each layer can be considered independent of the other.

2. If the drug under consideration has many strengths and these different strengths are formulated according to the ratio specified in Clause 1 of this section, the bioequivalence research data report of the drug can be used. One or two contents are considered to have the highest risk of not achieving bioequivalence according to the provisions of Clause 3 of this section for consideration and do not require *in vivo* bioequivalence testing for the remaining contents if the contents are not bioequivalent. Different amounts of the drug satisfy both of the following conditions:

a) The recommended concentrations do not require submission of bioequivalence research data reports and are produced using the same production process as the concentrations used in bioequivalence testing.

b) The solubility chart of the contents recommended for not performing in vivo bioequivalence testing must be similar to the dissolution chart of one of the concentrations used in the bioequivalence test (based on the percentage of pharmaceutical product). substance released compared to label content over time).

3. The contents that need to report bioequivalence study data to be considered do not require in vivo bioequivalence testing for the remaining contents are selected as follows:

a) For drugs with linear pharmacokinetics (absorption level increases proportionally with dose): Required to report bioequivalence study data at one concentration, usually the highest concentration (except cases where it is not possible to study the highest concentration for reasons of safety or drug tolerance).

b) For drugs with non-linear pharmacokinetics:

- When the level of drug absorption increases more than the dose increase in the therapeutic dose range, bioequivalence study data at at least the highest concentration is required to be reported.

- When the level of drug absorption increases less than the increase in dose within the therapeutic dose range, the known cause is not due to poor solubility of the drug substance but due to the phenomenon of saturation of drug transporters into cells. and neither the test drug nor the reference drug contain any excipients that could affect gastrointestinal motility or transport proteins , requiring reporting of bioequivalence test data at the concentration level. lowest dose or a dose range with linear pharmacokinetics.

- When the level of drug absorption increases less than the increase in dose and the cause is known to be due to the poor solubility of the drug substance, it is required to report bioequivalence test data at two concentrations including the highest and either the lowest concentration or a concentration within the dose range with linear pharmacokinetics.

Refer to the current version of the Guidelines for conducting ASEAN bioequivalence studies , section 3.6.1. Research content (Strength to be investigated) to consider other exceptions that may be applicable in selecting the content to report bioequivalence study data to be considered without requiring testing *in vivo* bioequivalence for the remaining concentrations for each of the above cases.

c) Special cases:

- For intramuscular/subcutaneous injection drugs that create drug storage bags: If different concentrations are achieved only due to differences in the total volume of drug contained in a unit dose (total volume of drug injected), there is Can report bioequivalence test data of any content. In cases where it is not possible to use doses within the therapeutic range for research on healthy volunteers for safety reasons, it is acceptable to report bioequivalence study data at doses lower than the therapeutic dose.

- For drugs in enteric-coated dosage form containing many subunits that are homogeneous particles: If different concentrations contain the same type of enteric-coated particles (produced from the same manufacturing process).) and has a proportional formulation: bioequivalence test data can be reported at the highest concentration or the concentration considered to have the highest risk of not achieving bioequivalence.

- For drugs in extended-release dosage forms containing multiple subunits that are homogeneous particles: If different concentrations contain the same type of extended-release particles (manufactured from the same manufacturing process).) and has a proportional formulation: bioequivalence test data can be reported at the highest concentration or the concentration considered to have the highest risk of not achieving bioequivalence.

- For drugs that require reporting of bioequivalence test data both when using the drug in a fasted state and when using the drug in a fed state (as prescribed for oral extended-release drugs) and has non-linear pharmacokinetics, leading to the need to report bioequivalence test data at 02 different concentrations to suggest not requiring *in vivo* bioequivalence testing for the remaining concentrations. On the contrary, it is possible to only report bioequivalence test data both when using the drug in an empty state and when using the drug in a fed state of one content and it is recommended not to require a *printed bioequivalence test. vivo* either when administered in a fasted state or when administered in a satiated state of residual content - depending on which administration condition is considered less sensitive for detecting inequivalence between the test drug and allopathic medicine. Refer to the provisions in Clause 3, Section II of this Appendix to choose which drug use condition is considered less sensitive and suggest not requiring *in vivo* bioequivalence studies *in* this drug use condition for this drug. remaining content.

