English translation of **Attachment 3 of Clerical Notification** of Pharmaceutical and Food Safety Bureau dated February 29, 2012

Guideline for Bioequivalence Studies for Different Oral Solid Dosage Forms
Q&A

Q-1 The introduction states that, "Oral extended-release products are outside the scope of this guideline, in principle." What is the reason for this statement?

(A) Dissolution of extended-release products in the gastrointestinal tract largely depends on formulation properties such as the release mechanism, the size, and the shape of the formulation, which are different from immediate release and enteric-coated products. Therefore, in extended-release products, it is difficult to appropriately estimate and ensure bioequivalence between different dosage forms, such as between tablets and granules, only by an ordinary bioequivalence study. Thus, oral extended-release products are outside the scope of this guideline, in principle, when dosage forms and release mechanisms are different.

However, products that meet all the following conditions are within the scope of this guideline:

· When a pharmaceutical company changes its own product

·When units forming the dosage forms are powders, granules, or the fillings in capsule that fundamentally have a substantial extended-release function and they exist in the formulation, maintaining their composition and shape without being broken.

·When the units forming the dosage forms of both reference and test products disperse in the gastrointestinal tract immediately after administration, and the transition of both units in the gastrointestinal tract is considered to be similar.

For example, in the case where one product is extended-release granules and the other is a capsule filled with the same granules, bioequivalence can be confirmed by the tests required in level B formulation change in the Guideline for Bioequivalence Studies for Formulation Changes of Oral Solid Dosage Forms. In the cases like a change to an orally disintegrating tablet consisting of extended-release units, after confirming that the units disperse immediately in water, a bioequivalence study can be conducted according to the Guideline for Bioequivalence Studies of Generic Products under the condition that the release mechanism of test products are not significantly different from that of the reference product. Requirements regarding the size, shape, and density stipulated in the Generic products and Formulation changes guideline are not needed.

Q-2 The reference product should be the innovator product. Why can generic products not be used as a reference product in this guideline?

(A) The extent of change in dosage form changes is larger, compared to those in different strengths and composition/component changes; therefore, the innovator product should be used as the reference product, in principle.

Q-3 When it is difficult to obtain innovator products, can generic products be used as a reference product in this guideline?

(A) If it is difficult to obtain an innovator product, any generic product can be used as the reference product; this will be assessed on a case-by-case basis, and it should be acceptable only when the innovator product is not available in the market owing to cancellation of approval or when the amount of the innovator product distributed is extremely small.

Q-4 In the case that innovator products are marketed in different dosage forms (e.g., tablets, capsules, powders), which product should be used as a reference product for applications of dosage form addition (e.g., addition of solutions)?

(A) Any innovator product can be used as a reference product in accordance with the definition of innovator product in the guideline.

Q-5 Explain the following points regarding a bioequivalence study of enteric-coated products under fed conditions:

(1) In the case like an orally disintegrating tablet consisting of enteric-coated particles, can the size of the particles having the enteric function be considered as that of the basic units?

(2) Why is an additional bioequivalence study under fed conditions conducted with a high-fat diet?

(3) When administration is limited to before meal, should a bioequivalence study under fed conditions be unnecessary?

(A)(1) When the units disperse in the stomach as units having an enteric function, the diameter of a dispersed unit can be considered as that of a basic unit having the enteric function.

(2) Foods may affect dissolution and gastric emptying of drugs. The gastric emptying rate may change, depending on the diameter of the unit having an enteric function, including the units dispersed after disintegration. Therefore, there is a possibility that blood concentration-time profiles may differ, and the similarity of the blood concentration-time profiles of the reference and test products after a lag time should be confirmed under both fasted and fed conditions. A high-fat diet is considered to have a larger effect on bioavailability in the fed state, compared

to a light diet, so a bioequivalence study under fed conditions should be conducted with a high-fat diet.

(3) In the case that administration is only before meal, a bioequivalence study under fed conditions should not be necessary.

Q-6 A bioequivalence study under fed conditions should also be conducted for cases of extended-release products and enteric products where the size of the units having an enteric function is different. In the case of orally disintegrating tablets consisting of extended-release units, should a bioequivalence study under fed conditions be conducted both with and without water?

(A) There is no guideline describing the procedures for bioequivalence studies of orally disintegrating tablets. Current approval reviews of orally disintegrating tablets require that the bioequivalence studies are conducted both with and without water given to the subjects. According to the bioequivalence study guidelines, a study under fed conditions is required for extended-release products (to confirm that extended-release function also works in the fed state, which is considered a stress condition compared to the fasted state) and enteric products where the sizes of the units having an enteric function are different; this is because there is a possibility that the blood concentration-time profiles may differ between the 2 products. Therefore, a bioequivalence study of orally disintegrating tablets under fed conditions performed only under the without-water condition can be acceptable. However, these results cannot be applied to all pharmaceutical products. The necessity of a bioequivalence study with water should depend on the product's properties.

Q-7 In products containing acidic drugs, when the reference product is a film-coated product and the test product is a capsule, dissolution test fluids are different for the reference and test products. Which dissolution fluids should be used?

(A) In the case under question, the dissolution test fluids for the reference product should be used. The dissolution test conditions should be determined according to the Guideline for Bioequivalence Studies of Generic Products.

Q-8 Does the guideline cover the applications of dosage form addition of different strengths, for example, a case wherein the innovator product is a tablet with 20 mg strength and the test product is a capsule with 10 mg strength?

(A) The above case falls within the scope of this guideline. The number of formulation units in the dissolution test should be determined in accordance with the Guideline for Bioequivalence Studies for Different Strengths of Oral Solid Dosage Forms.