(3) Sugar-coated tablets

Change of component and composition

・Core tablets

		Standard formulation	Test product
Active ingredient A		10 mg (8.33%)*1)	10 mg (8.33%)
Binder	Povidone	3.6 mg (3.00%)	3.4 mg (2.83%)
Lubricant	Ca stearate	0.4 mg (0.333%)	0.6 mg (0.500%)
Filler	Lactose monohydrate	86 mg (71.67%)	82 mg (68.33%)
	Microcrystalline cellulose	12 mg (10.00%)	14 mg (11.67%)
	Cornstarch	8 mg (6.67%)	10 mg (8.33%)
Total weight of the core tablet		120 mg	120 mg

*1) The figure in parentheses is the % of respective ingredient out of weight of core tablet.

・Film layer

	Standard formulation	Test product
Ingredient A	1.17 mg (13.30%)*2)	1.2 mg (13.48%)*2)
Ingredient B	1.63 mg (18.52%)*2)	1.63 mg (18.31%)*2)
Ingredient C	6 mg (68.18%)*2)	6.07 mg (68.20%)*2)
Total weight of film layer	8.8 mg	8.9 mg
Surface area of core tablet	1.495 cm^2	1.495 cm^2
Film layer weight/cm^2	5.89 mg/cm^2	5.95 mg/cm^2 (101.02%)*3)

*2) The figure in parentheses is the % of the respective ingredient out of total weight of film layer.

*3) The figure in parentheses is the % of the test product/Standard formulation.

・Sugar-coating layer

	Standard formulation	Test product
Ingredient D	7.64 mg (12.32%)*2)	7.6 mg (13.10%)*2)
Ingredient E	4.36 mg (7.03%)*2)	4.4 mg (7.59%)*2)
Ingredient F	50 mg (80.65%)*2)	46 mg (79.31%)*2)
Total weight of sugar-coating layer	62 mg	58 mg
Surface area of core tablet	1.495 cm^2	1.495 cm^2
Sugar-coating layer weight/cm^2	41.5 mg/cm^2	38.8 mg/cm^2 (93.49%)*3)

*2) The figure in parentheses is the % the respective ingredient out of the total weight of the sugar-coating layer.

*3) The figure in parentheses is the % of the test product/Standard formulation.

Calculation of Difference of % ingredient and % changed

・Core tablets

Function of excipients and component		Difference of % ingredient	Level
Binder	Povidone	−0.17%	(B)
Lubricant	Ca stearate	0.167%	(B)
Filler	Lactose monohydrate	−3.34%	
	Microcrystalline cellulose	1.67%	
	Cornstarch	1.66%	
Sum of absolute values of filler differences		6.67%	(C)
Sum of absolute values of difference of changed components in the core tablet (0.17 + 0.17 + 6.67))		7.01%	(C)

・Film layer

Ingredient	Difference of % ingredient	Level
Ingredient A	0.18%	
Ingredient B	−0.21%	
Ingredient C	0.02%	
Sum of absolute values of difference of changed components in film layer	0.41%	(B)

	% Changed	Level
% changed weight of film layer/cm^2	1.02%	(B)

・Sugar-coating layer

Ingredient	Difference of % ingredient	Level
Ingredient D	0.78%	
Ingredient E	0.56%	
Ingredient F	−1.34%	
Sum of absolute values of difference of changed components in sugar-coating layer	2.68%	(B)

	% Changed	Level
% changed weight of sugar-coating layer/cm^2	−6.51%	(B)

The highest change level is C for "Sum of absolute values of difference of fillers" and "Sum of absolute values of difference of changed components in core tablet." Thus, in the example, the change level is C.

A-2 : Formulation Change of Different Strength Oral Dosage Forms

(1) Plain tablets

Change of component and composition

		Standard formulation	Test product
Active ingredient A		40 mg (13.33%)*1)	80 mg (17.02%)
Disintegrant	Cornstarch	40 mg (13.33%)	60 mg (12.77%)
Binder	Povidone	20 mg (6.667%)	30 mg (6.383%)
Lubricant	Mg stearate	4 mg (1.333%)	6 mg (1.277%)
Filler	Lactose monohydrate	100 mg (33.33%)	135 mg (28.72%)
	Microcrystalline cellulose	96 mg (32.00%)	159 mg (33.83%)
Total dosage form weight		300 mg	470 mg

*1) The figure in parentheses is the % the respective ingredient out of total dosage form weight.