4. How to establish the similarity of dissolution diagrams between recommended concentrations that do not require in vivo bioequivalence testing with concentrations that report bioequivalence trial data of the drug under consideration Consideration is specified in Appendix I. Solubility test and similarity of dissolution diagrams - Guidelines for conducting ASEAN bioequivalence studies .

II. The drug under consideration has the same dosage form, formulation, and manufacturing process but has a different pharmaceutical content than the drugs tested in the bioequivalence study (based on the polarity approach):

1. If different concentrations of the same drug (with the same dosage form, manufactured by the same manufacturer) do not meet the conditions for application, in vivo bioequivalence testing is not required. for formulations according to the ratios specified in Clauses 1 and 2, Section I of this Appendix for one of the following two reasons:

- The preparation formula of different concentrations has the same pharmaceutical ingredients and excipients but the combination ratio between these ingredients does not meet the regulations in Clause 1, Section I of this Appendix;

- *The solubility chart between the recommended concentrations does not require in vivo* bioequivalence testing and the concentrations for which bioequivalence test data are reported are not the same, the numerical report can be used. The in vivo *bioequivalence study data* on 02 concentrations was selected in a polarized approach to suggest not requiring in vivo *bioequivalence testing for the remaining concentrations of the drug.*

2. If the drug under consideration is in a sustained-release dosage form or in an enteric-coated dosage form, it is recommended that in vivo bioequivalence testing be not required as a polar approach is considered only. Consider when different strengths of the drug have the same drug release mechanism and use the same excipients that control drug release in the formulation (for sustained-release drugs) or have the same layers coating to control drug release (for enteric-coated drugs).

3. In all cases, there must be a report of bioequivalence test data both when the drug is used in a fasted state and when the drug is used in a fed state (as prescribed for oral modified-release drugs).), if the application does not require an *in vivo* bioequivalence test based on a polar approach, it may be recommended to not require an *in vivo* bioequivalence test or when the drug is administered in the fasted state or when administered in the saturated state of one of the two concentrations selected for the study - depending on which administration condition is considered less sensitive for detecting inequivalence between the test drug and the control drug , As follows:

a) If the information in the summary of product characteristics of the reference drug prescribes taking the drug on an empty stomach or does not pay attention to the state of fullness or hunger when taking the drug (the drug can be taken both when full and hungry): condition Taking the drug under consideration does not require performing an *in vivo* bioequivalence study for either dose, which is to take the drug on a full stomach.

b) If the information in the summary of product characteristics of the reference drug prescribes to take the drug on a full stomach: the drug use situation under consideration does not require performing an in vivo bioequivalence test for either dose. medicine when hungry.

III. The drug being considered is prepared in solid form with immediate release of active ingredients for oral administration, equivalent in preparation to the control drug and the active ingredient belongs to the group of fast-dissolving and rapidly-absorbing substances according to the classification table of the biopharmaceutical system (based on the biopharmaceutical system). biopharmaceutical classification system):

1. Generic drugs prepared in conventional oral solid immediate release form are equivalent in preparation to reference drugs, drugs that disperse/dissolve in the oral cavity but are not absorbed in the oral cavity, are equivalent. prepared with reference drugs, containing pharmaceutical substances that have been shown to have good solubility and good permeability (belonging to group I in the biopharmaceutical classification system), not among the pharmaceutical substances with a therapeutic range will be considered narrowly not to require *in vivo* bioequivalence testing when registering for drug circulation or when requesting to declare a drug that has been granted marketing registration as a drug with proven bioequivalence if provided. provide the following evidence:

a) The drug under consideration has very rapid dissolution properties (more than 85% of the drug in a dose unit is dissolved in environments with pH from 1 to 6.8 within 15 minutes), or the drug under consideration considered to have rapid dissolution properties (more than 85% of the drug in a dose unit is dissolved in environments with pH from 1 to 6.8 within 30 minutes) and the dissolution diagram of the drug under consideration is Similar to the solubility diagram of the control drug in the tested environments.

b) For excipients that are known to have the ability to affect the bioavailability of the drug (mannitol, sorbitol, surfactants...): Qualitative and quantitative composition of these excipients in the drug under consideration must be similar in the reference drug.

c) Other excipients in the drug formulation under consideration are either qualitatively similar to the excipients used in the reference drug formulation, or qualitatively similar to the excipients used in the first formulation the drug has a formulation equivalent to the drug under consideration that has been approved in one of the reference countries, or are common excipients of known properties with amounts used in the formulation falling within the limits of normal use. usually matches the dosage form of the drug under consideration.

