English translation of **Attachment 4 of Clerical Notification** of Pharmaceutical and Food Safety Bureau, dated February 29, 2012

Bioequivalence Studies of Generic Products for Ethical Combination Drug Products
Q&A

General matters

Q-1 How should bioequivalence studies for generic ethical combination drug products (solid dosage forms containing more than one active ingredient) be performed?

(A) Bioequivalence study should be conducted for each active ingredient separately according to the Guideline for Bioequivalence Studies of Generic Products.

Glossary

Q-2 How should reference product be selected in the case of ethical combination drug products?

(A) In principle, dissolution tests should be conducted for each active ingredient for three lots of innovator products according to the Guideline for Bioequivalence Studies of Generic Products, and reference product should be selected based on the dissolution data of the active ingredient showing the largest variation of dissolution among the lots. However, when the combination drug products contain narrow therapeutic range drugs, reference product should be selected based on the dissolution data of the narrow therapeutic range drug.

Dissolution, Bioequivalence studies

Q-3 When categories of drug products ('Products containing acidic drugs', 'Products containing neutral or basic drugs, and coated products', 'Products containing poorly soluble drugs', 'Enteric- coated products', 'Extended release products') are different for respective active ingredient, how dissolution tests should be performed?

(A) Dissolution tests of each active ingredient in the respective drug product should be conducted according to the Guideline for Bioequivalence Studies of Generic Products.

Q-4 Dissolution tests (paddle method, 50rpm) of multi-layer combination drug tablets often result in significantly varied profiles depending on whether the active ingredient (to be assessed for bioequivalence) layer faces upward or downward in the bottom of vessels. How the test be performed for these products?

(A) When the state of dropped tablets such as directions in the vessels vary the dissolution profiles largely, jig or sinker for the tablets can be used to obtain steady dissolution profiles.