

Considerations for Safety Assurance Measures in Bioequivalence Studies
in Healthy Adults for the Development of Generic Drugs
(Early Consideration)

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Pharmaceuticals and Medical Devices Agency (PMDA)

Office of Generic Drugs

1. Introduction

As a recent trend in the development of generic drugs in Japan, there has been an increase in the development of products associated with risks such as psychiatric and neurological symptoms, including suicidal ideation and suicide attempts, interstitial lung disease, and bone marrow depression, for which appropriate measures to ensure the safety of study participants are required when conducting clinical studies. Accordingly, the Office of Generic Drugs of the PMDA has received questions on safety management systems for bioequivalence (BE) studies in healthy adults through generic drug BE consultations (Scientific Advice).

For clinical trials of an active substance administered to humans for the first time, the “Guidance for Establishing Safety in First-in-Human Studies during Drug Development” (attachment to Notification PFSB/ELD No. 0402-1 dated April 2, 2012 from the Director of Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW; partially amended by Notification PSEHB/PED No. 1225-1 dated December 25, 2019) and the related Questions and Answers (Q&A) (Administrative Notice from Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW dated April 2, 2012) provide guidance on ensuring the safety of study participants. In contrast, no corresponding guidance has been established for the development of generic drugs. Therefore, although safety management systems for human BE studies should be appropriately established under the responsibility of the sponsor, study site, and principal investigator with reference to such guidance, this document has been prepared to present a general approach based on discussions in BE consultations conducted to date, with the aim of contributing to the planning of human BE studies and the protection of study participants.

The perspectives presented in this document are based on currently available knowledge regarding BE studies in healthy adult participants and may be subject to change as new findings emerge in the future. The approach described in this document may also be useful, as appropriate, when conducting BE studies in patients. Furthermore, as this document presents only general considerations, safety management systems for products that require special safety measures — such

* This English version of the Japanese Early consideration is provided for reference purposes only. In the event of any inconsistency between the Japanese original and the English translation, the former shall prevail.

as products used only under the control of a specific medical institution or physician — should be considered on a case-by-case basis according to the risks of the product.

This document does not preclude sponsors or other relevant parties from seeking BE consultations on safety management systems for human BE studies of products with particular safety concerns. In addition, because the optimal safety management system may vary depending on the risks of each product, approaches that differ from those described in this document may continue to be discussed through BE consultations.

2. General Matters Regarding the Safety Management System

<Basic Matters>

- When considering the safety management system, establish a system that reflects the latest safety information, precautions, and instructions for the innovator drug, with reference to the electronic package insert of the innovator drug, Risk Management Plans, various information materials, and the Manuals for Management of Individual Serious Adverse Drug Reactions, among others.
- When judging the eligibility of study participants, it is desirable to include objective indicators such as clinical laboratory values. As a rule, the reference values used to judge eligibility should be set within ranges regarded as medically normal.
- In examining the appropriateness of the safety management system (including the implementation structure, the necessity and frequency of test items, and the appropriateness of decision reference values), it is also useful to seek the opinions of experts in the relevant disease area, including with respect to feasibility and clinical significance.
- To ensure that the established safety management system is implemented appropriately, the prescribed content and response procedures should be described in advance in the clinical trial protocol or related documents.

<Study Design>

- Inclusion/Exclusion Criteria
 - In addition to the general criteria used in human BE studies in healthy adults (age, sex, body weight, eligibility based on screening test results, presence or absence of consent to voluntary study participation, history of concomitant medication use, history of intake of foods or supplements that may affect the pharmacokinetics or safety of the investigational product, blood sampling history, etc.), the sponsor should establish criteria that can appropriately exclude study participants with a history of adverse reactions or a risk of developing adverse reactions, based on the safety information of the innovator drug. In particular, where the innovator drug specifies the target population or dosage and administration according to laboratory values because of concern regarding health damages from adverse reactions, the reference values at enrollment should be set with a sufficient

safety margin so that harm to participants can be avoided to the extent possible even if such adverse reactions occur.