2. The conditions for consideration that do not require performing in vivo bioequivalence testing based on the biopharmaceutical classification system specified in Clause 1 of this section can also be applied in cases, instead of For the condition of pharmaceutical equivalence, the drug under consideration and the reference drug are preparations that differ only in the salt form of the drug substance - provided that both salt forms are present. good solubility and good permeability (both in group I in the biopharmaceutical classification system). Do not apply and do not require *in vivo* bioequivalence testing according to the biopharmaceutical classification system when the pharmaceutical substance used between the drug under consideration and the reference drug differs in ester form, ether form , isomer form, mixture of isomers, complexes or other derivatives.

3. For drugs with fixed-dose combinations, it may be considered not to require in vivo bioequivalence testing based on the biopharmaceutical classification system if all pharmaceutical substances in the formulation are soluble. good quality and good permeability (also belonging to group I in the biopharmaceutical classification system), the excipients in the drug formula under consideration meet the regulations stated in Points b and c, Clause 1 of this section and the dissolution properties The solubility of the drug under consideration for each active ingredient in the drug meets the regulations stated in Point a, Clause 1 of this section.

4. Sublingual drugs, oral lozenges and drugs in modified release dosage forms are not considered to not require *in vivo* bioequivalence testing based on the biological classification system. Pharmacy.

5. Criteria for evaluating a pharmaceutical substance with good solubility and good permeability properties are specified in section III. Pharmaceutical substances - Appendix III. There is no requirement to perform *in vivo* equivalence testing based on the biopharmaceutical classification system - Current version of Guidelines for conducting ASEAN bioequivalence studies .

6. How to evaluate the dissolution properties of the drug under consideration and establish the solubility equivalence between the drug under consideration and the reference drug specified in section IV. Finished drugs are included in Appendix III. No requirement to perform *in vivo* equivalence testing based on the biopharmaceutical classification system - Current version of ASEAN Bioequivalence Research Guidelines .

IV. The drug under consideration is produced at a manufacturing location other than the manufacturing location of the reagent in the bioequivalence study:

1. This difference in production location is due to:

- There is a change in the manufacturer of the drug from the drug owner's manufacturer to a new manufacturer under contract with the drug owner or a change from one contract manufacturer to a contract manufacturer other of the drug owner, or

- There are variations between different production locations of the same manufacturer.

2. For drugs manufactured abroad: Both the drug manufactured at the old manufacturing site and the drug under consideration must be approved by one of the drug regulatory agencies under the Strict Drug Regulatory Authority (SRA) group. for circulation in the host country.

3. The drug under consideration must be similar to the drug produced at the old location in terms of:

- Preparation formula;

- Pharmaceutical substance quality standards, including quality characteristics of the pharmaceutical substance known to affect the bioavailability of the finished drug;

- Quality standards of excipients;

- Drug production process and standard operating procedures;

- Type of equipment used in drug production;

- Environmental conditions during drug production;

- Quality standards for finished drugs.

4. The dissolution diagram of the drug under consideration must be similar to the dissolution diagram of the drug produced at the old production site. How to establish the similarity of the dissolution diagram between the drug under consideration and the drug produced at the old production site specified in Appendix I. Solubility test and similarity of dissolution diagrams - Directions Guide to implementing ASEAN bioequivalence research .

5. In addition to the above conditions, drugs in modified release dosage forms must establish *in vivo- in vitro correlation.*

6. Exemption from conditions 4 and 5 in cases where the difference in production location is only related to one or several stages including primary packaging without dosing of the drug (for example, primary packaging of dosage form tablets, capsules), quality control, batch release and secondary packaging.