Calculation of difference of % ingredient

Function of excipients and component		Difference of % ingredient	Level
Disintegrant	Cornstarch	−0.56%	(B)
Binder	Povidone	−0.284%	(B)
Lubricant	Mg stearate	−0.056%	(B)
Filler	Lactose monohydrate	−4.61%	
	Microcrystalline cellulose	1.83%	
Sum of absolute values of difference of fillers		6.44%	(C)
Sum of absolute values of difference of changed components (0.56 + 0.28 + 0.06 + 6.44)		7.34%	(C)

The highest level of "Sum of absolute values of difference of fillers" and "Sum of absolute values of difference of changed components" is C. Thus, in the example, the change level is C.

(2) Film-coated tablets

Change of component and composition

・Core tablets

		Standard formulation	Test product
Active ingredient	A	40 mg (13.33%)*1)	80 mg (17.02%)
Disintegrant	Cornstarch	40 mg (13.33%)	60 mg (12.77%)
Binder	Povidone	20 mg (6.667%)	30 mg (6.383%)
Lubricant	Mg stearate	4 mg (1.333%)	6 mg (1.277%)
Filler	Lactose monohydrate	100 mg (33.33%)	135 mg (28.72%)
	Microcrystalline cellulose	96 mg (32.00%)	159 mg (33.83%)
Total weight of the core tablet		300 mg	470 mg

*1) The figure in parentheses is the % the respective ingredient out of weight of core tablet.

・Film layer

	Standard formulation	Test product
Ingredient A	7.5 mg (75.00%)*2)	8.5 mg (73.91%)*2)
Ingredient B	2.5 mg (25.00%)*2)	3.0 mg (26.09%)*2)
Total weight of film layer	10.0 mg	11.5 mg
Surface area of core tablet	2.12 cm^2	2.76 cm^2
Film layer weight/cm^2	4.72 mg/cm^2	4.17 mg/cm^2 (88.35%)*3)

*2) The figure in parentheses is the % the respective ingredient out of the total weight of the film layer.

*3) The Figure in parentheses is the % of the test product/Standard formulation.

Calculation of Difference of % ingredient and % changed

・Core tablets

Function of excipients and component		Difference of % ingredient	Level
Disintegrant	Cornstarch	−0.56%	(B)
Binder	Povidone	−0.284%	(B)
Lubricant	Mg stearate	−0.056%	(B)
Filler	Lactose monohydrate	−4.61%	
	Microcrystalline cellulose	1.83%	
Sum of absolute values of filler differences		6.44%	(C)
in core tablet			
Sum of absolute values of changed component differences in core the tablet (0.56 + 0.28 + 0.06 + 6.44)		7.34%	(C)

・Film layer

Ingredient	Difference of % ingredient	Level
Ingredient A	−1.09%	
Ingredient B	1.09%	
Sum of absolute values of difference of changed components in film layer	2.18%	(B)

	% changed	Level
% changed weight of film layer/cm^2	−11.65%	(C)

The highest level of "Sum of absolute values of difference of fillers," "Sum of absolute values of difference of changed components in core tablet" and "% changed weight of film layer/cm^2," is C. Thus, the change level is C in the example.

(3) Sugar-coated tablets

Change of component and composition

・Core tablets

		Standard formulation	Test product
Active ingredient A		40 mg (13.33%)*1)	80 mg (17.02%)
Disintegrant	Cornstarch	40 mg (13.33%)	60 mg (12.77%)
Binder	Povidone	20 mg (6.667%)	30 mg (6.383%)
Lubricant	Mg stearate	4 mg (1.333%)	6 mg (1.277%)
Filler	Lactose monohydrate	100 mg (33.33%)	135 mg (28.72%)
	Microcrystalline cellulose	96 mg (32.00%)	159 mg (33.83%)
Total weight of the core tablet		300 mg	470 mg

*1) The figure in parentheses is the % the respective ingredient out of weight of core tablet.

