Q-54 Is there a referred alternate dissolution method to address the following: "when a phenomenon that disintegrants deposit in the bottom of vessel or paddle is observed, the paddle method at 75 rpm or the rotating basket method at 100 rpm can be used instead of the paddle method at 50 rpm"? Also, is it necessary to compare the dissolution profiles in the paddle method at 50 rpm?

(A) Either the paddle method at 75 rpm or the rotating basket method at 100 rpm can be selected arbitrarily. Comparison of dissolution using the paddle method at 50 rpm should be performed to show the dissolution profile in that condition. "...[A] phenomenon that disintegrants deposit in the bottom of vessel or paddle" may be objectively demonstrated, for example, with photographs.

Q-55 When the paddle method at 75 rpm or the rotating basket method at 100 rpm is used instead of the paddle method at 50 rpm, which "Significant difference in dissolution" should be evaluated?

(A) The "significant difference in dissolution" should be evaluated in the dissolution condition where the dissolution profile is evaluated.

Q-56 In the case that active ingredients adsorb to the vessel or paddle, is it acceptable to use the vessel or paddle to which the active ingredient adsorb the least?

(A) The Japanese Pharmacopoeia does not stipulate the materials used to construct the vessel and paddle, therefore vessels and paddles made of appropriate materials can be used.

Q-57 When formulations float on the dissolution testing solution, is it acceptable to use sinkers?

(A) When formulations float on the dissolution testing solution, sinkers can be used. In this case, the sinkers should be used for both reference and test products.

Q-58 What is the significance in adding surfactants in the dissolution test of low solubility drugs?

(A) Comparing dissolution rates of products containing low solubility drugs is difficult because those products reach their saturated solubility at a lower dissolution rate. Surfactants are added in the dissolution tests of those products in order to compare dissolution rates between the products by increasing the drug solubility. Polysorbate 80 is recommended as the first choice to examine the effect of surfactant.

Q-59 Please indicate the acceptable range of values when the average dissolutions are compared in the assessment of similarity and equivalence in the dissolution profiles. For example, the Guideline states that, "the average dissolution rate of the test drug product is within the range of the average dissolution rate of the reference drug product ± 15%" Does the "±15%" indicate the relative or absolute value of the difference in the dissolution rates?

(A) The acceptable criteria (±15%) indicates the absolute value of the difference in the average dissolution rate of the test and reference product. For example, the Guideline states, "the average dissolved amount of test products does not deviate by more than 15% from that of the reference

product at two time points when the average dissolved amount of the reference product is around 60% and 85%," in determining dissolution similarity in immediate-release products and enteric-coated products. For a reference product that has average dissolution rates of 63% and 87%, the acceptable range of the test product would be 48% to 78% and 72% to 102%, respectively. For determining dissolution equivalence between extended-release products, the Guideline also states, "When the average dissolution of the reference products reaches between 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." For a reference product that has average dissolution rates of 73% at the specified testing time and 35% at the time specified for the half of the average dissolution, the acceptable range of the test product would be 65% to 81% and 27% to 43% respectively.

Q-60 Why are some of the dissolution rate sampling times for calculation of the similarity factor (f2) in this Guideline different from those in the US SUPAC (Scale-up and Post-Approval Changes) guidance?

(A) The value of the f2 function depends on the time point at which the dissolution rates are compared. For example, f2 values become larger if the number of comparison points increases at the point at which the difference in the dissolution rates is small in the dissolution curve. The time for comparison is specified in the Guideline in order to avoid such errors. It is acceptable to set the comparison time points that are appropriate to implement dissolution tests that satisfy the dissolution rates specified for reference products, rather than the exact time that exhibits the specified dissolution rates when either comparing the mean value or applying the f2 calculation.

Q-61 The Guideline states that, "If dissolution of the reference product or test product has a lag time, the dissolution curve can be adjusted with the dissolution lag time." Is it acceptable to compare dissolution profiles without the adjustment even when there are lag times? Please explain how to adjust dissolution curves in dissolution tests with lag times.

(A) Adjustment with lag times is not always needed for comparing dissolution rates. Refer to Appendix A for the methods to adjust dissolution profiles with lag times.

VI. Reporting of bioequivalence study results

Q-62 Items (6) to (9) such as solubility, particle size, and crystal form, are generally published by the innovator product manufacturers. Is it necessary to submit these items?

(A) A formulation design needs to be conducted with full knowledge of those physicochemical characteristics. Therefore, these items for the generic products should be investigated and reported, as much as possible.

Q-63 Why is the narrower criterion, the dissolution equivalence, employed for extended-release products to compare dissolution similarity for immediate-release products and also applied when determining bioequivalence when it is difficult to judge bioequivalence by human studies alone?