Appendix III

SPECIFIC REQUIREMENTS IN REPORTING BIOEQUIVALENCE STUDY DATA ACCORDING TO DRUG RELEASE CHARACTERISTICS AND ROUTE OF DRUG ADMINISTRATION

(Issued together with Circular No. 07/2022/TT-BYT dated September 5, 2022 of the Ministry of Health)

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I. Drug *in* immediate release dosage form

1. Reporting bioequivalence study data must be in accordance with the current version of the ASEAN Guideline for the conduct of bioequivalence studies or equivalent technical guidelines. other EMA or US-FDA.

2. For oral medications:

2.1. If the information in the Summary of Product Characteristics of the reference drug clearly indicates a recommendation to take the drug only in an empty state or does not clearly indicate whether to take the drug in a fasted or full state, data reporting is required. Research on bioequivalence when using the drug in a fasted state.

2.2. If the information in the Summary of Product Characteristics of the reference drug has clear instructions recommending only taking the drug in a full state, request to report bioequivalence study data when taking the drug in a full state.

2.3. In case the drug has special preparation properties such as solid dispersion system, microemulsion, if the information in the Summary of Product Characteristics of the reference drug does not recommend taking the drug in an empty or full state (with The drug can be taken both on an empty stomach and on a full stomach), requiring reporting of bioequivalence study data when using the drug on both an empty stomach and a full stomach.

3. For drugs that disperse/dissolve in the oral cavity:

3.1. In case the drug under consideration is equivalent in preparation to the reference drug:

a) When the reference drug can be used both with and without water, it is required to report bioequivalence test data between the test drug without water and the control drug without water. water (a drug use condition with a greater risk of not achieving bioequivalence).

b) When the reference drug is only used in one of two ways (with water or without water), it is required to report research data and bioequivalence research data between the reagent used according to the method of use or other methods. Uses registered with the reference drug are used in the same way as the reference drug (The drug being considered for registration is accepted with more uses than the reference drug on the condition that it can be proven that the drug under consideration is bioequivalent to the drug). control when used according to registered uses).

3.2. In case the drug under consideration is intended to replace a control drug in conventional oral immediate-release form (the drug under consideration is a pharmaceutical substitute of the control drug):

Requirement to report bioequivalence study data between the reagent used both with and without water and the control drug used with water or to report bioequivalence study data Study between reagents not used with water and control drugs used with water.

II. The drug is in a modified release dosage form

1. The drug under consideration is in a modified release dosage form designed with the aim of achieving a drug release rate similar to the reference drug:

1.1. Reporting bioequivalence trial data must be in accordance with the Council's Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms. European medicine (EMA) current version - Bridged application for modified release forms refering to a marketed modified release drugs (Abridged application for modified release forms reffering to a marketed modified release forms) form).

1.2. Other special notes include:

a) Except for drugs in enteric-coated dosage forms, for the remaining drugs in modified release dosage forms, add a report of bioequivalence test data according to multi-dose design at the conclusion. The results of bioequivalence studies using a single-dose design showed that the drug accumulates (AUC (0- ăn)/ AUC (0- ∞) ratio < 90%).

b) When the drug is in a modified release dosage form using a multi-phase release mechanism (two-phase release, pulsatile release): The bioequivalence test data report must demonstrate that the reagent is equivalent. biological with control drug in all phases.

c) When the drug is in a modified release dosage form for oral use: The bioequivalence study data report must demonstrate that the drug tested is bioequivalent to the control drug even when using these drugs in the following conditions: hungry as well as full.

d) When the drug is in a modified release dosage form and is a transdermal therapy system: In addition to reporting bioequivalence research data between the test drug and the control drug, comparative research research data must be reported. ability to adhere to the skin, local irritation, and photosensitivity between the test drug and the control drug to demonstrate that the test drug has the same or better skin adhesion ability than the control drug and is irritating. topical and sensitive to light equivalent or lower than the control drug. Refer to Appendix I. Sensitization and irritation tests for transdermal products (Appendix I. Sensitization and irritation tests for transdermal products) and Appendix II. *In vivo* skin adhesion test (Appendix II. *In vivo* skin adhesion) in the European Medicines Council Guidelines for the Pharmacokinetic and Clinical Evaluation of Modified-Release Dosage Forms for the Design and Conduct of Studies this comparison.

