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Guideline for Bioequivalence Studies for Formulation Changes of Oral Solid Dosage Forms

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Section 1: Introduction

This guideline describes the principles of procedures of bioequivalence studies for post-approval changes in the components and composition of oral solid dosage forms other than the active ingredients, which is hereafter called the formulation changes. The objective of the guideline is to assure the bioequivalence between products before and after the formulation change. The tests required for bioequivalence assessment differ depending on the levels of the formulation changes from the original product whose therapeutic efficacy and safety were established by clinical studies or whose bioequivalence to the innovator product was demonstrated by a human bioequivalence study.

Section 2: Terminology

Standard formulation: The formulation for which therapeutic efficacy and safety were established by clinical studies or bioequivalence to the innovator product was demonstrated by a human bioequivalence study.

Reference product: The dissolution test (Sec. 4.) should be performed with three lots of the product before the formulation change, using the following test solution 1) or 2) (limited to the paddle methods at 50rpm, with 6 vessels or more). Among the three lots, the one which shows intermediate dissolution should be selected as the reference product. In the case of Level A change, the specification test conditions can be used when the dissolution specifications are established in the specifications and test procedures of the reference product. When the average dissolutions of the three lots reach 85% within 15 min, any lots 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 Sec. 4., 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.

Test product: A product after the formulation change. 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.

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.

In the case of extended release products, the test product should not significantly differ from the reference product in size and shape of dosage form, specific gravity and release mechanism. The dissolution profiles of the test product should be similar to those of the reference product as required in Sec. 3.B.IV.4 of the Guideline for Bioequivalence Studies of Generic Products (an attachment of Division-Notification No. 487 of the Pharmaceutical and Food Safety Bureau dated, on December 22, 1997, (partial revision in Division-Notification 0229 No. 10 of the Pharmaceutical and Food Safety Bureau, dated February 29, 2012).

Products containing poorly soluble drugs: See Sec. 3.A.V.3.3 of the Guideline for Bioequivalence Studies of Generic Products.

Section 3: Levels of formulation changes and required tests

1. Levels of formulation changes

The level of formulation changes is calculated based on the standard formulation. The degree of the changes should be evaluated by separated-calculation of difference of content (%) regarding “function of excipient and component” as shown in Table 1 and Table 2. When the calculation is equal to or less than Level B, change level is B. When the calculation is more than Level B and equal to or less than Level C, the change level is C. When the calculation is more than Level C and equal to or less than Level D, the change level is D. The changes more than Level D are Level E.

The level of the formulation changes of the following 1) - 3) is Level A irrespective of the levels in Table 1 and Table 2.

1) Changes of components described as "trace use".
2) Except narrow therapeutic range drugs, the change of excipients categorized as "Others" within the range not more than 0.5% (w/w) where the total weight of formulation is not changed with compensation of the weight change by increasing or reducing diluting agents.
3) Except narrow therapeutic range drugs, the exchange of excipients categorized as "Others" in the same use within the range not more than 1.0% (w/w) as sum of absolute values of difference of content (% w/w). (e.g. change of sweeteners to

other sweeteners).

Except narrow therapeutic range drugs, when the change of the film coating weight is not more than 7.0% (w/w) of core tablet and it is demonstrated that the film coating does not affect dissolution according to Appendix 3, the change level is B irrespective of the film coating change levels of Table 2.

The highest level of these changes is defined as the formulation change level to the product. However, in the case of enteric-coated products, the changes in the diameter of the units having substantial enteric function from less than 4 mm to more than 4 mm or more, or vice versa, is Level E change, and bioequivalence studies at fed state should be additionally performed according to the Guideline for Bioequivalence Studies of Generic Products (Sec. 3. B. II. 1.), and estimated according to Sec. 3, A. II. 2.

Table 1　Levels of Changes in Uncoated Product

Function of Excipient and Component	Difference of Content (% W/W) Compared to Standard Formulation		
	B	C	D
Disintegranting agents			
Starch	３．０	６．０	９．０
Others	１．０	２．０	３．０
Binders	０．５０	１．０	１．５
Lubricants・Polishers			
Stearate salts	０．２５	０．５０	０．７５
Others	１．０	２．０	３．０
Fluidizing agents			
Talc	１．０	２．０	３．０
Others	０．１０	０．２０	０．３０
Diluting agents	５．０	１０	１５
Others (Preservatives, Sweeteners, Stabilizers, etc.) [1)]	１．０	２．０	３．０
Sum of absolute values of difference of content (%) of changed components	５．０	１０	１５

[1)] A change level of excipients categorized as "Others" is also determined by separated-calculation of difference of content (%) regarding the respective use.
Ignore the components of which composition is described as "trace use".