・Film layer

	Standard formulation	Test product
Ingredient A	7.5 mg (75.00%)*2)	8.5 mg (73.91%)*2)
Ingredient B	2.5 mg (25.00%)*2)	3.0 mg (26.09%)*2)
Total weight of film layer	10.0 mg	11.5 mg
Surface area of core tablet	2.12 cm^2	2.76 cm^2
Film layer weight/cm^2	4.72 mg/cm^2	4.17 mg/cm^2 (88.35%)*3)

*2) The figure in parentheses is the % the respective ingredient out of the total weight of the film layer.

*3) The figure in parentheses is the % of the test product/Standard formulation.

・Sugar-coating layer

	Standard formulation	Test product
Ingredient C	11.5 mg (12.37%)*2)	13.0 mg (11.71%)*2)
Ingredient D	6.5 mg (6.99%)*2)	8.0 mg (7.21%)*2)
Ingredient E	75.0 mg (80.65%)*2)	90.0 mg (81.08%)*2)
Total weight of sugar-coating layer	93.0 mg	111.0 mg
Surface area of core tablet	2.12 cm^2	2.76 cm^2
Sugar-coating layer weight /cm^2	43.9 mg/cm^2	40.2 mg/cm^2 (91.57%)*3)

*2) The figure in parentheses is the % of the respective ingredient out of the total weight of the sugar-coating layer.

*3) The figure in parentheses is the % of the test product/Standard formulation.

Calculation of Difference of % ingredient and % changed

・Core tablets

Function of excipients and component		Difference of % ingredient	Level
Disintegrant	Cornstarch	−0.56%	(B)
Binder	Povidone	−0.284%	(B)
Lubricant	Mg stearate	−0.056%	(B)
Filler	Lactose monohydrate	−4.61%	
	Microcrystalline cellulose	1.83%	
Sum of absolute values of filler differences		6.44%	(C)
Sum of absolute values of changed component differences in core the tablet (0.56 + 0.28 + 0.06 + 6.44)		7.34%	(C)

・Film layer

Ingredient	Difference of % ingredient	Level
Ingredient A	−1.09%	
Ingredient B	1.09%	
Sum of absolute values of difference of changed components in the film layer	2.18%	(B)

	% Changed	Level
% changed weight of film layer/cm^2	−11.65%	(C)

・Sugar-coating layer

Ingredient	Difference of % ingredient	Level
Ingredient C	−0.66%	
Ingredient D	0.22%	
Ingredient E	0.43%	
Sum of absolute values of difference of changed components in sugar-coated layer	1.31%	(B)

	% Changed	Level
% changed weight of sugar-coating layer/cm^2	−8.43%	(B)

The highest level of "Sum of absolute values of difference of fillers," "Sum of absolute values of difference of changed components in core tablet" and "% changed weight of film layer/cm^2," is C. Thus, the change level is C in the example.

Appendix B Formulation Changed or Different Strength Dosage Forms of Soft Capsules

Bioequivalence studies of soft capsules formulated with readily soluble drugs where average dissolutions of the reference product reach 85% within 15 minutes under all the dissolution test conditions, can be conducted according to this guideline. Readily soluble drugs are those where the amount corresponding to the highest dose completely dissolves in 250 mL of all the dissolution test fluids. The applicable components in filling are limited to preservatives or stabilizers. A similar calculation to film-coated dosage form should be performed for the shell.

1. Level of formulation changes

The level of the formulation change is B when the calculation in the table below is not more than Level B. The level of the formulation change is C when the calculation is more than level B and not more than level C. The level of the formulation change is D when the calculation is more than level C.

Table Level of formulation change of soft capsules

	Difference of Content or Changed Percent (%)		
Part	Excipient	B	C
Filling	Preservative, Stabilizer	1	3
Shell	Base (gelatin, etc.)	5	15
	Plasticizer (Sorbitol, Glycerol, etc.)	2	6
	Preservative, Stabilizer, Lubricant	1	3
	Sum of absolute values of Difference of Content (%) of changed components in the shell	5	15
	Changed % of film-coating weight per surface area unit of the shell	10	30

* Surface area of the filler is calculated depending on the shape. When the calculation is difficult, surface area should be calculated assuming that the core is a sphere and that the core specific gravity does not change with the formulation change.