(A) Extended-release products usually contain larger amounts of active ingredients compared to immediate-release products because they have a longer dose interval. They may also remain for a longer time in the gastrointestinal tract. In addition, extended-release products have functions that control the release of the active ingredients. In order to ensure safety and assess function, the similarity criterion for dissolution profiles of extended-release products is stricter than that for immediate-release products.

Q-64 Should physicochemical studies of the drug substance be used for a generic product, based on disclosed information on the drug substance used in the innovator product? For example, should the same measurement methods for items such as particle size be used? If information on the innovator product is not available, are those data required for the generic product?

(A) Any method for physicochemical measurement can be used as long as the method is regarded as scientifically appropriate. However, the methods and devices used in the measurement, and the measured values, must be reported. Regardless of the availability of information on the innovator product, the required information on the drug substance used in the generic product should be reported.

Q-65 How should the time points used to determine the elimination rate constant (k_{el}) be represented? Is it acceptable to calculate k_{el} from mean blood concentrations?

(A) The data should be represented in a table, or the points can be marked on individual subject blood concentration–time profiles because the individual profile should be attached. It is important to know mean and standard deviation of k_{el} and thus it is not acceptable to calculate k_{el} from the mean blood concentration curve.

Q-66 Are the items in "VI. Reporting of test results" those to be reported in the application form (E-5-1)? Are these reporting items also required for the clinical study report? Please explain how to relate "the Guideline for Bioequivalence Studies for Generic Products" with "the Guideline of structure and Contents for Clinical Study Report" when the clinical study report is attached to the application documents.

(A) The items should be those included in the (E-5) "Bioequivalence" part of the documentation, and should be submitted when applying for manufacturing/marketing approval of medicinal product for ethical use. The report of the items listed in "the Guideline for Bioequivalence Studies of Generic Products" should be prepared and should refer to "Structure and Content of Clinical Study Reports," Director-Notification No. 335 of the Pharmaceutical Affairs Bureau, dated May 1, 1996.

B. Oral extended-release products

I. Reference and test products

Q-67 The Guideline states that in oral extended-release products, the size, shape, density, and release mechanism of generic products should not differ markedly from those of the innovator products. What is the reason for imposing these conditions?

(A) Unlike immediate-release products, extended-release products often transit through the digestive tract retaining their original shape for relatively long periods of time. Bioavailability of formulations with different shapes, sizes, specific gravity, and release mechanisms tend to vary depending on the subject and administration conditions because the properties of these formulations are susceptible to different physiological factors in the digestive tract. Therefore, generic oral extended-release products are required to have the same release mechanisms as the innovator product. The similarity of release mechanisms should be explained by distinguishing the formulation characteristics: whether they use a matrix system or a controlling membrane, a single unit or multiple units, and disintegrating or non-disintegrating types.

Q-68 Unlike immediate-release products, it is a prerequisite for the initiation of a bioequivalence study that the dissolution profile of extended-release test products is similar to that of the reference products. What is the reason for this?

(A) It is possible, under the diverse physiological conditions of the digestive tract, that 2 formulations with different release mechanisms may have different movement and/or release within the digestive tract. In human studies, bioequivalence is assessed only under fasting and certain fixed conditions, which does not always ensure bioequivalence under other conditions. Formulations with similar release mechanisms are expected to show similarity in movement and in releasing performance in the gastrointestinal tract, even under diverse physiological conditions. Therefore, as a prerequisite for conducting bioequivalence studies using extended-release formulations, it must be demonstrated that the formulations have the same control release mechanism. This condition must be met as a proof that the release mechanism of a test product is not different from that of a reference product. If comparison of dissolution profiles is not possible because of limited active ingredient solubility in any of the specified dissolution test solutions, other information is required to explain that the release mechanism of the test product does not differ from that of the reference product.

II. Bioequivalence studies

1. Test methods

Q-69 Why should bioequivalence be assessed in fasted and fed states?

(A) Extended-release products usually contain higher doses compared to immediate-release

products, and their releasing performance is guaranteed by the special releasing control mechanisms. Therefore, it is important to confirm that the test and reference product mechanisms work equivalently in both the fasting state and in the fed state, which is the more severe condition. The tests should be performed with a high fat diet to mimic the most severe conditions.

Q-70 What is the reason for the product to be administered 10 minutes after a high-fat diet but 30 minutes after a low-fat diet?

(A) Administration in the fed state is conducted in order to confirm that bioavailability of the product does not relatively change between formulations because of a meal. To investigate the effect of a meal on bioavailability, a shorter interval between the meal and administration is an optimal condition. Therefore, for a high-fat diet, it has been decided that the products are to be administered 10 minutes after the meal. When studies in the fasted state are difficult to implement, the products are to be administrated 30 minutes after eating a low-fat meal to minimize the effect of the meal.