2. The drug under consideration is a drug in a modified release dosage form with a different drug release rate than the control drug:

- Because it is impossible to establish bioequivalence between the drug under consideration and the reference drug due to differences in drug release rates, instead of reporting bioequivalence test data, a report is required. Report research data on the pharmacokinetics of the drug under consideration, accompanied by a report on research data comparing the safety and clinical effectiveness between the drug under consideration and the control drug prepared in release form. right.

- Reports on research data on pharmacokinetic studies of the drug under consideration and reports on research data comparing the safety and clinical effectiveness between the drug under consideration and the control drug prepared in the form of Immediate release must be in accordance with the Guidelines for the pharmacokinetic and clinical evaluation of modified-release dosage forms of the European Medicines Council current version - Section Registration of modified-release drugs with a pharmaceutical release rate Application for modified release formulation of a drug that is authorized in a formulation with a different release rate.

Appendix IV

GENERAL REQUIREMENTS FOR REPORTING SOLUTION EQUIVALENCE TEST RESEARCH DATA

(Issued together with Circular No. 07/2022/TT-BYT dated September 5, 2022 of the Ministry of Health)

1. The solubility equivalence test data report must demonstrate the similarity of the solubility diagram between the test drug and the reference drug under specified test conditions in at least 03 dissolution environments including pH 1.2; pH 4.5 and pH 6.8. In case of not providing enough test data in all three of these 03 dissolution environments or providing test data in dissolution environments with different pH , there must be explanation about the appropriateness of removing the dissolution medium. dissolve or use a dissolution medium with a different pH in the test.

2. Components of a solubility equivalence test data report include:

a) Test outline;

b) Report on research data and test results, including:

- Information about test samples, testing conditions, testing methods, testing time and place of implementation.

- Data tables,

- Solubility charts,

- Statistical analysis,

- Discuss the results.

c) Report on research data to validate the analytical process used in testing (attached with original monitoring data representing the appraisal results).

Appendix V

REGULATIONS ON PRODUCTION BATCH SIZE AT EXPERIMENTAL SCALE

(Issued together with Circular No. 07/2022/TT-BYT dated September 5, 2022 of the Ministry of Health)

The batch size produced on a trial scale, also known as the pilot batch size , is specifically determined as follows:

1. Drugs that are immediate-release tablets/capsules, modified-release tablets/capsules: Minimum 1/10 of the registered production lot size or 100,000 dosage units, whichever is greater. In case the registered production batch size is less than 100,000 dose units, the production batch size at trial scale must be equal to the registered production batch size.

2. Powders, solutions, suspensions: At least 1/10 of the largest registered production lot size.

3. Injectable drugs including solutions, lyophilized powder/powder mixed with injection solution, suspension, emulsion: At least 1/10 of the largest registered production batch size or 50 liters (for liquid drugs with a volume of in 01 smallest packaging unit greater than 2ml) and 30 liters (for liquid drugs with volume in 01 smallest packaging unit equal to or less than 2ml), whichever value is greater. In case of registering multiple packaging specifications with different volumes in 01 different packaging unit, choose at least 1/10 of the largest registered production batch size or 50 liters, whichever is greater.

4. Transdermal therapy system: Minimum 1/10 of the registered production batch size or 25,000 units, whichever is greater.

Appendix VI

REFERENCE TECHNICAL GUIDELINES

(Issued together with Circular No. 07/2022/TT-BYT dated September 5, 2022 of the Ministry of Health)

1. ASEAN Guideline for the conduct of bioequivalence studies - 2015 version (ASEAN Guideline for the conduct of bioequivalence studies).

2. ASEAN Variation Guideline for Pharmaceutical Products - 2014 .

3. Guidance on the layout and content of clinical trial research data reports (Structure and Content of Clinical Study Reports- ICH E3 Guideline, CPMP/ICH/137/95)

4. General considerations for clinical trials (General Considerations for Clinical Trials- ICH Topic E8, CPMP/ICH/291/95).

5. Guideline for Good Clinical Practice (ICH E6 (RI), CPMP/ICH/135/95).

6. Statistical principles for clinical trials (Statistical Principles for Clinical Trials- ICH E9, CPMP/ICH/363/96).

7. Guidance on validating biological fluid analysis procedures (Guideline on Bioanalytical Method Validation- EMEA/CHPM/EWP/ 192217/2009).

