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

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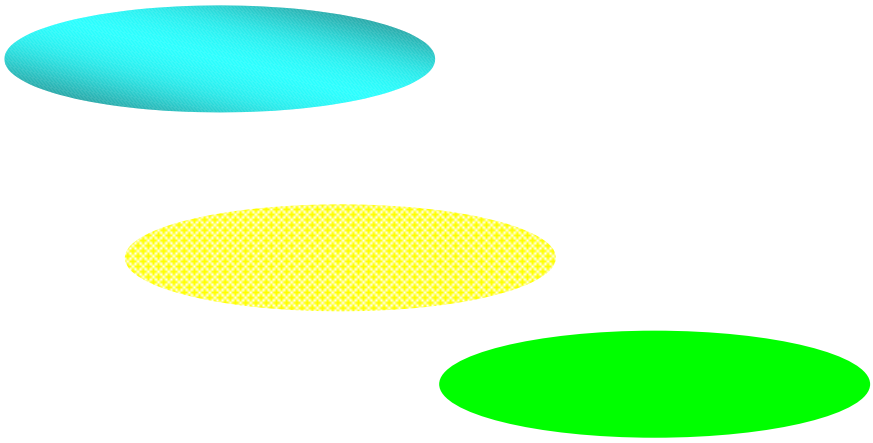
経口固形製剤の処方変更の生物学的同等性試験ガイドライン



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Section 1: Introduction

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

Section 2: Terminology

Original formulation: The formulation for which therapeutic efficacy and safety were established by clinical trials or bioequivalence was demonstrated by human studies.

Reference product: The product prior to formulation change which should be selected from among three marketed lots. The reference product should show intermediate dissolution among the three lots under the most discriminative condition, where the difference in dissolution between the fastest and slowest lots is the largest. The dissolution tests (Sec. 4) should be performed using 6 units, by the paddle method at 50 rpm.

Test product: Products after formulation change which should be manufactured in an production scale or 1/10 production scale or larger. The test product should be the same as the production lots in manufacturing method, quality and bioavailability. In the case of controlled release dosage forms test products should not significantly differ from the reference product in shape of dosage form, density and release mechanism. The dissolution characteristics of the test product should be similar to those of the reference product as required in the Guideline for Bioequivalence Studies of Generic products (Sec.3.B.1.2) published on December 22 in 1997 (http://www.nihs.go.jp/drug/be-guide(e)/be97E.pdf).

Products containing low solubility drugs: When the average dissolution from the reference product does not reach 85% in the testing time specified, that is, 2 hr at pH1.2 and 6 hr at other pHs (pH3.0-7.5), by the paddle method at 50 rpm without surfactants, they are defined as products containing low solubility drugs (see the Guideline for Bioequivalence Studies of Generic products (Sec.3.A.V.3.3).

Section 3: Level of formulation change and test

1. Level of formulation change

First, levels of changes in individual excipients and categorized excipients, shown in Table 1 and Table 2, should be determined. If the change is equal to or less than the ranges of Level B, it is level B. If the change is more than the ranges of level B and equal to or less than the ranges of level C, it is level C. Similarly, the change in excipients in the range between C and D is level D. All changes exceeding the ranges of level D are level E. Any change in excipients whose use is limited to a trace belong to level A.

Among the above changes, the highest level of change is defined as the level of formulation change. In the case of enteric coated products, the change in the size of the dosage form from less than 4 mm to more than 4 mm or vice versa is a formulation change of level E.

Table 1. Level of Change in Individual and Categorized Excipients
(Uncoated Product)

Excipient	Level		
Category and component	B	C	D
Disintegrant			
Starch	3.0	6.0	9.0
Other	1.0	2.0	3.0
Binder	0.5	1.0	1.5
Lubricant or Polisher			
Ca or Mg stearate	0.25	0.50	0.75
Other	1.0	2.0	3.0
Glidant			
Talc	1.0	2.0	3.0
Other	0.10	0.20	0.30
Filler	5.0	10	15
Others[1)]	1.0	2.0	3.0
Total change[2)]	5.0	10	15

Figures show the percent excipient (w/w) compared to total dosage form weigh

1) e.g., preservatives, stabilizer. Excipients of trace use are excluded.

2) Total additive effects of all excipient changes

Table 2. Level of Change in Individual and Categorized Excipients
(Coated Product)

Core/ coated layer	Excipient Category and component	Level B	C	D
Core	Disintegrant			
	Starch	3.0	6.0	9.0
	Other	1.0	2.0	3.0
	Binder	0.5	1.0	1.5
	Lubricant or Polisher			
	Ca or Mg stearate	0.25	0.50	0.75
	Other	1.0	2.0	3.0
	Glidant			
	Talc	1.0	2.0	3.0
	Other	0.10	0.20	0.30
	Filler	5.0	10	15
	Other[1)]	1.0	2.0	3.0
	Total change[2)]	5.0	10	15
Film-coated layer[3)]	Total change in components[2,4)]	5.0	10	15
	Weight of film coated layer/surface of core[5)]	10.0	20	30
Sugar-coated layer	Total change in components[2,4)]	5.0	10	15
	Weight of sugar coated layer/surface of core[5)]	10.0	20	30

Figures show percent excipient (w/w) compared to total dosage form weight.

