

Administrative Notice

July 19, 2021

To: Pharmaceutical Affairs Section,
Prefectural Health Department (Bureau)

Pharmaceutical Evaluation Division,
Pharmaceutical Safety and Environmental Health Bureau,
Ministry of Health, Labour and Welfare

Basic Concept on Bioequivalence Evaluation for Addition of Formulations with
Different Dosage Forms in Ethical Kampo Formulations

"Basic Concept on Bioequivalence Evaluation for Addition of Formulations with Different Dosage Forms in Ethical Kampo Formulations" has been compiled in the "Research on Application Guidelines for Approval of New Kampo Formulations" within the framework of "Research on International Harmonization and Reorganization of Approval-Related Standards, etc. for Quality Assurance of Kampo Formulations and Crude Drug Preparations" (Chief Researcher: Takashi Hakamatsuka, Director of Division of Pharmacognosy, Phytochemistry and Narcotics, National Institute of Health Sciences. FYs 2018-2020 Medical Research and Development Grants by the Japan Agency for Medical Research and Development for Research on Regulatory Science of Pharmaceuticals and Medical Devices), as shown in the Attachment. We ask you to inform relevant parties under your administration about this basic concept.

Attachment

Basic Concept on Bioequivalence Evaluation for Addition of Formulations with Different Dosage Forms in Ethical Kampo Formulations

This basic concept provides a basis for the tests required for bioequivalence evaluation in the case where a formulation with a different dosage form is added to the approved ethical Kampo formulation (hereinafter referred to as "additional dosage form"). It is noted that the formulation with an additional dosage form uses the same extracts of Kampo formulations as that of the approved Kampo formulation.

Kampo formulation is a multicomponent drug containing many chemical compounds. When the extracts of Kampo formulations, i.e., intermediate products, are listed in the Japanese Pharmacopoeia (JP), three compounds are specified as marker compounds for quality specifications, in principle. For the quality specifications of the extracts of Kampo formulations that are not listed in the JP, several marker compounds for assay are also prescribed in each marketing approval document. However, these marker compounds for assay are not necessarily appropriate as an index for bioequivalence evaluation when they are greatly affected by biological reactions, such as metabolism by intestinal bacteria, absorption in the gastrointestinal tract, metabolism after absorption, or when the same compounds are contained in a meal. Under such circumstances, it will be difficult to track the blood kinetics after oral administration of the formulation. Therefore, marker compounds suitable for bioequivalence evaluation should be selected from the compounds or their metabolites of the extract, and then a series of tests should be performed to assess the equivalence. This basic concept regarding adding a different dosage form to ethical Kampo formulations is intended to provide basic logic on the following:

- Bioequivalence studies between the reference formulation (old dosage form) and the test formulation (new dosage form) conducted in accordance with Attachment 1 "Guideline for Bioequivalence Studies of Generic Products" (PMSB/ELD Notification No. 487 dated December 22, 1997, issued by the Director of Evaluation and Licensing Division, Pharmaceuticals and Medical Safety Bureau [subsequently amended by PSEHB/PED Notification No. 0319-1 dated March 19, 2020). (The guideline is hereinafter referred to as "Generic Product Guideline."); and
- Similarity evaluation of dissolution profiles in a dissolution test performed before

bioequivalence studies, and verification of equivalence of elution patterns (hereinafter referred to as "Chromatographic Patterns") obtained by chromatography.

When adding a dosage form to an ethical Kampo formulation in accordance with this basic concept, it is advisable to consult with the regulatory authority in advance, as appropriate.

I. Formulations used for bioequivalence evaluation

The proposed formulation with an additional dosage form should use the same extracts of Kampo formulations as that of the approved formulation. Its indications should be the same as those of the approved formulation, and its dosage and administration should be within the scope of approved formulation. The approved formulation is a formulation with the dosage form already approved at the time when this basic concept was issued.

The reference formulation should be a formulation of the lot showing intermediate characteristics among 3 lots subjected to a dissolution test. If an appropriate reference formulation cannot be selected by the dissolution test due to the quality characteristics of compounds contained in the reference formulation, the lot exhibiting intermediate characteristics by an alternative physicochemical test should be used for the reference formulation.

The test formulation should be a proposed formulation with an additional dosage form manufactured using the extracts of Kampo formulations of the same manufacturing lot used for the reference formulation. It is desirable to use the formulation of the lot manufactured at a commercial scale (hereinafter referred to as "commercial-scale lot"), but it is also acceptable to use a formulation of the lot manufactured at $\geq 1/10$ scale of the commercial scale. The manufacturing method of commercial-scale lot and the lot used in a bioequivalence study should be the same, and the quality of both lots should be equivalent.

II. Marker compounds used for bioequivalence evaluation

In principle, one marker compound should be selected from the marker compounds for assay or their major metabolites, specified in the JP or in the marketing approval document. If it is difficult to evaluate the bioequivalence by the marker compounds for assay specified in the JP or the marketing approval document, another marker compound

may be selected.

III. Similarity evaluation of dissolution profiles

Prior to the bioequivalence study, a dissolution test should be performed on the reference and test formulations to evaluate the similarity of dissolution profiles of several marker compounds for assay. Furthermore, the chromatograms of the test solutions after the dissolution test should be compared to confirm the equivalence of Chromatographic Patterns.

For the dissolution test method and the judgment of similarity of dissolution profiles, refer to Sec. 3 A.V. Dissolution tests in the Generic Product Guideline. However, if the dissolution cannot be evaluated appropriately due to coning phenomenon of disintegrated products in the bottom of the vessel, the test conditions can be changed based on the Generic Product Guideline.

1. Marker compounds used for dissolution test

- 1) The marker compound evaluated in bioequivalence studies (or the parent compound, if a metabolite is being evaluated), and
 - 2)-1 Marker compounds for assay specified in the JP and the marketing approval document for Kampo products of which extracts of Kampo formulations are listed in the JP.
 - 2)-2 Marker compounds for assay specified in the marketing approval document for Kampo formulations of which extracts of Kampo formulations are not listed in the JP.

2. Test solutions

Test solutions prescribed in Sec. 3 A.V.3. Testing conditions in the Generic Product Guideline.

3. Confirmation of equivalence of Chromatographic Patterns

To confirm the equivalence of the Chromatographic Patterns, compare the comprehensive chromatograms obtained by HPLC analysis with gradient elution, etc., and confirm that the Chromatographic Patterns of reference and test formulations are practically equivalent by the following method. The equivalence of the Chromatographic Patterns should be checked with the test solutions used in the dissolution test previously performed on the marker compounds to be evaluated in the bioequivalence study.

- 1) Compare the retention time of each peak corresponding to the reference and test formulations in both chromatograms.
- 2) Evaluate the peak intensity in both chromatograms of the reference and test formulations by an appropriate method.

IV. Bioequivalence study

After confirming the similarity of dissolution profiles and the equivalence of Chromatographic Patterns in Section III. Similarity evaluation of dissolution profiles in this attachment, the bioequivalence study should be performed on the reference and test formulations according to Sec. 3 A. II. Bioequivalence studies in the Generic Product Guideline using the marker compound selected in Section II in this attachment as indicators.