2. Required tests

Level B

Dissolution tests should be performed under the conditions shown in Sec. 4. The test product is regarded as bioequivalent to the reference product when their average dissolution at 30 minutes are not less than 85% under all the testing conditions, and their dissolution is judged to be equivalent according to the criteria in Sec. 5. When their dissolution is not equivalent, bioequivalence tests should be performed according to the guideline for bioequivalence studies of generic products.

Level C

For products containing narrow therapeutic range drugs, bioequivalence tests should be performed according to the guideline for bioequivalence studies of generic products.

For other drugs, dissolution tests should be performed under the conditions shown in Sec. 4. The test product is regarded as bioequivalent to the reference product when their average dissolution at 30 minutes is not less than 85% under all the testing conditions and their dissolution is judged to be equivalent according to the criteria in Sec. 5. When their dissolution is not equivalent, bioequivalence tests should be performed according to the guideline for bioequivalence studies of generic products.

Level D

Bioequivalence tests should be performed according to the guideline for bioequivalence studies of generic products.

Attachment 6

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

Index

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.

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.

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.

English translation of **Attachment 5 of Clerical Notification** of Pharmaceutical and Food Safety Bureau, dated February 29, 2012

Bioequivalence Studies for Different Strengths of Ethical Combination Drug Products and Formulation Changes of Ethical Combination Drug Products Q&A

General matters

Q-1 How should bioequivalence studies for different strengths and formulations of ethical combination drug products (solid dosage forms containing more than one active ingredient) be conducted?

(A) A bioequivalence study should be conducted separately for each active ingredient, according to the Guideline for Bioequivalence Studies for Different Strengths of Oral Solid Dosage Forms and the Guideline for Bioequivalence Studies for Formulation Changes of Oral Solid Dosage Forms, referring to the descriptions in this Q & A.

Levels of Formulation Changes

Q-2 In drug products (single layer) that contain multiple active ingredients in one layer, how is the level of formulation change in the combination drug product calculated?

(A) Since efficacy and safety have been evaluated separately for each active ingredient, and each active ingredient has distinct physicochemical properties, it is not acceptable to calculate the level of formulation change by regarding all active ingredients as one active ingredient. The active ingredients that are not to be assessed for bioequivalence, are regarded as the filler in Tables 1 and 2 in the Guideline for Bioequivalence Studies for Different Strengths of Oral Solid Dosage Forms, and the formulation change level should be determined by calculating the difference from the formulation of which therapeutic efficacy and safety have been established in clinical trials or of which bioequivalence has been demonstrated by human studies.

Q-3 How should formulation change level be calculated in multi-layered combination drug products (e.g., double layer tablets) for improvement of stability, etc.?

(A) Change levels should be calculated separately for each layer. Examples of calculations are shown in Appendix.

Dissolution test, bioequivalence studies

Q-4 In applications of different strengths products of generic products, which have different

content ratios of active ingredients, is it possible to calculate formulation change level according to the Guideline for Bioequivalence Studies for Different Strengths of Oral Solid Dosage Forms?

(A) Yes, it is possible. Examples for calculations are shown in Appendix. When human bioequivalence study is required following the Guideline for Bioequivalence Studies for Different Strengths of Oral Solid Dosage Forms, the study should be conducted by using innovator products with the same content ratios of active ingredients as reference product according to the Guideline for Bioequivalence Studies of Generic Products because it is impossible to administer different strengths products which have different content ratios of active ingredients at the same doses.

Q-5 When the highest strength product are different depending on the active ingredients to be assessed for bioequivalence (example of different strengths: active ingredients A 10mg/B 1mg, active ingredients A 5mg/B 2 mg) in the applications of multi different strengths products at the same time, which strength should be used as reference product in the Guideline for Bioequivalence Studies for Different Strengths of Oral Solid Dosage Forms?

(A) The product that contains the highest strength of an active ingredient which is considered more important from the viewpoint of clinical significance and/or discrimination in dissolution should be used as reference.

Q-6 When the formulation change levels calculated separately for each active ingredient in combination products are different, how bioequivalence studies should be conducted?

(A) The required studies for each active ingredient depending on the respective formulation change level, should be conducted. For example, when formulation change level for active ingredients A and B are Level B and E, respectively, bioequivalence can be confirmed by dissolution equivalence for ingredient A, and bioequivalence study should be conducted according to the Guideline for Bioequivalence Studies of Generic Combination Drug for ingredient B.

