Administrative Notice
November 29, 2018

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

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

Basic Principles on Bioequivalence Studies of Generic Ophthalmic dosage forms*

Basic principles on bioequivalence evaluation of generic aqueous ophthalmic solutions are presented in "Basic Principles on Bioequivalence Evaluation of Generic Aqueous Ophthalmic Solutions," Administrative Notice issued by the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare dated March 11, 2016. As provided in the attachment, a notice of "Basic Principles on Bioequivalence Evaluation of Generic Ophthalmic dosage forms" has been developed by a specific research project "Consideration about International Trends of Bioequivalence Evaluation Methods and Improvement of the Guidelines" (Researcher: Hiroyasu Ogata, Director of the Japanese Society of Generic and Biosimilar Medicines) under the project of "Research for Prescription Drug Bioequivalence Evaluation Methodology" (Chief Researcher: Ken-ichi Izutsu, Director of Division of Drugs, National Institute of Health Sciences) supported by FY2016-2018 Japan Agency for Medical Research and Development Grants (research on regulatory science of pharmaceuticals and medical devices). We ask you to inform related business operators placed under your administration of this notice.

This administrative notice supersedes the notice issued in 2016.

***This document is a literal translation of Japanese original for reference purpose only.**

(attachment)

Basic Principles on Bioequivalence Studies of Generic Ophthalmic Dosage Forms

The principles apply to development of generic ophthalmic dosage forms and are intended to discuss studies required for their bioequivalence evaluation with reference drugs. In this document, evaluation methods are discussed to assure therapeutic equivalence in view of formulation, dosage form, and attributes of each product including physicochemical characteristics, pharmacological properties, and corneal/conjunctival tissue permeability. [1)]

In addition, it is desirable to access reference documents, consult with the reviewing office in advance as appropriate, plan and conduct appropriate studies.

1. Reference and test products

The test and reference products should be the same dosage form and contain the same active ingredient at the same concentration (same strength). The reference product should be subjected to physicochemical tests (viscosity, pH, particle size, etc.) depending on the formulation characteristics, and the lot with intermediate attributes should be used as the reference product. It is recommended to use a lot manufactured at the same lot size as the full-scale production (hereinafter referred to as production lot). However, a lot manufactured at a scale of not less than 1/10 of a full-scale production also can be used. Manufacturing method of the test product and commercial products should be same and physicochemical characteristics of both products should be equivalent.

A reference product whose content or potency is as close as possible to the labelled claim should be used. Furthermore, it is preferable that the difference between the content or potency of the test product and that of the reference product be within 5% of the labelled claim.

2. Bioequivalence evaluation

(1) In principle, a clinical study should be conducted in an appropriate subject population to evaluate bioequivalence using an index of clinical effectiveness. Appropriate endpoints related to the clinical effectiveness should be selected according to the drug. The number of subject enough to evaluate equivalence statistically should be specified, and the study should be conducted. An appropriate equivalence acceptable range for each endpoint should be specified to assess equivalence of the clinical effectiveness between the test and reference products.

(2) When it is difficult to evaluate bioequivalence using an index of clinical effectiveness in a clinical study in an appropriate subject population, the clinical study should be conducted to confirm that the clinical effectiveness of the test product is similar to that of the reference product and evaluate bioequivalence by either Method A or B. Method B, however, should be chosen only if it is difficult to evaluate equivalence by Method A. As acceptance criteria, an appropriate acceptable range for each of the active ingredient and endpoint should be specified.

Method A: In an appropriate non-clinical pharmacological evaluation system with high discriminatory power for the difference in formulation characteristics between products, evaluate equivalence between the test and reference products by using the index of pharmacological effect.

Method B: Evaluate similarity of the physicochemical characteristics of the test product to that of the reference product.

The appropriate non-clinical pharmacological evaluation system with high discriminatory power for the difference in formulation characteristics between products should be a system in which a dose-response relationship can be detected at an appropriate common ratio in a range of the active ingredient concentration with that in the test product around the middle. In addition, conditions showing time-dependent (timing of ocular administration) and dose-response relationships should be investigated to justify the evaluation system.

The clinical study should be conducted to confirm that the clinical effectiveness of the test product is similar to that of the reference product. The study design and endpoints should be specified in view of the active ingredient, evaluation system, and attributes of changed excipients. In addition, sample size should be specified so that similarity of the clinical effectiveness can be adequately evaluated. For instance, similarity can be evaluated as follows: If the difference in mean value of the parameter for efficacy evaluation between the test and reference products falls within a prespecified range of the acceptance value, the test product can be judged to be similar to the reference product. The acceptance value is the clinically acceptable maximum difference and should be smaller than the observed difference in a superiority study that has demonstrated the efficacy of the active control drug.