- Dosing Criteria
 - The investigator should, as a basic principle, confirm from pre-dose examinations and other test results that the participant's health status and eligibility remain appropriate, and then determine whether the investigational product may be administered. Specific criteria for confirming health status and eligibility should be established based on the safety information of the innovator drug. In crossover studies, even when an adverse event that occurred in a preceding period is mild and administration in the next period is permitted after recovery of the participant's health status has been confirmed, the participant's health status and eligibility should be reconfirmed at the time of dosing in the next period. In such cases, the criteria should be within ranges regarded as medically normal.
- Discontinuation Criteria
 - In addition to the general discontinuation criteria used in human BE studies in healthy adults (for example, where the participant wishes to withdraw from the study, where the principal investigator or other responsible personnel determine that discontinuation is necessary, or where the inclusion/exclusion criteria are no longer met), criteria should be established, based on the safety information of the innovator drug, to appropriately identify participants who are unable to continue receiving the investigational product due to adverse events.
- Discharge Criteria
 - The investigator should, as a basic principle, confirm from observations and test results obtained at discharge that there are no concerns regarding the participant's health status, and then determine whether discharge is permissible. Specific criteria for confirming the participant's health status should be established based on the safety information of the innovator drug. This confirmation should demonstrate that there are no safety concerns after the participant leaves the study management on the study site and that, as a rule, the participant has recovered to the health status before administration of the investigational product. In order to ensure participant safety, whether discharge is permissible should, as a rule, be determined after confirming all test results obtained at discharge during the relevant dosing period. However, if there are unavoidable test items for which results cannot be obtained by the time of the discharge decision, the acceptability of discharge without sufficient results should be examined to ensure the safety of participants. Also, the sponsor should specify the test items to be confirmed at discharge, the test items to be confirmed later, and the response to any abnormalities identified in the items confirmed later.
- Washout Period
 - In human BE studies, a washout period of at least five elimination half-lives of the unchanged active substance or active metabolite to be measured is generally established to

prevent carryover effects. In addition, in order to ensure participant safety, the washout period should be sufficiently long to allow participants' condition, including laboratory values, to return approximately to the healthy baseline state.

- Follow-up Observation
 - Select appropriate follow-up observation items and confirmation methods so that participants' health status after discharge can be confirmed and adverse reactions can be promptly detected if they occur. The follow-up observation period should be established with reference to the periods during which adverse reactions frequently occur with the innovator drug or drugs with a similar mechanism of action. Where detailed confirmation of participants' health status after discharge is necessary, such as when delayed adverse reactions may occur, participants' health status should be confirmed by appropriate methods during the follow-up observation period, such as tests and examinations at visits or contact by telephone.
- Provisions Related to Contraception
 - Based on the developmental toxicity and genotoxicity risks of the innovator drug, establish an appropriate contraception period with reference to the “Guidance on the Necessity of Contraception Related to Drug Administration” (joint Notification PSEHB/PED No. 0216-1 and PSEHB/SD No. 0216-1 dated February 16, 2023 from the Director of Pharmaceutical Evaluation Division and the Director of Pharmaceutical Safety Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW). The relevant provisions should be adequately explained to participants to ensure reliable compliance with the contraception requirements.

<Study Operational Structure>

- When selecting the principal investigator and subinvestigators, consider the following:
 - Where physician requirements (such as having sufficient knowledge of the drug and sufficient knowledge/experience in treating the indicated disease) are stipulated in the electronic package insert of the innovator drug for its use, the sponsor should establish a system involving physicians who meet those requirements.
 - The sponsor should ensure the involvement of physicians who can respond appropriately if adverse events or signs that could lead to serious outcomes are observed in participants (for example, giving instructions for appropriate response and conducting in-person examinations of the participant in response to contact from the study site).
 - Where specialized knowledge/techniques are required for the diagnosis and treatment of adverse reactions reported for the innovator drug, the sponsor should establish a system in which physicians meeting such requirements are involved in important decisions and procedures concerning the diagnosis and treatment of adverse reactions. When involving physicians who meet such requirements, seek the opinions of the physicians and

specifically stipulate the timing and manner of their involvement in the clinical trial protocol or related documents.