8. Guideline on the Pharmacokinetic and Clinical Evaluation of Modified Release Dosage Forms (EMA/CPMP/EWP/280/96 Corrl).

9. Regulations on registration requirements to establish interchangeability of multisource pharmaceutical products (Multisource (generic) pharmaceutical products: Guidelines on registration requirements to establish interchangeability) -WHO Technical Reports Series, No. 992, Annex 7 (2015).

10. USFDA: Product-Specific Guidances for Generic Drug Development

11. USFDA: Guidance for Industry: Food-Effect Bioavailability and Fed Bioequivalence Studies (Guidance for Industry: Food-Effect Bioavailability and Fed Bioequivalence Studies).

12. USFDA: Guidance for industry: Statistical Approaches to Establishing Bioequivalence (Guidance for industry: Statistical Approaches to Establishing Bioequivalence).

13. USFDA: Guidance for Businesses: Batch Size Increases and Post-Approval Changes for Solid Immediate-Release Oral Drugs - Documents to Be Submitted on Chemistry, Manufacturing and Control, and Solubility Testing *in vitro* dissolution and bioequivalence testing (SUPAC-IR).

14. USFDA: Guidance for businesses: Batch size increases and post-approval changes for solid modified-release oral medications - Documents to be submitted on chemistry, manufacturing and control, and testing *in vitro* dissolution and bioequivalence testing (SUPAC-MR).

15. MA: Guideline for assessing bioequivalence (Guideline thanks to the investigation of bioequivalence (European Medicines Agency, London, 20 January 2010, CPMP/EWWP/QWP/1401/98 Rev 1).

16. EMA classification guidelines for minor changes type IA, minor changes type IB and major changes type II.

17. ICH HARMONISED GUIDELINE: Test exemption instructions based on the pharmacological classification system (BIOPHARMACEUTICS CLASSIFICATION SYSTEM-BASED BIOWAIVERS, Topic M9, 2019)

(*) The latest versions of the above instructions will be automatically updated to replace the current version mentioned in this appendix.

Appendix

VII FORMS U

(Issued together with Circular No. 07 /2022/TT-BYT dated September 5 , 2022 of the Ministry of Health)

FORM 01/BE

COMMITMENT ON SIMILARITY BETWEEN REGISTERED DRUGS (*) AND REAGENT MEDICINES USED IN BIOEQUIVALENCE TESTS

To: Drug Administration - Ministry of Health (Vietnam)

We include:

Drug registration facility ....*(Full name according to establishment license)*

Address at.... (*Full address according to establishment license).*

And the drug manufacturer..... *(Full name according to legal documents submitted with the application)*

Address at..... *(Full address according to legal documents submitted with the application)*

Same commitment to reagents in bioequivalence test/solubility equivalence test number ...*(research code/test code)* performed at ....*(full name and address of facility where the research/test was conducted)* during the period from date....month...year.... to date....month...year...is appropriate to represent The registered drug/drug proposed to be declared is a drug with proven bioequivalence with the name ....*(drug name/dosage form/content of drug),* with the following specific information:

Comparative content	**Same (1)**	**Various (1)**
- Drug production location		
- Preparation formula for 01 dose unit includes:		
Ingredient		
Amount of ingredients		
Quality standards of ingredients		
- Drug manufacturing process, including equipment used in production.		
- Production lot size		

Table detailing the differences between trial drugs used in research and drugs being considered for registration/ drugs proposed to be declared as drugs with proven bioequivalence (2)

Content varies	Reagents used in research	Registered drugs/Drugs proposed to be announced are drugs with proven bioequivalence	Attached documents (3)
Drug manufacturing location			
The preparation formula for 01 dose unit includes: - Ingredient - Amount of ingredients - Quality standards of ingredients			
Drug manufacturing process (including equipment used in production)			
Production lot size (4)			

(1) Check "X" in the appropriate content

(2) Applicable when there is a difference between two drugs

(3) List attached documents proving that the differences between the reagents used in research and the registered drug do not affect the representativeness of the registered drug.

(4) Documents are not required when the batch size of the reagent used in the in vivo bioequivalence test compared to the batch size of the drug under consideration meets the regulations in Appendix V of this Circular.

(*) In the case of applying Point d, Clause 5, Article 7 of this Circular, the registered drug is replaced by a drug with a certificate of pharmaceutical product (CPP).