Table 2　Levels of Changes in Coated Product

Part	Function of Excipient and Component	Difference of Content or Rate of Change (% W/W) Compared to Standard Formulation B	C	D
Core	Disintegranting agents			
	Starch	３．０	６．０	９．０
	Others	１．０	２．０	３．０
	Binders	０．５０	１．０	１．５
	Lubricants・Polishers			
	Stearate salts	０．２５	０．５０	０．７５
	Others	１．０	２．０	３．０
	Fluidizing agents			
	Talc	１．０	２．０	３．０
	Others	０．１０	０．２０	０．３０
	Diluting agents	５．０	１０	１５
	Others (Preservatives, Sweeteners, Stabilizers, etc.) [1)]	１．０	２．０	３．０
	Sum of absolute values of difference of content (%) of changed components	５．０	１０	１５
Film coating [2)]	Sum of absolute values of difference of content (%) of changed components in film coating layer [1)]	５．０	１０	１５
	Rate of change (%) of film coating weight/cm^2 of surface area of core [3)]	１０	２０	３０
Sugar coating	Sum of absolute values of difference of content (%) of changed components in sugar coating layer [1)]	５．０	１０	１５
	Rate of change (%) of sugar-coating weight/cm^2 of surface area of core [3)]	１０	２０	３０

1) A level of changes of excipients categorized as "Others" is also determined by separated-calculation of difference of content (%) regarding respective use.
Ignore the components of which composition is described as "trace use".

2) All coatings, such as water-proofing coating, under coating, enteric coating, and release control coating, are included except sugar coating.

3) The surface area of the core is calculated depending on the shape of the formulation. When it is impossible to calculate the surface area of the shape, it is allowed to assume that the shape of the core is a sphere and the specific gravity of the core is not changed with the formulation change.

2. Required Tests

Level A

When the dissolution test is established in the specifications and test procedures of the reference product, the dissolution test should be performed using 12 vessels or more under the testing conditions specified in the specifications. However, when it is not established, perform the dissolution test under the condition shown in Sec. 4. The test and reference products are regarded as bioequivalent, if their dissolution profiles are judged to be equivalent according to the criteria in Sec. 5. When the test and reference products are not regarded as bioequivalent from the results of the dissolution test, a bioequivalence

study should be performed according to the Guideline for Bioequivalence Studies of Generic Products.

Level B

The dissolution test should be performed under the conditions shown in Sec. 4. When the film coating change where it is demonstrated that the film coating does not affect dissolution in products, and the average dissolution of the reference product does not reach 85% in any test conditions specified, the dissolution test in Level A defined above can be used.

The test and reference products are regarded as bioequivalent, if their dissolution profiles are judged to be equivalent according to the criteria in Sec. 5. When the test and reference products are not regarded as bioequivalent from the results of the dissolution tests, a bioequivalence study should be performed according to the Guideline for Bioequivalence Studies of Generic Products.

Level C

For immediate release and enteric-coated products, perform the dissolution test shown in Sec. 4 (unless the product containing poorly soluble drugs). The test and reference products are regarded as bioequivalent, if their dissolution profiles are judged to be equivalent according to the criteria in Sec. 5. However, in the case of products containing the drugs in Table 3 (narrow therapeutic range drugs), the test and reference products are regarded as bioequivalent, only if their average dissolution at 30 min are not less than 85% under all the testing conditions in Sec. 4, and at the same time, their dissolution profiles are judged to be equivalent according to the criteria in Sec. 5. When the test and reference products are not regarded as bioequivalent from the results of the dissolution test, a bioequivalence study should be performed according to the Guideline for Bioequivalence Studies of Generic Products.

For products that contain narrow therapeutic range drugs, perform a bioequivalence study according to the Guideline for Bioequivalence Studies of Generic Products.

For extended release products, perform the dissolution test shown in Sec. 4 (unless the product contains narrow therapeutic range drugs). The test and reference products are regarded as bioequivalent, if their dissolution profiles are judged to be equivalent according to the criteria in Sec. 5. When the test and reference products are not regarded as bioequivalent from the results of the dissolution test, a bioequivalence study should be

performed according to the Guideline for Bioequivalence Studies of Generic Products.
For products that contain narrow therapeutic range drugs, perform a bioequivalence study according to the Guideline for Bioequivalence Studies of Generic Products.