- As a system for responding to adverse events and emergencies, the sponsor should establish procedures for responding to contact from participants and a coordination structure inside the study site, including medical staff responsible for care and decision-making, information to be shared, and the system for contacting emergency transport destinations. These procedures should be specified as clearly as possible, using flowcharts or similar tools, so that prompt coordination with emergency transport destinations is possible. Study information should be shared in advance with the study site and emergency transport destinations by the start of the study.
- In order to respond promptly if a participant's condition suddenly changes, the sponsor should establish a system that can respond even during nighttime hours of the confinement period, as well as a system that can receive contact from participants 24 hours a day for an appropriate period after discharge; describe the means of contact in the informed consent document and explain its content to participants at the time of obtaining consent and at discharge.
- For adverse reactions for which particular precautions are given in the electronic package insert of the innovator drug, the sponsor should ask medical staff on the study site to explain the symptoms and signs to participants at the time of informed consent and before discharge, and request that participants immediately contact the study site if such symptoms or signs are observed. In addition, stipulate confirmation items as specifically as possible so that the presence or absence of subjective and objective symptoms can be actively confirmed by the study site — not only through self-report by participants — for example at the timing of physician examinations.
- Where the onset of adverse reactions is anticipated even after participants' discharge, the sponsor should establish not only a system enabling participants to make contact so that even minor changes can be reported by participants, but also a system enabling proactive safety management, such as having the study site contact participants regularly during the period in which such adverse reactions frequently occur.

3. Perspective on Safety Management for Individual Adverse Reactions

In addition to the general matters described in Section 2, where precautions regarding the individual adverse reactions presented in this section are included in the electronic package insert of the innovator drug, the following should also be taken into account. Additional adverse reactions for which specific safety management considerations are presented may be added in future.

3.1 Bone Marrow Suppression or Cytopenias

<Observation/Test Items and Timing of Testing>

- Physician examination
 - At an appropriate frequency (screening, before administration of the investigational product

(at admission for each period or before dosing), at discharge, follow-up observation, etc.), subjective symptoms (fever, bleeding tendency, symptoms of anemia, etc.) and infection risk should be confirmed during the study period.

- Hematological tests (white blood cell count, white blood cell differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils), red blood cell count, hemoglobin, hematocrit, platelet count)
 - The timing of testing should be considered so that signs of bone marrow suppression can be detected early.

<Study Design>

- The washout period and follow-up observation period should be established by taking into account the duration of the drug's bone marrow suppression or cytopenia effect and the period necessary for recovery to the healthy baseline state.

3.2 Thromboembolism

<Observation/Test Items and Timing of Testing>

- Physician examination
 - At an appropriate frequency (screening, before administration of the investigational product (at admission for each period or before dosing), a time point up to discharge including around t_{max} , at discharge, follow-up observation, etc.), subjective symptoms during the study period (limb weakness/paralysis, sensory disturbances (diplopia, blurred vision, enlargement of blind spots), dysarthria, vomiting/nausea, headache, chest pain, arrhythmia, heart failure symptoms, shock, sudden unilateral swelling/pain/numbness of a lower limb (rarely an upper limb), redness, heat sensation, sudden shortness of breath, dyspnea, bloody sputum/hemoptysis, loss of consciousness, sudden visual impairment, etc.¹⁾) should be confirmed. If these symptoms are observed, consider additional clinical tests (including imaging examinations).
- Coagulation/fibrinolysis biomarkers (D-dimer, etc.)
 - The timing of testing should be considered so that the tendency toward thrombus formation can be detected early. Regarding tests conducted at discharge, for the response where results cannot unavoidably be obtained by the time of the discharge decision, refer to “Discharge Criteria” under <Study Design> in Section 2.

<Study Operational Structure>

- To enable participants to report symptoms or seek consultation even outside physician examinations, subjective symptoms of thromboembolism should be described in the informed consent document and explained to participants.