Q-71 The paddle method at 200 rpm or the method using the disintegration testing apparatus is quite severe. Why are these methods used?

(A) Dissolution tests are used to demonstrate that the release-controlling mechanisms between formulations are the same and to assess their bioequivalence as supportive data. Therefore, if the dissolution profiles of the products under certain severe conditions are the same, it is possible to infer, in some cases, that functions of the products would be similar under severe conditions within the body.

C. Non-oral dosage forms

Q-72 In non-oral dosage products, the Guideline states that a dissolution (release) test or alternative physicochemical tests should be performed. What sort of physicochemical tests are required?

(A) Possible examples of physicochemical tests include release tests for suppositories and dissolution tests for aqueous suspensions for injections.

D. Dosage forms for which bioequivalence studies are waived

Q-73 Should the bioequivalence studies in the Guideline be performed even for solutions for subcutaneous or intramuscular injection where special excipients are not used?

(A) Bioequivalence studies should be performed for such medicinal products according to the Guideline because sufficient information on the effect of excipients and on the absorption rates of subcutaneous or intramuscular injections are not available currently.

Q-74 Can bioequivalence studies of "Injections for arterial administration, administered as an

aqueous solution" and "Injections for intraspinal administration, administered as an aqueous solution" be waived?

(A) Bioequivalence studies of medicinal products such as arterial injections and intraspinal or epidural injections are not waived. These medicinal products, different from intravenous injections, are categorized as a product for topical use that are applied directly on, or near to, the targeted tissues. Bioequivalence of these medicinal products should be assessed on the basis of the clinical studies specified in the Guideline, Section C.III.

Attachment 2

Appendix A: Adjusting Dissolution Curves with Lag Times

The dissolution curve with a lag time is adjusted according to the steps below. If adjustment of the dissolution curve or calculation of dissolution rates by interpolation is anticipated before initiating the study, the frequency of measurement should be arranged such that the rates can be measured at intervals of about 5 minutes, or at intervals of about 10% in the dissolution rate to avoid increasing the errors caused by interpolation.

Lag times of the individual reference and test products are determined using the following steps:

1. Predict the time interval in which a lag time (t_L) appears by obtaining the entire profile of the dissolution rate–time curve in the preliminary test. Select measurement points at small intervals before and after the time interval, and obtain the curve by connecting the points with a line. Determine the time (t_L) at which the dissolution rate of 5% is obtained by reading the curve (or graph) or by interpolation. The time obtained in these methods is defined as "lag time."
2. Calculate adjusted measurement times by adjusting measurement times for lag times for each medicinal product to obtain a dissolution curve with adjusted measurement times.
3. Obtain the average dissolution curve of the reference and test products as follows:
4. Determine the time needed to obtain an average dissolution curve (t_{si}). The number of measurement points should be almost the same as the number of points after the lag time in the unadjusted dissolution curve. The dissolution rates at t_{si} of the reference and test medicinal products are determined by interpolation or by reading the values on the curve (graph). Calculate average dissolution rates at each t_{si} to obtain an average dissolution curve.
5. The average dissolution curve of the test product is determined according to steps (1) to (3) of Section A-1 and A-2, described below. The t_{si}, the time needed to calculate average dissolution rates, should be the same as that for the reference product.
6. According to the Guideline, determine comparison times (t_{ci}) at which the dissolution rates of the reference and test products are compared. Determine an average dissolution rate of the reference product at t_{ci} by interpolation or by reading the curve.

Examples for adjusting the dissolution curves are shown below when the average dissolution rates of the reference product reach 85% within the specified time and for cases in which they do not.

A-1 An example when the average dissolution rate of the reference product reaches 85% within the specified time:

Assume that a dissolution test is performed using 12 units of the reference product and the results in Table 1 are obtained.

Step 1. Calculating a lag time.

In each dissolution curve t_A where a dissolution rate reaches d_A% is calculated according to the

Attachment 2

formula below:

$$t_A = t_1 + (d_A - d_1) \times (t_2 - t_1) / (d_2 - d_1) \quad (1)$$

Here, t_1: measurement time just before a dissolution rate reaches d_A%.

t_2: measurement time just after a dissolution rate exceeds d_A%.

d_1: dissolution rate at t_1.

d_2: dissolution rate at t_2.