1) e.g., preservatives, stabilizer. Excipients of trace use are excluded.

2) Total additive effects of all excipient changes

3) Except for sugar-coated layer, all film coated layers for water-proofing, undercoating, enteric coating and controlled release are included.

4) Excipients of trace use are excluded.

5) The surfaces of cores are determined from the shapes of dosage forms. If it is difficult, the surface should be clcuated under the assumption that the cores are spheres and the densities do not change with the formulation change.

2. Tests

Level A

Dissolution tests should be performed using 12 units under the conditions specified in the registration or under the condition shown in Sec. 4 when the dissolution test is not specified. The equivalence in dissolution between test and reference products should be assessed according to the criteria described in Sec. 5 (1) and (2). There is no need for submission of the dissolution data which, however, have to be retained so as to be shown on demand.

Level B

Dissolution tests should be performed under the conditions shown in Sec. 4. Test and reference products are considered to be bioequivalent when their dissolution is judged to be equivalent according to the criteria in Sec. 5. If test and reference products are not equivalent in dissolution, bioequivalence tests should be performed according to the guideline for bioequivalence studies of generic products.

Level C

Conventional dosage forms and enteric coated products For products containing low solubility drugs, bioequivalence tests should be performed according to the guideline for bioequivalence studies of generic products. For other products, dissolution tests should be performed under the conditions shown in Sec. 4. Test and reference products are considered to be bioequivalent when their dissolution is equivalent according to the criteria in Sec. 5, except for narrow therapeutic range drugs listed in Table 3, For narrow therapeutic range drugs, test and reference products are considered to be bioequivalent if their average amounts dissolved at 30 min are equal to or more than 85% under all testing conditions and their dissolution is judged to be equivalent according to the criteria in Sec. 5. If test and reference products do not meet the requirement, bioequivalence tests should be performed according to the guideline for bioequivalence studies of generic products.

Controlled release dosage forms For products containing narrow therapeutic range drugs in Table 3, bioequivalence tests should be performed according to the guideline for bioequivalence studies of generic products. For other products, dissolution tests should be performed under the conditions shown in Sec. 4. Test and reference products are considered to be bioequivalent when their dissolution is equivalent according to the criteria in Sec. 5, If test and reference products are not equivalent in dissolution, bioequivalence tests should be performed according to the guideline for bioequivalence studies of generic products.

Table 3. Narrow Therapeutic Range Drugs[1)]

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

1) Whether the 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

Level D

Conventional dosage forms For products containing low solubility drugs and narrow therapeutic range drugs, bioequivalence tests should be performed according to the guideline for bioequivalence studies of generic products. For other products, dissolution tests should be performed under the conditions shown in Sec. 4. Test and reference products are considered to be bioequivalent when their average amounts dissolved at 30 min are equal to or more than 85% under all testing conditions and their dissolution is judged to be equivalent according to the criteria in Sec. 5. If test and reference products do not meet the requirement, bioequivalence tests should be performed according to the guideline for bioequivalence studies of generic products.

Controlled release dosage form and enteric coated products Bioequivalence tests should be performed according to the guideline for bioequivalence studies of generic products.

Level E

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

Section 4. Dissolution test

Dissolution tests should be performed according to the conditions shown in Sec.3.A.V and Sec.3.B.I. When polysorbate 80 is added to test fluids for the dissolution tests of products containing low solubility drugs, the concentration should not exceed 0.1%. In the case of enteric coated products, the following test should be added to the dissolution tests specified in the guideline for bioequivalence studies of generic products (Sec.3.A.V);

Paddle method at 50 rpm in 900 ml of pH 6.0 buffer prepared with 0.01mol/L sodium monohydrogenphosphate and 0.005mol/L citric acid.

Section 5. Judgement of equivalence in dissolution

Test and reference products are considered equivalent when they meet both requirements (1) and (2) shown below. The rule is not applicable to conventional dosage forms and enteric coated products, unless the average dissolution from the reference product reaches 85% under any of the testing conditions within the testing time (2 hr at pH1.2 and 6 hr at other pHs) specified in Sec. 3.A.V.2 in the guideline for bioequivalence studies of generic products. When similarity factor, f2 is used, the dissolution data at the time points specified in Appendix 1 should be employed. If dissolution lag is observed for reference products, the equivalence in dissolution can be assessed using the dissolution profile normalized for the lag time. (see Appendix 2)