3.3 QT Prolongation

<Observation/Test Items and Timing of Testing>

- Physician examination
 - At an appropriate frequency (screening, before administration of the investigational product (at admission for each period or before dosing), at discharge, follow-up observation, etc.), subjective symptoms suggestive of arrhythmia during the study period (palpitations, chest pain, chest discomfort, dizziness, presyncopal darkening of vision, syncope, etc.) should be confirmed.
- 12-lead electrocardiogram examination
 - The sponsor should consider the timing of testing so that QT prolongation can be detected early. For drugs in which QT prolongation may occur as blood drug concentrations increase, testing at least before administration of the investigational product and at discharge, and additionally around the t_{max} of each drug should be conducted, and participant safety should be confirmed at the time points with a high risk of QT prolongation. If abnormalities are observed, perform electrocardiographic monitoring, medical procedures, etc. as necessary.

<Study Design>

- For establishing the safety management system, the sponsor also should refer to “The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-antiarrhythmic Drugs” (Notification PFSB/ELD No. 1023-1 dated October 23, 2009 from the Director of Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW).

3.4 Psychiatric Symptoms

Where the electronic package insert of the innovator drug includes precautions regarding suicidal ideation, suicide attempts, or other psychiatric or central nervous system symptoms, an appropriate safety management system should be established to ensure the safety of participants, with reference to the “Publication of Investigation Results Concerning a Fatal Case in a Clinical Trial in Healthy Adults (Attachment 2): Investigation Results Report” (Notification PMDA No. 1127020 dated November 27, 2019) and the following considerations.

The “Guideline on Clinical Evaluation Methods for Antidepressants” (Notification PFSB/ELD No. 1116-1 dated November 16, 2010 from the Director of Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW) states that “the exclusion criteria for clinical studies should be specifically stipulated using symptom rating scales and the like, and the enrollment of patients at high risk of suicide should be avoided,” and cites the Columbia Suicide Severity Rating Scale (C-SSRS) as a scale for assessing suicide risk. Because the C-SSRS is an indicator used to assess the severity of suicide risk and monitor its progression, it is recommended, in order to ensure participant safety, to establish a study operational structure that includes C-SSRS assessment. In addition, psychiatric and central nervous system symptoms other than suicidal ideation and suicide attempts, such as depressive symptoms, should be confirmed by appropriate methods at the time of participant enrollment, when determining whether discharge is permissible, and at other appropriate

times.

<Criteria for the Study Site and for the Principal Investigator or Subinvestigators>

- The sponsor should select study sites, principal investigators, and subinvestigators capable of appropriately implementing the safety management system described below. For clinical trials of drugs associated with a risk of psychiatric symptoms, including suicidal ideation and suicide attempts, consider the participation, as a principal investigator or subinvestigator, of a physician with substantial knowledge and clinical experience in psychiatry who can respond appropriately to adverse events; for example, a physician meeting both of the following requirements (psychiatric specialist, etc.):
 - A Designated Mental Health Physician, or a Certified Psychiatrist of the Japanese Board of Psychiatry; and
 - A physician who routinely provides care to patients with psychiatric disorders.

<Assessment of Suicide-Related Events>

- To appropriately detect signs of suicide-related events, including changes in a participant's condition before and after administration of the investigational product, C-SSRS assessment should be conducted and the risk of suicide-related events should be evaluated comprehensively through examination by a psychiatric specialist, etc.
- C-SSRS assessment should be conducted at least before and after administration of the investigational product (at admission or before dosing, and at discharge, with follow-up observation assessment as necessary) in order to detect any effects of investigational product administration.
- Regarding the C-SSRS rater, because the purpose of the assessment is to appropriately detect the risk of suicide-related events in participants, it is considered important that a psychiatric specialist, etc. trained in C-SSRS assessment conduct the assessment while directly confirming the participant's condition. Where, unavoidably, a physician other than a psychiatric specialist, etc. conducts the C-SSRS assessment, the suitability of the rater should be ensured by taking into account at least the following points, so that physicians who are not psychiatric specialists, etc. can also appropriately assess the participant's condition: **
 - Having received C-SSRS training and obtained a Certificate as a C-SSRS rater; and
 - Having received education/guidance from a psychiatric specialist, etc. (sharing questioning methods and points of caution that allow appropriate elicitation of participants' suicidal ideation and the like, and knowledge of psychiatric and non-psychiatric disorders with high suicide risk, and guidance for capturing signs of suicide risk, etc.) and having been judged by a psychiatric specialist, etc. to be suitable as a C-SSRS rater.
 - (Furthermore, it is desirable to have experience conducting clinical trials of central nervous system drugs.)