Level D

For immediate release products, perform the dissolution test shown in Sec. 4 (unless the products containing poorly soluble drugs or products containing narrow therapeutic range drugs). The test and reference products are regarded as bioequivalent, if their average dissolution at 30 min are not less than 85% under all the testing conditions in Sec. 4, and at the same time, their dissolution profiles are judged to be equivalent according to the criteria in Sec. 5. When the test and reference products are not regarded as bioequivalent from the results of the dissolution test, a bioequivalence study should be performed according to the Guideline for Bioequivalence Studies of Generic Products.

For products containing poorly soluble drugs or products containing narrow therapeutic range drugs, perform a bioequivalence study according to the Guideline for Bioequivalence Studies of Generic Products.
Foe extended release products and enteric-coated products, perform a bioequivalence study according to the Guideline for Bioequivalence Studies of Generic Products.

Level E

Perform a bioequivalence study according to the Guideline for Bioequivalence Studies of Generic Products.

Table 3 Narrow Therapeutic Range Drugs [1)]

Aprindine	Carmazepine
Clindamycin	Clonazepam
Clonidine	Cyclosporine
Digitoxin	Digoxin
Disopyramide	Ethinyl Estradiol
Ethosuximide	Guanethidine
Isoprenaline	Lithium
Methotrexate	Phenobarbital
Phenytoin	Prazosin
Primidone	Procainamide
Quinidine	Sulfonylurea antidiabetic drugscompounds [2)]
Tacrolimus	Theophylline compounds [3)]
Valproic Acid	Warfarin
Zonisamide	Glybuzole

[1)] Whether drugs approved after 1999 belong to the narrow therapeutic category or not, should be determined referring to the above listed drugs.
[2)] Acetohexamide, glibenclamide, gliclazide, glyclopyramide, tolazamide, tolbutamide
[3)] Aminophylline, choline theophylline, diprophylline, proxyphylline, theophylline

Section 4. Dissolution tests

The dissolution test should be performed according to the conditions shown in Sec. 3.A.V and Sec. 3.B.IV of the Guideline for Bioequivalence Studies of Generic Products, however, the paddle method at 75 rpm cannot be used instead of that at 50 rpm. In the case that active ingredient is adsorbed to excipients or vessels in water, 0.2% sodium chloride solution can be used instead of water. When polysorbate 80 is added to the test fluids for the dissolution tests of products containing poorly soluble drugs, the concentration should not exceed 0.1%. In the case of enteric-coated products, the following test condition should be added. When sodium lauryl sulfate is used, the solubility of active ingredient in the sodium lauryl sulfate-buffer solution should be not more than that in polysorbate 80 buffer solution at the stipulated maximum concentration.

Test: Paddle method at 50 rpm, using 900 mL of dissolution media adjusted at pH 6.0 by 0.01 mol/L of disodium hydrogen phosphate and 0.005 mol/L citric acid.

Section 5. Judgement of equivalence of dissolution profiles

Dissolution profiles of the test and reference products are judged to be equivalent, when they meet both requirements (1) and (2) shown below under each dissolution test condition. The average dissolution of the reference product should reach 85% within the testing time specified at least under one test condition in the case of immediate release products and enteric-coated products, and should reach 80% in the case of extended release products. The prescribed testing time is specified in Sec. 3.A.V.2 or Sec. 3.B.IV.2 in the Guideline for Bioequivalence Studies of Generic Products. In addition, when similarity factor, f2 is used for the judgement, the time points for comparing dissolution rates specified in Appendix 1(2) should be employed. When there is a lag time for dissolution of the reference product in immediate release products and enteric-coated products, it is allowed to adjust the dissolution curve with the lag time (Appendix 2), and the acceptance criteria can be applied after the lag time, however, the difference in average lag time between the test and reference products should be within 10 min.

When the dissolution comparison time points are less than 15 min, it is acceptable that the dissolution profiles are estimated at 15 min. When the lag time between the test and reference products is compensated, the 15 min means the time before the adjustment.

In the case of enteric-coated products, it is acceptable that the dissolution profiles are estimated at the stipulated dissolution time (after 2 hr) of pH 1.2 dissolution test fluid.

(1) Average dissolution rate

1) When the average dissolution of the reference product reaches 85% within 15 min: the average dissolution of the test product reaches 85% within 15 min or is within that of the reference product ± 10% at 15 min.
2) When the average dissolution of the reference product reaches 85% at between 15 and 30 min: the average dissolution of the test product are within that of the reference product ±10% at two appropriate time points when the average dissolution of the reference product are around 60% and 85%. Or f2 value is not less than 50.
3) When the average dissolution of the reference product does not reach 85% within 30 min: the results meet one of the following criteria.

