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.

・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	−1.78 %	
	Lactose monohydrate	1.22 %	
	Microcrystalline cellulose	0.89 %	
Sum of absolute values of filler differences		3.89%	(B)
Sum of absolute values of difference in changed components		5.00%	(B)

All the change levels are B. Thus, in the above example where the intended ingredient is B, the change level is B.

(3) Change of component and composition for combination drugs (in the case of double layers tablets)

Change of component and composition

The total weight of layer A is changed and there was no change in layer B in double layer tablets.

		Standard formulation	Test product
Active ingredient	A	20 mg (7.69%)[*1)]	20 mg (10.53%)
Disintegrant	Cornstarch	20 mg (7.69%)	15 mg (7.89%)
Binder	Povidone	5 mg (1.923%)	4 mg (2.105%)
Lubricant	Mg stearate	1 mg (0.384%)	1 mg (0.526%)
Filler	Lactose monohydrate	194 mg (74.62%)	135 mg (71.05%)
	Microcrystalline cellulose	20 mg (7.69%)	15 mg (7.89%)
Total weight of layer A		260 mg	190 mg
Active ingredient	B	10 mg (4.17%)	10 mg (4.17%)
Disintegrant	Cornstarch	20 mg (8.33%)	20 mg (8.33%)
Binder	Povidone	5 mg (2.083%)	5 mg (2.083%)
Lubricant	Mg stearate	2 mg (0.833%)	2 mg (0.833%)
Filler	Lactose monohydrate	183 mg (76.25%)	183 mg (76.25%)
	Microcrystalline cellulose	20 mg (8.33%)	20 mg (8.33%)
Total weight of layer B		240 mg	240 mg
Total dosage form weight		500 mg	430 mg

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

・Differences in the percent ingredient in the changed layer A are calculated.

Function of excipients and component		Difference of % ingredient	Level
Disintegrant	Cornstarch	＋0.20%	(B)
Binder	Povidone	＋0.182%	(B)
Lubricant	Mg stearate	＋0.142%	(B)
Filler	Lactose monohydrate	－3.57%	
	Microcrystalline cellulose	＋0.20%	
Sum of absolute values of filler differences		3.77%	(B)
Sum of the absolute values of difference in changed components		4.29%	（B）

All the change levels are B. Thus, in the above example where the intended ingredient is A, the change level is B. Regarding layer B, there was no change in the layer, so the change level is A.