** Where a clinical trial is conducted at a specialized psychiatric facility, or in other cases where appropriate monitoring of psychiatric symptoms is possible including by other staff engaged in the trial, it is also possible for an appropriate healthcare professional other than a physician to serve as the rater.

- Based on the results of examination by a psychiatric specialist, etc. and of C-SSRS assessment by a physician who is qualified as a rater, establish a system in which a psychiatric specialist, etc. is involved in judging whether the participant may be enrolled in the study, whether the investigational product may be administered, whether discharge is permissible, and whether the study should be discontinued.

<Study Operational Structure>

- To enable participants, their family members, or others to proactively consult the trial physician or other study staff regarding participants' symptoms, examples of symptoms and signs should be described in the informed consent document and explained to participants.
- During the confinement period, a system in which the study site staff actively confirm the participants' condition, including proactive outreach by the trial physician and other study staff, should be established. In addition, a survey on the status of onset of psychiatric symptoms should be conducted at an appropriate time after discharge.
- In order to establish a system that enables prompt contact with the participant or their family, etc. as an emergency contact when a psychiatric or neurological adverse event occurs, the contact information of family members, etc. should be ascertained as far as possible, in addition to the participant's own contact information at the time of screening.
- A system should be established to enable study participants who report psychiatric symptoms or similar complaints to promptly receive evaluation by a psychiatric specialist, etc., and appropriate treatment or other necessary measures, as appropriate.

3.5 Interstitial Lung Disease

<Observation/Test Items and Timing of Testing>

- Physician examination
 - At an appropriate frequency (screening, before administration of the investigational product (at admission for each period or before dosing), a time point up to discharge including around $t_{\max}$, at discharge, follow-up observation, etc.), auscultation should be performed to confirm the presence or absence of fine crackles, and respiratory symptoms during the study period (cough, especially dry cough; shortness of breath; fever; etc.²⁾) should be confirmed.
- SpO₂ (percutaneous capillary oxygen saturation)
 - SpO₂ should be measured in addition to physician examination in order to monitor oxygenation.
- Imaging examinations
 - Taking into account the risk of radiation exposure, the timing of testing should be considered to enable early detection of interstitial lung disease if it occurs. In order to ensure participant safety, it is desirable to conduct imaging examinations at least before administration of the investigational product and at discharge from the final dosing period, and to confirm that there are no abnormalities. Depending on the periods during which

interstitial lung disease frequently occurs and the level of risk, consideration should also be given to conducting imaging examinations at discharge from each period and during follow-up observation.

- Where interstitial lung disease is suspected based on respiratory symptoms such as cough or shortness of breath, or where the electronic package insert of the innovator drug advises conducting a chest CT examination, conducting a chest CT examination should be considered in addition to a chest X-ray examination, depending on the situation.
- Pulmonary fibrosis biomarkers (SP-A, SP-D, KL-6) and CRP
 - The timing of testing should be considered to enable early detection of interstitial lung disease if it occurs. In addition, to detect the onset or signs of interstitial lung disease with high sensitivity, it is desirable to measure multiple types of pulmonary fibrosis biomarkers. Regarding tests conducted at discharge, if results cannot unavoidably be obtained by the time of the discharge decision, refer to “Discharge Criteria” under <Study Design> in Section 2 for the appropriate response.

4. References

- 1) Manual for Handling Serious Adverse Drug Reactions by Disease — Thrombosis (thromboembolism, embolism, infarction) (June 2007 (revised April 2021)).
- 2) Manual for Handling Serious Adverse Drug Reactions by Disease — Interstitial Pneumonia (pneumonitis, alveolitis, pulmonary fibrosis) (November 2006 (revised February 2026)).