   Immediate release products and enteric-coated products

   a. When the average dissolution of the reference product reaches 85% within the testing time specified: the average dissolution of the test product are within that of the reference product ± 10% at two appropriate time points when the average dissolution of the reference product are around 40% and 85%. Or f2 value is not less than 50.

   b. When the average dissolution of the reference products reaches 50% and does not reach 85% within the testing time specified: the average dissolution of the test product are within that of the reference product ± 8% at the testing time specified and at an appropriate time point when the average dissolution of the reference product reaches about a half of the average dissolution at the testing time specified. Or f2 value is not less than 55.

   c. When the average dissolution of the reference product does not reach 50% within the testing time specified: the average dissolution of the test product are within that of the reference product ± 6% at the testing time specified and at an appropriate time point when the average dissolution of the reference product is about a half of the average dissolution at the testing time specified. Or f2 value is not less than 61. However, when the average dissolution of the reference products is not more than 10% at the stipulated dissolution time, the average dissolution of the test product is within that of the reference product ± 6% at the testing time specified only.

Extended release products

a. When the average dissolution of the reference product reaches 80% within the testing time specified: the average dissolution of the test product are within that of the reference product ± 10% at three appropriate time points when the average dissolution of the reference product are around 30%, 50% and 80%. Or f2 value is not less than 50.

b. When the average dissolution of the reference product reaches 50% and does not reach 80% within the testing time point: the average dissolution of the test product are within that of the reference product ± 8% at the testing time specified and at an appropriate time point when the average dissolution of the reference product reaches about a half of the average dissolution at the testing time specified. Or f2 value is not less than 55.

c. When the average dissolution of the reference product does not reach 50% within the testing time specified: the average dissolution of the test product are within that of the reference product ± 6% at the testing time specified and at an appropriate time point when the average dissolution of the reference product is about a half of the average dissolution at the testing time specified. Or f2 value is not less than 61. However, when the average dissolution of the reference products is not more than 10% within the testing time specified, the average dissolution of the test product is within that of the reference product ± 6% at the testing time specified only.

(2) Individual dissolution rate

Each individual dissolution rate of the test product (out of n=12) should meet one of the following criteria at the last point where the average dissolution of the test product is compared to that of the reference product.

a. When the average dissolution of the reference product reaches 85 % (80% for extended release products): the number of the test product of which dissolution is out of the range of the average dissolution of the test product ± 15% and ± 25% should be "1 or less" and "0", respectively.

b. When the average dissolution of the reference product reaches 50% and does not reach 85% (80% for extended release products): the number of the test product of which dissolution is out of the range of the average dissolution of the test product ± 12% and ± 20% should be "1 or less" and "0", respectively.

c. When the average dissolution of the reference product does not reach 50%: the number of the test product of which dissolution is out of the range of the average dissolution of the test product ± 9% and ± 15% should be "1 or less" and "0", respectively.

Appendix 1. **f2 (similarity factor) and time points for comparisons**

(1) Definition of f2

The following equation defines f2, Ti and Ri show the average dissolution of the test and reference products at the time point (i), respectively, and n is the number of time points at which the average dissolution are compared.

$$f_2 = 50 \log \left[\frac{100}{\sqrt{1 + \frac{\sum_{i=1}^{n} (Ti - Ri)^2}{n}}} \right]$$

(2) Time points for f2

1) When the average dissolution of the reference product reaches 85% (80% for extended release products) between 15 and 30 min: 15, 30, 45 min.
2) When the average dissolution of the reference product reaches 85% (80% for extended release products) between 30 min and the testing time point specified: at Ta/4, 2Ta/4, 3Ta/4 and Ta, where Ta is the time point at which average dissolution of the reference product reaches approximately 85% (80% for extended release products).
3) When the average dissolution of the reference product does not reach 85% (80% for extended release products) within the testing time point specified: at Ta/4, 2Ta/4, 3Ta/4 and Ta, where Ta is the time point at which average dissolution of the reference product reaches approximately 85% (80% for extended release products) of the amount dissolved at the testing time point specified.

Appendix 2. **Adjusting dissolution curves with lag times**

The lag time is defined as the time when 5% of the labeled claim of the active ingredient dissolves from the product. A lag time should be determined for respective product by linear interpolation, and then respective dissolution curve is obtained by adjusting dissolution curve with the lag time. Average dissolution curves of the test and reference products are obtained, which can be used for the assessment of dissolution equivalence.