We take full responsibility for the truthfulness of the information provided above.

Legal representative of the drug registration facility

(Sign directly, clearly state title, full name and seal)

Day month Year ….

Legal representative of the drug manufacturing facility

(Sign directly, clearly state title, full name and seal)

FORM 02/BE

APPLICATION NOT TO PERFORM BIOEQUIVALENCE TEST

A. DETAILS OF REGISTRATION AND PRODUCTION FACILITIES

Registration facility: Address:	**Production facilities [1] :** Address:

B. CONTENT:

It is recommended to apply regulations that do not require bioequivalence testing *(in vivo)* in the following cases: *(Check the corresponding box)*

a) The drug does not require bioequivalence testing *(in vivo)* for proportional formulations	
b) The drug does not require bioequivalence testing *(in vivo)* based on a polar approach	
c) The drug does not require bioequivalence testing *(in vivo)* based on the biopharmaceutical classification system	
d) The drug does not require bioequivalence testing *(in vivo)* when the drug under consideration is produced at a production location other than the production location of the reagent in the bioequivalence test *(in vivo).*	

To submit an application for a drug registration certificate/a request for declaration of a drug that has been granted a circulation registration certificate as a drug with proven bioequivalence to the drug:

- Drug name: ... .*(trade name of the drug)*
- Circulation registration number: *(if the drug has been granted a circulation registration certificate)*
- Dosage forms:
- Pharmaceutical ingredients/pharmaceutical content in 01 dose unit:

C. INFORMATION ABOUT REAGENTS IN BIOeQUIVALENCE TESTING (*When requesting to apply cases a, b, d)*

- Drug name: *(trade name of the drug)*
- Number of circulation registration certificate [2] :
- Manufacturer *(list the manufacturers involved in the production process)*

Name	Address	Role

D. LIST OF ATTACHED DOCUMENTS:

(attached with a copy of the Drug Administration's official letter agreeing to change for drugs that have been granted circulation registration)

D. COMMIT:

We, the registration facility and the drug manufacturer, commit to check, sign and stamp the relevant parts of the documents submitted with this application and ensure the truthfulness of the submitted documents. . If there is any falsification, we take full responsibility and will be punished according to the law.

Legal representative of the drug registration facility

Date …. year …

Legal representative of the drug manufacturing facility

(Sign directly, clearly state title, full name and seal)

(Sign directly, clearly state title, full name and seal)

(1): Record the name of the manufacturer/manufacturers involved in the production process of the dosage form for non-sterile drugs; manufacturer of dosage forms and secondary packaging of sterile drugs.

(2): Applicable in cases where the reagent used in in vivo bioequivalence testing has been announced as a drug with proven bioequivalence.

FORM U 03 / BE

COMMITMENT ABOUT THE SOURCE AND ORIGIN OF COMPARATIVE MEDICINES USED IN BIOEQUIVALENCE TESTS

To: Drug Administration - Ministry of Health (Vietnam)

We include:

Drug registration facility... .*(Full name according to establishment license)*

Address at.... *(Full address according to establishment license).*

And the drug manufacturer …… *(Full name according to legal documents submitted with the application)*

Address at. *(Full address according to legal documents submitted with the application)*

We jointly commit to the authenticity of the following information related to the reference drug used in the bioequivalence test/numerical solubility equivalence test *...(research code/test code)* performed. at *....(name and full address of the facility where the research/test was conducted)* during the period from date....month....year…. to date....month...year...:

Content	Information
Drug name	
Production facility (production address)	
Buy locally	
Production batch number	
Due date	
Attached supporting documents (if any)	

Attached documents (if any) (*) :..... .....

(*) Required for research conducted before the effective date of this Circular.

We, the registration facility and the manufacturing facility commit to:

The above control drug was transported and stored in accordance with the drug's storage conditions stated on the label from the time of purchase to the time the study began.

We take full responsibility for the truthfulness of the information provided above. If there is any falsification, we take full responsibility and will be punished according to the law

Legal representative of the drug registration facility

Date… . year …..

Legal representative of the drug manufacturing facility

(Sign directly, clearly state title, full name and seal)

(Sign directly, clearly state title, full name and seal)