Administrative Notice
March 11, 2016

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 Evaluation of Generic Dry Powder Inhalers*

As provided in the attachment, a notice of "Basic Principles on Bioequivalence Evaluation of Generic Dry Powder Inhalers" has been developed by a specific research project "Research for Appropriate Bioequivalence Evaluation of Generic Drugs" (Researcher: Hiroyasu Ogata, Director of the Japanese Society of Generic and Biosimilar Medicines) under the project of "Research for Revision of Test Conditions in the Equivalence Guideline for Generic Drugs" (Chief Researcher: Chikako Yomota, Visiting Researcher, Division of Drugs, National Institute of Health Sciences) supported by FY2015 Health and Labour Sciences Research Grants (multidisciplinary research project on regulatory science for drugs, medical devices, etc.). We ask you to inform related business operators placed under your administration of this notice.

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

(attachment)

Basic Principles on Bioequivalence Evaluation of Generic Dry Powder Inhalers

The basic principles apply to development of generic dry powder inhalers for treatment of bronchial asthma and chronic obstructive pulmonary disease (COPD) and are intended to discuss studies required for their bioequivalence evaluation with reference drugs.

For bioequivalence evaluation of dry powder inhalers, conduct of clinical studies is required in principle. Because it is difficult to cover all the patient populations potentially eligible for the reference drug in the clinical studies for a test drug, pharmaceutical equivalence studies should be conducted to complement therapeutic equivalence evaluation conducted in a representative patient population if the drug is not indicated for a limited patient population and delivery of the active ingredient to the affected part in a pathological condition largely depends on pharmaceutical attributes. In the above case, therefore, bioequivalence between a test and the reference drug products of dry powder inhaler should be comprehensively evaluated by various studies including pharmaceutical equivalence, pharmacokinetic, and clinical studies.

Because the evaluation should be designed for each product, it is desirable to consult with the reviewing office in advance, plan and conduct appropriate studies.

1. Reference and test products

In principle, in vitro studies should be performed. Among the three lots, the one which shows intermediate fine particle dose (dose of the drug with an aerodynamic particle size ≤5 μm expected to be delivered into the lung per inhalation) (hereinafter referred to as the "fine particle dose") should be selected 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 and formulation of the test product and commercial products should be same. Quality, effectiveness and safety of both products should be equivalent.

A reference product whose content or drug delivery dose (hereinafter referred to as "delivery dose") is as close as possible to the labelled claim should be used. Furthermore, it is preferable that the difference between the content or delivery dose of the test product and that of the reference product be within 5% of the labelled claim.

2. Pharmaceutical equivalence, pharmacokinetic, and clinical studies

The test and reference products should be conducted to pharmaceutical equivalence study, pharmacokinetic study, and clinical study. Basic principles on conduct of the studies are as follows. The basic principles do not have to be applied if bioequivalence can be demonstrated as a dry powder inhaler without conducting the required tests following the basic principles.

(1) Pharmaceutical equivalence study

Pharmaceutical equivalence should be confirmed to complement therapeutic equivalence evaluation conducted in a representative patient population if the drug product is not indicated for a limited patient population and delivery of the active ingredient to the target tissue largely depends on pharmaceutical characteristics. In the above case, therefore, the evaluation of pharmaceutical equivalence between the test and reference products is a precondition for conduct of clinical studies.

(A) Parameters to be measured

(i) The evaluation parameters should be the delivery dose, fine particle dose, and drug amount in each of at least 4 aerodynamic size groups.

(ii) For instance, the delivery dose can be measured using a dosage unit sampling apparatus (delivered drug capture), and particles can be divided into the groups according to aerodynamic size using an Andersen Cascade Impactor or Next Generation Impactor.

(iii) The size range for each group should be determined in a scientifically valid manner.

(B) Test flow rate

Test flow rates should be specified based on the inspiratory flow rate achievable in the patient population (10%, 50%, and 90% of the achievable rate for the minimum, medium, and maximum rates) (for instance, 30, 60, and 90 L/min).

(C) Acceptance criteria

Scientifically valid acceptance criteria should be appropriately established.

(2) Pharmacokinetic study

Pharmacokinetic studies should be conducted to demonstrate that systemic exposure of the test product is the same as that of the reference product or falls within the acceptable range.

(A) Study design

In principle, the study should be conducted in a cross-over manner. Subjects should be randomly allocated.

(B) Number of subjects

An appropriate sample size should be specified in light of individual differences.

(C) Selection of subjects

In principle, healthy adults should be included as subjects.

(D) Drug administration

Regimen: In principle, subjects should receive a single inhalation dose in a fasted condition in the study.

(E) Measurement of biological samples

(i) Biological fluids to be sampled: Blood should be collected.

(ii) Sampling schedule: The number of sampling timing should be enough to evaluate AUC_t and C_{max}.

(iii) Substances to be measured: In principle, the unchanged active ingredient should be measured.

(iv) Analytical method: An analytical procedure to be used should be a method for determining drug concentrations in biological samples, which has been validated to assure adequate reliability.

(v) Assessment of equivalence: For the test and reference products, parameters of AUC_t and C_{max} should be evaluated.

(3) Clinical studies

For a clinical study comparing the test and reference products, the primary endpoint (equivalence evaluation parameter) and equivalence acceptable range should be prespecified based on published data in principle, and the study should be conducted in a parallel-group or cross-over design to confirm the equivalence.

(A) Number of subjects

The appropriate sample size should be specified to evaluate equivalence based on the confidence interval in view of the equivalence acceptable range in the clinical study.

(B) Selection of subjects

Of the approved indications, bronchial asthma or COPD should be selected as the target disease in the study. The selection of the patients should be considered so that the study can be conducted in a homogenous patient population wherever possible.

(C) Study conditions

(i) In principle, the study should be conducted using a strength appropriate for evaluation of therapeutic equivalence between the products.

(ii) In the study, the drug product should be administered as a single or multiple dose.

(D) Evaluation parameters

Change from baseline in trough forced expiratory volume in 1 second (FEV_1)

Change from baseline in morning PEF

Change from baseline in FEV_1-time area under the curve (FEV_1-AUC_t)

An appropriate primary endpoint (equivalence evaluation parameter) may differ depending on the target disease, pharmacological effect, therapeutic purpose, and duration of the effect and thus should be specified in view of characteristics of the drug.

(E) Acceptance criteria

A clinically acceptable range should be prespecified based on the difference between the reference drug and an appropriate control treatment in patients.

Reference literature

1. FDA. Product-Specific Recommendations for Generic Drug Development. Aclidinium bromide.2015. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM460918.pdf
2. FDA. Product-Specific Recommendations for Generic Drug Development. Fluticasone Propionate; Salmeterol xinafoate.2013. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM367643.pdf
3. FDA. Product-Specific Recommendations for Generic Drug Development. Formoterol fumarate.2015. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM461064.pdf
4. EMA. Guideline on the requirements for clinical documentation for orally inhaled products (OIP) including the requirements for demonstration of therapeutic equivalence between two inhaled products for use in the treatment of asthma and chronic obstructive pulmonary disease (COPD) in adults and for use in the treatment of asthma in children and adolescents.2009. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003504.pdf#search='EMA%2C+bioequivalence%2Cinha led'
5. Notification about “Guideline on Bioanalytical Method Validation for Drug Development” (PFSB/ELD Notification No. 0711-1 dated July 11, 2013)