3. If the target tissue of the active ingredient is the ocular surface only, the clinical study in humans may be replaced by pharmacological studies (*in vitro* and/or animal studies) in addition to demonstration that physicochemical characteristics of the test product are similar to those of the reference product.

4. For aqueous ophthalmic solutions in which all the ingredients and excipients are completely dissolved, neither clinical nor animal studies will be required in principle if components and amounts (concentrations) of excipients in the test product are judged to be the same as those in the reference product in view of their impacts on formulation characteristics of drug product, and both test and reference products are deemed to have similar physicochemical characteristics such as viscosity, pH, and osmolality.

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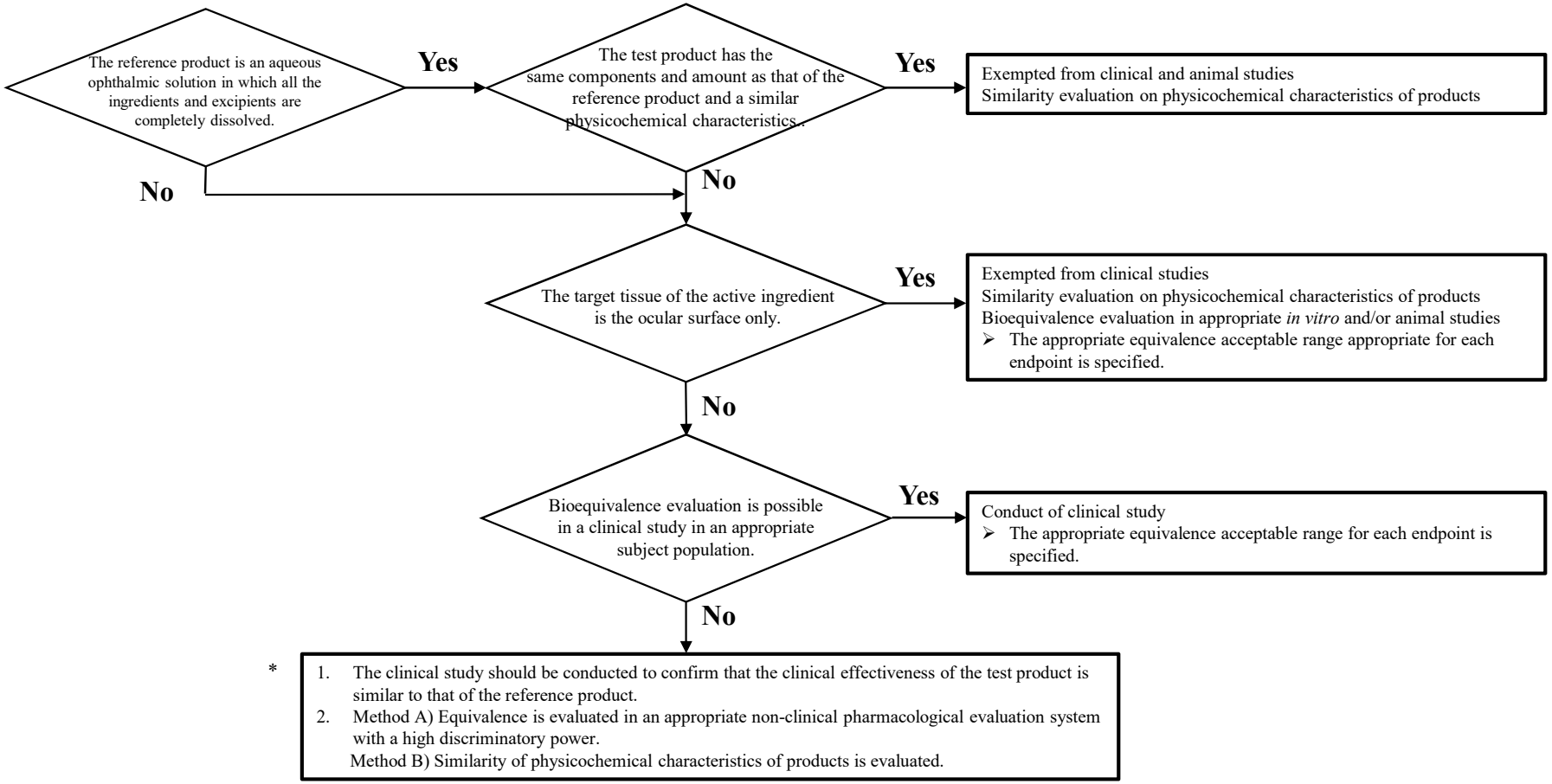
1) The basic principles may apply to bioequivalence evaluation for a partial change (formulation change) of the excipients qualitatively and quantitatively in an approved ophthalmic dosage form.

Reference documents



*: Method B may be chosen only if it is difficult to evaluate equivalence by Method A.