English translation of **Attachment 4 of Division-Notification 0229 No. 10** of the Pharmaceutical and Food Safety Bureau, dated February 29, 2012

Guideline for Bioequivalence Studies for Different Oral Solid Dosage Forms

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Section 1: Introduction

This guideline describes the principles of procedures of bioequivalence studies for drug products which are the same in the route administered and dosage regimen but differing in dosage form. The objective of the study is to assure the bioequivalence between innovator products of original dosage form and test products of additional different dosage forms. Oral extended release products are out of the scope of this guideline, in principle, except the cases that after administration both reference ant test products disintegrate and disperse as units having substantial extended release function.

The test for the products for topical use should be following the Guideline for Bioequivalence Studies of Different Dosage Forms for Topical Use, an attachment of Division-Notification No. 1124001 of the Pharmaceutical and Food Safety Bureau, Amendments to the Guideline for Bioequivalence Studies of Generic Products and Other Guidelines, dated November 24, 2006.

Section 2: Terminology

Innovator products:

Drug products being approved as new drugs or comparable drug products.

Reference product: Dissolution tests (Immediate release products; Sec.3.A. V., Extended release products Sec.3. B. IV,) according to the Guideline for Bioequivalence Studies of Generic products (Attachment 1 of Division-Notification No. 487, dated December 22, 1997, partial revision in Division-Notification 0229 No. 10 of the Pharmaceutical and Food Safety Bureau, dated February 29, 2012), should be performed using the following test solution 1) or 2), using 6 vessels or more for three lots of innovator products by the paddle method at 50 rpm. Among the three lots, the one which shows intermediate dissolution should be selected as the reference product. When the average dissolutions of the three lots reach 85% within 15 min, any lot can be used as the reference product.

1) The specification test solution when the dissolution specifications are established in the specifications and test procedures.
2) Among the test solutions described in the dissolution conditions in the Guideline for Bioequivalence Studies of Generic products, when the average dissolution of at least one lot reaches 85%, the test solution providing the slowest dissolution should be selected. When the average dissolution of any of the lots does not reach 85%, the test solution providing the fastest dissolution should be used.

If the reference products cannot be selected by the dissolution test described above, suitable release

tests or alternative physicochemical tests should be performed for three lots of innovator products and one lot providing intermediate characteristics should be selected as the reference product.

For non-oral dosage forms, suitable release tests or alternative physicochemical tests should be performed for three lots of an innovator product from which one lot providing intermediate characteristics should be selected as a reference product.

If the drug is administered as a liquid where the active ingredient dissolves, an appropriate lot can be used as a reference product without performing dissolution (release) tests.

Test product: Products of which dosage is different from that of reference products. It is recommended to use a lot manufactured at the same lot size as the full-scale production. However, a lot manufactured at a scale of not less than 1/10 of a full-scale production also can be used. If the product is a homogeneous liquid where the active ingredient dissolves, a lot of which manufacturing scale is less than the 1/10 can be use. The manufacturing method of the test product and full-scale production products should be the same, and quality and bioavailability of both products should be equivalent.

Section 3: Bioequivalence study

Bioequivalence study should be performed according to Sec.3 of the Guideline for Bioequivalence Studies of Generic Products. In the case of enteric-coated products, the change in the diameter of the units forming the dosage forms and having substantial enteric function from less than 4 mm to more than 4 mm or vice versa is level E change and bioequivalence study at fed state should be additionally performed according to Sec.3. B. II. 1. of the Guideline for Bioequivalence Studies of Generic Products and estimated according to Sec. 3, A. II. 2.

In the case of changes where powder, granules, or tablets being approved are filled in capsules without changing formulation or shapes or vice versa, the tests of Level B of the Guideline for Bioequivalence Studies for Formulation Changes of Oral Solid Dosage Forms (Attachment 3 of Division-Notification No. 67, dated February 14, 2000, partial revision in Division-Notification 0229 No. 10 of the Pharmaceutical and Food Safety Bureau, dated February 29, 201) can be applied.

In the case of non-oral dosage forms, bioequivalence tests should be performed according to Sec.3. C of the Guideline for Bioequivalence Studies of Generic Products.