Appendix Examples of Calculation of Change Levels for Combination Drug Products

Calculation of the levels of change in components and compositions for combination drug products should be done as described below. The percentage is calculated to at least hundredths of a percent after the decimal point, as required in the guideline, and rounded off at the end of the calculation.

Levels of change are determined separately for each active ingredient that is assessed for bioequivalence (hereafter, intended ingredient)

(1) Change in the component and composition of combination drug products (for 1-layer tablets):

Change in component and composition

		Standard formulation	Test product
Active ingredient	A	250 mg (50.00%)[*1)]	250 mg (55.56%)
Active ingredient	B	2.5 mg (0.50%)	2.5 mg (0.56%)
Disintegrant	Cornstarch	40 mg (8.00%)	40 mg (8.89%)
Binder	Povidone	5 mg (1.000%)	5 mg (1.111%)
Lubricant	Mg stearate	5 mg (1.000%)	5 mg (1.111%)
Filler	Lactose monohydrate	157.5 mg (31.50%)	117.5 mg (26.11%)
	Microcrystalline cellulose	40 mg (8.00%)	30 mg (6.67%)
Total dosage form weight		500 mg	450 mg

[*1)] The figure in parentheses is the percentage of the assessed ingredient out of the total dosage form weight.

・Calculation of the difference in the percent of the ingredient when the intended ingredient is A

Function of excipients and component		Difference of % ingredient	Level
Disintegrant	Cornstarch	0.89%	(B)
Binder	Povidone	0.111%	(B)
Lubricant	Mg stearate	0.111%	(B)
Filler	Active ingredient B	+0.06%	
	Lactose monohydrate	−5.39%	
	Microcrystalline cellulose	−1.33%	
Sum of absolute values of filler differences		6.78%	(C)
Sum of absolute values of difference in changed components		7.89%	(C)

The highest change level of "Sum of absolute values of difference of fillers" and "Sum of absolute values of difference of changed components" is level C. Thus, in the above example where the intended ingredient is A, the change level is C.

・Calculation of difference of % ingredient in the case that the intended ingredient is B.

Function of excipients and component		Difference of % ingredient	Level
Disintegrant	Cornstarch	0.89 %	(B)
Binder	Povidone	0.111 %	(B)
Lubricant	Mg stearate	0.111 %	(B)
Filler	Active ingredient A	+5.56 %	
	Lactose monohydrate	−5.39 %	
	Microcrystalline cellulose	−1.33 %	
Sum of absolute values of filler differences		12.28 %	(D)
Sum of the absolute values of difference in changed components		13.39 %	(D)

The highest change level of "Sum of absolute values of difference of fillers" and "Sum of absolute values of difference of changed components" is level D. Thus, in the above example where the intended ingredient is B, the change level is D.

(2) Change of different strengths for combination drug products (in the case of single layer tablets)

Change of component and composition

		Standard formulation	Test product
Active ingredient A		20 mg (4.00%)*1)	10 mg (2.22%)
Active ingredient B		10 mg (2.00%)	2.5 mg (0.56%)
Disintegrant	Cornstarch	40 mg (8.00%)	40 mg (8.89%)
Binder	Povidone	5 mg (1.00%)	5 mg (1.111%)
Lubricant	Mg stearate	5 mg (1.00%)	5 mg (1.111%)
Filler	Lactose monohydrate	380 mg (76.00%)	347.5 mg (77.22%)
	Microcrystalline cellulose	40 mg (8.00%)	40 mg (8.89%)
Total dosage form weight		500 mg	450 mg

*1) The figure in parentheses is the percentage of the assessed ingredient out of total dosage form weight.

・Calculation of difference of percent ingredient in the case that the intended ingredient is A

Function of excipients and component		Difference of % ingredient	Level
Disintegrant	Cornstarch	0.89 %	(B)
Binder	Povidone	0.111 %	(B)
Lubricant	Mg stearate	0.111 %	(B)
Filler	Active ingredient B	−1.44 %	
	Lactose monohydrate	1.22 %	
	Microcrystalline cellulose	0.89 %	
Sum of absolute values of difference of fillers		3.55%	(B)
Sum of absolute values of difference in changed components		4.66%	(B)

All the change levels are B. Thus, in the above case that the intended ingredient is A, the change level is B.