Guideline for Bioequivalence Studies for Different Strengths of Oral Solid Dosage Forms

(24, December 2006)

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Section 1: Introduction

This guideline describes the principles of procedures of bioequivalence studies for oral solid drug products which are the same in active ingredient, dosage form, therapeutic indication and dosage regimen with a product already approved but differing in strength. The objective of the study is to assure the bioequivalence between products with different strengths when the same doses are administered. The tests required for bioequivalence assessment differ depending on the level of the change in formulation from the approved product.

Section 2: Terminology

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

Reference product: One lot should be selected from among three marketed lots of products The reference product should show intermediate dissolution among the three lots using the following test solution(1) or (2). The dissolution tests (Sec. 4) should be performed using 6 units, by the paddle method at 50 rpm.

(1) The specification test condition should be used, if the dissolution specifications are established in the specifications and test procedures.

(2) Among the test solutions described in the dissolution conditions in Sec. 3.A.V., if the dissolution rate reaches to 85% for at least one lot, the test solution should be selected which provides the slowest dissolution from the reference product. If the dissolution from the reference product does not reach 85 % in any lot, the test solution providing the fastest dissolution should be used

Test product: These are products with different strengths from that of reference products. The test product 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. 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.IV.4) published on December 22 in 1997,and miner revised on 31

May 2001 and again on Nobember 24 2006..

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

Level of formulation change is calculated comparing to the basic products.When the ratios of compositions are identical between test and reference products, the formulation change is Level A. This means that test and reference products are the same in ratios of all components including coating agents and, in the case of coated products, the weight of film and/or sugar-coated layers per surface area of the core must be same.

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

When the ratios are not identical, 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 is 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 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

Bioequivalence tests should, in principle, be performed with the same dose, less than the maximum dose shown in the dosage regimen. When the use of different doses is unavoidable, the pharmacokinetic parameters should be normalized for the dose administered which, however, is limited to drugs with linear pharmacokinetics. If more than one dosage unit is used in a dissolution vessel, the drug amount of in the vessel should not exceed the amount of a higher strength product.

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. Test and reference products are considered to be bioequivalent when their dissolution is judged to be equivalent according to the criteria in Sec. 5 (1) and (2). 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 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	Glybuzole

1)Whether the drugs approved after 1999 belong to the narrow therapeutic category or not, should be determined referring to the above linted drugs.
2)Acetohexamine, 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.IV. 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 dissolution from reference products should be over 85% within the testing time specified in at least one test condition.in case of conventional dosage forms and enteric coated products, and should be over 80% in case of oral controlled release dosage forms. The 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. When similarity factor, f2 is used, the dissolution data at the time points specified in Appendix 1(2) 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:

he results meet one of the following criteria.

Conventional dosage forms and enteric coated products

a. The average dissolution from reference products reaches 85% within the testing time specified: the average dissolved amount of the test products does not deviate by more than 10% from that of the reference product at three time points when the average dissolved amount of the reference product is around 40% and 85%. When f2 is used, the f2 value should be not less than50.

b. When the average dissolution of reference products is between 50 and 85 % at the testing time point: There is no sample of test product that shows a deviation of more than 8% in dissolution from the average dissolution of the test product at the testing time specified as well as at a time point when the average dissolved amount of the reference product reaches half of the average dissolved amount at the testing time specified. When f2 is used, the f2 value should be not less than 55.

c. 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 6% in dissolution from the average dissolution of the test product at the testing time specified as well as at a time point when the average dissolved amount of the reference product reaches half of the average dissolved amount at the testing time specified. When f2 is used, the f2 value should be not less than 61.

Oral controlled release dosage forms

a. The average dissolution from reference product reaches 80% within the testing time specified: the average dissolved amount of the test product does not deviate by more than 10% from that of the reference product at three time points when the average dissolved amount of the reference product is around 30%, 50% and 80%. When f2 is used, the f2 value should be not less than 50.

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 8% in dissolution from the average dissolution of the test product at the testing time specified as well at a time point when the average dissolved amount of the reference product reaches half of the average dissolved amount at the testing time specified. When f2 is used, the f2 value should be not less than 55.

c. 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 6% in dissolution from the average dissolution of the test product at the testing time specified as well at a time point when the average dissolved amount of the reference

product reaches half of the average dissolved amount at the testing time specified. When f2 is used, the f2 value should be not less than 61.

(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 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 reference product, and one or no sample that shows a deviation of more than 15%.

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 reference product, and one or no sample that shows a deviation of more than 12%.

c. 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 reference product, and one or no sample that shows the deviation of more than 10%.

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%(80% for controlled release dosage forms) between 15 and 30 min: 15, 30, 45min.
2) When the average dissolution from the reference product reaches 85%(80% for controlled release dosage forms) 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%(80% for controlled release dosage forms) 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% (80% for controlled release dosage forms) 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.

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.