(1) Average dissolution

1) When the average dissolution from the reference product reaches 85% within 15 min: The average dissolution from the test product also reaches 85% within 15 min or does not deviate by more than 10% from that of the reference product at 15 min.
2) When the average dissolution from the reference product reaches 85% between 15 and 30 min: The average dissolution from the test product does not deviate by more than 10% from that of the reference product at two time points where the average amounts dissolved from the reference product are around 60 and 85%. When f2 is used, the f2 value should be not less than 50.
3) When the average dissolution from the reference product does not reach 85% in 30min: The following criteria should be applied to the comparison of average dissolution profiles determined in the testing times specified in Sec. 3.A.V.2 or Sec. 3.B.I.2 in the guideline for

bioequivalence studies of generic products (2 hr at pH1.2, 6 hr at other pHs for conventional and enteric coated products and 24 hrs for controlled release products). When the dissolution profiles are normalized for the lag time, the difference in average lag time between test and reference products should be not more than 10 min. The time points where the dissolutions are compared without use of f2, are the same as specified in the guideline for bioequivalence studies of generic products (Sec. 3.A.V.4).

a. When the average dissolution from the reference product does not reach 50% at the testing time point: The average dissolution of test product does not deviate by more than 6 % from that of the reference product at the time points specified, or f2 value is equal to or more than 60.
b. When the average dissolution from the reference product is between 50 and 85 % at the testing time point: The average dissolution of test product does not deviate by more than 8 % from that of the reference product at the time points specified, or f2 value is equal to or more than 55.
c. When the average dissolution from the reference product reaches 85 % within the testing time: the average dissolution from test product does not deviate by more than 10 % from that of the reference product at the time points specified, or f2 value is equal to or more than 50.

(2) Individual dissolution

Test products (n=12) should meet one of the following requirements at the final time points where the average dissolution is compared between test and reference products.

a. When the average dissolution of reference product does not reach 50% within the testing time: There is no sample of test products that shows the deviation of more than 15% in dissolution from the average dissolution of the test product, and one or no sample that shows the deviation of more than 9 %.

b. When the average dissolution of reference product is between 50 and 85 % at the testing time point: There is no sample of test product that shows a deviation of more than 20% in dissolution from the average dissolution of the test product, and one or no sample that shows a deviation of more than 12%.

c. When the average dissolution of reference product reaches 85 % within the testing time: There is no sample of test product that shows a deviation of more than 25% in dissolution from the average dissolution of the test product, and one or no sample that shows a deviation of more than 15%.

Appendix 1.

f2 (similarity factor) and time points

(1) Definition of f2

The following equation defines f2, where Ti and Ri show the average percents dissolved from test and reference products at the time point (i), and n is the number of time points.

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

(2) Time point for f2

1) When the average dissolution from the reference product reaches 85% between 15 and 30 min: 15, 30, 45min.
2) When the average dissolution from the reference product reaches 85% between 30min and the testing time point*: Ta/4, 2Ta/4, 3Ta/4 and Ta where Ta is the time point at which average dissolution from the reference product reaches approximately 85%.
3) When the average dissolution from the reference product does not reach 85% at the testing time point*: Ta/4, 2Ta/4, 3Ta/4 and Ta where Ta is the time point at which average dissolution from the reference product reaches approximately 85% of the final amount dissolved in the testing time.

When there is a lag in dissolution, dissolution data normalized for the lag time should be used for the calculation of f2.

* The testing time is specified in Sec. 3.A.V.2 or Sec. 3.B.I.2 in the guideline for bioequivalence studies of generic products.

Appendix 2.

Normalization of dissolution profiles with lag time

The lag time is conventionally defined as the time when 5% of the drug dissolves. The lag time should be determined for individual dissolution by linear interpolation, followed by normalization of dissolution profiles for the lag time. Then, the average dissolution profiles are determined which can be used for the assessment of equivalence in average dissolution.

Appendix 3.

Level of Formulation Change and Tests

Level	Dosage form[1)]	Therapeutic range	Solubility[2)]	Dissolution	Test[3)]
A	-	-	-	-	A single dissolution test
B	-	-	-	-	Multiple dissolution tests
C	IR, DR	Not narrow	Not low	-	Multiple dissolution tests
	〃	〃	Low	-	In vivo test
	〃	Narrow	Not low	≧85%, 30min	Multiple dissolution tests
	〃	〃	〃	<85%, 30min	In vivo test
	〃	〃	Low	-	In vivo test
	CR	Not narrow	-	-	Multiple dissolution tests
	〃	Narrow	-	-	In vivo test
D	IR	Not narrow	Not low	≧85%, 30min	Multiple dissolution tests
	Other IR, DR, CR	-	-	-	In vivo test
E	-	-	-	-	In vivo test

1) IR, DR and CR mean immediate release (conventional), delayed-release (enteric coated) and controlled release dosage forms, respectively.

2) Products containing low solubility drugs are determined by dissolution tests. When dissolution from the reference product does not reach 85% at 2 hr at pH1.2 and 6 hr at other pHs by paddle method at 50 rpm without surfactants, the drug is low solubility.

3) Single and multiple dissolution tests mean the test performed under specification conditions and those under multiple conditions. When equivalence in dissolution is not shown, in vivo tests should be performed according to the guideline for bioequivalence studies of generic products.