Appendix 3. **Method to evaluate effect of film coating on dissolution**

1) When the average dissolution of the reference product reaches 85% in at least one test condition: the dissolution tests of core tablets (or uncoated tablets) and film-coated tablets for before and after the film-coating change should be performed under the conditions shown in Sec. 4. When the dissolution profile of the film-coated tablets before and after the film-coating change is judged to be equivalent to the corresponding core tablets according to the criteria in Sec. 5, it should be considered that the film coating does not affect dissolution. Core tablets (or uncoated tablets) and film-coated tablets manufactured by the same manufacturing method and process as those of the reference and test products can be used.

2) When the average dissolution of the reference product does not reach 85% in any of the test conditions: using a high solubility drug such as acetaminophen etc, core tablets of which the components and composition except the active ingredient are the same and the average dissolution of the core tablets reach 85% in all the test conditions are applied. Using the obtained core tablets, model film-coated tablets before and after the film-coating change are prepared respectively. The dissolution tests of the core tablets and model film-coated tablets before and after the film-coating change should be performed under the conditions shown in Sec. 4. When the dissolution profile of the model film-coated tablets before and after the film-coating changes are judged to be equivalent to the core tablets according to the criteria in Sec. 5, it should be considered that the film coating does not affect dissolution.

In any of the above cases of 1) or 2), when the composition rate is the same in the film-coated tablets before and after the film-coating change, the dissolution comparison can be done only for the thicker-film coated tablets (film-coated tablets of which the amount of film coating is higher).

The above 1) or 2) can be also applied to the changes from plain tablets to film-coated tablets and vice versa.

Appendix 4. Levels of formulation changes and required tests

(Guideline for Bioequivalence Studies for Formulation Changes of Oral Solid Dosage Forms)

Level	Immediate/ Extended Release	Therapeutic range [1]	Poorly soluble/Soluble	Rapid [3]/Non-rapid dissolution	Confirmation of bioequivalence
A	Immediate Release	Non-narrow			When the dissolution specification is established: if the dissolution profiles are judged to be equivalent in the dissolution test shown in the specifications, the test and reference products are regarded as bioequivalent. When the dissolution specification is not established: if the dissolution profiles are judged to be equivalent in the dissolution test shown in Sec. 4., they are regarded as bioequivalent.
B	Immediate Release Enteric coated [2] Extended Release				If the dissolution profiles are judged to be equivalent in the dissolution test shown in Sec. 4., they are regarded as bioequivalent. In the case of film coating change where it is demonstrated that film coating does not affect dissolution of products and the average dissolution of the reference product does not reach 85% in any test conditions specified, the dissolution test defined in Level A can be used. If the dissolution profiles are judged to be equivalent, they are regarded as bioequivalent.
C	Immediate Release Enteric coated [2]	Non-narrow	Soluble		If the dissolution profiles are judged to be equivalent in the dissolution test shown in Sec. 4., they are regarded as bioequivalent.
			Poorly soluble		Follow the Guideline for Bioequivalence Studies of Generic Products.
		Narrow	Soluble	Rapid	If the dissolution profiles are judged to be equivalent in the dissolution test shown in Sec. 4., they are regarded as bioequivalent.
				Non-rapid	Follow the Guideline for Bioequivalence Studies of Generic Products.
			Poorly soluble		
	Extended Release	Non-narrow			If the dissolution profiles are judged to be equivalent in the dissolution test shown in Sec. 4., they are regarded as bioequivalent.
		Narrow			Follow the Guideline for Bioequivalence Studies of Generic Products.
D	Immediate Release	Non-narrow	Soluble	Rapid	If the dissolution profiles are judged to be equivalent in the dissolution test shown in Sec. 4., they are regarded as bioequivalent.
				Non-rapid	Follow the Guideline for Bioequivalence Studies of Generic Products.
			Poorly soluble		
		Narrow			
	Enteric coated [2] Extended Release				
E	Immediate Release Enteric coated [2] Extended Release				Follow the Guideline for Bioequivalence Studies of Generic Products.

1) Non-narrow: Drugs that are not listed in Table 3 Narrow: Drugs that are listed in Table 3

2) In the change of the diameter of the units having substantial enteric function from less than 4 mm to 4 mm or more, or vice versa, the formulation change of the level is E, and bioequivalence studies at fed state should be additionally performed.

3) Average dissolutions of the reference and test products reach 85% at 30 min under all the testing conditions in Sec.4.