Table 1: Dissolution rate (%) of each reference product

Products	Time (minutes)														
	0	5	10	15	20	25	30	35	40	45	52.5	60	67.5	75	90
①	0.0	1.3	8.1	17.8	29.3	41.6	51.6	60.1	68.3	75.2	81.8	84.1	91.2	97.2	100.0
②	0.0	0.8	8.9	20.9	31.8	42.2	52.0	59.1	66.3	72.9	81.3	88.9	93.7	96.7	98.5
③	0.0	1.8	11.3	23.7	35.0	45.8	55.7	62.2	70.3	77.3	82.8	88.1	91.0	94.1	97.2
④	0.0	1.6	7.4	16.1	26.4	36.5	44.9	55.5	65.5	75.1	82.9	86.7	92.3	96.5	98.9
⑤	0.0	1.1	7.1	15.6	25.5	35.0	44.3	52.6	61.3	69.3	78.4	86.7	94.2	97.5	99.1
⑥	0.0	0.5	6.6	16.0	26.0	36.8	44.7	54.1	61.4	70.4	77.5	88.0	90.5	97.8	100.0
⑦	0.0	1.4	9.5	22.7	35.1	43.3	55.8	63.8	75.0	79.3	83.3	85.3	90.2	95.8	97.7
⑧	0.0	0.5	8.1	18.6	31.0	42.0	53.7	62.1	67.1	72.9	78.4	81.2	85.0	86.5	91.7
⑨	0.0	0.3	6.6	13.8	21.5	30.4	42.3	50.8	65.4	73.0	80.1	84.9	89.4	93.6	95.2
⑩	0.0	0.0	5.3	10.5	17.5	30.2	35.6	43.6	52.0	59.6	67.8	80.9	88.2	94.6	98.1
⑪	0.0	0.8	6.3	18.2	27.3	42.5	50.5	58.4	70.3	76.4	84.1	89.9	93.3	94.9	96.5
⑫	0.0	1.8	13.6	27.5	42.1	57.8	65.3	70.0	72.4	76.5	80.4	82.6	87.1	87.3	97.2
Mean before adjusting	0.0	1.0	8.2	18.5	29.0	40.3	49.7	57.7	66.3	73.2	79.9	85.6	90.5	94.4	97.5

A lag time (t_L) is calculated by placing d_A = 5% in formula (1). t_A can be read from the curve (graph).

Using the medicinal product ① in Table 1 as an example, t_L is calculated to be 7.7 min using t_1 = 5 min, d_1 = 1.3%, t_2 = 10 min, d_2 = 8.1%. Similarly, the lag times calculated for products No. 2 through No. 12 are shown in the third column of Table 2.

Step 2. Creating a dissolution curve adjusted for a lag time.

Subtract lag times from measurement times in individual products, and use the times obtained as adjusted measurement times. The dissolution rates and adjusted measurement times are shown in Table 2 and the dissolution curves before and after the adjustment are shown in Figs. 1 and 2.

Step 3. Calculating the average dissolution rates from the dissolution data of individual products whose lag times are adjusted.

The times (t_{si}) needed for calculating average dissolution rates are determined by the method described below. In Table 2, the slowest time among the first adjusted measurements (measurement at 10 min), 3.6 min, is obtained in product No. 12, and as a result, 4 min is set as the starting time for calculating the average dissolution rate, t_{s1}. Similarly, the fastest time among the last adjusted measurements (measurement at 90 min), 80.3 min, is obtained for product No. 10, and 80 min is set as the ending time, t_{slast}, to calculate the average dissolution rates. The time subtracted for an average lag time of 8.0 min from the actual measurement time is used as a medium measurement time to calculate

an average dissolution rate. Excluding zero, the original data have 14 measurement points (Table 1), and the data for calculating an average dissolution rate have 13 points (Table 2).

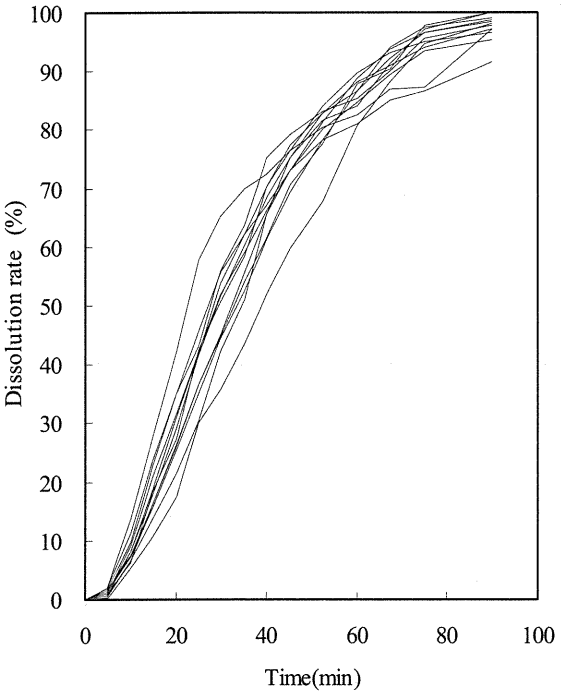

Figure 1: Dissolution curves of each product (measured values)

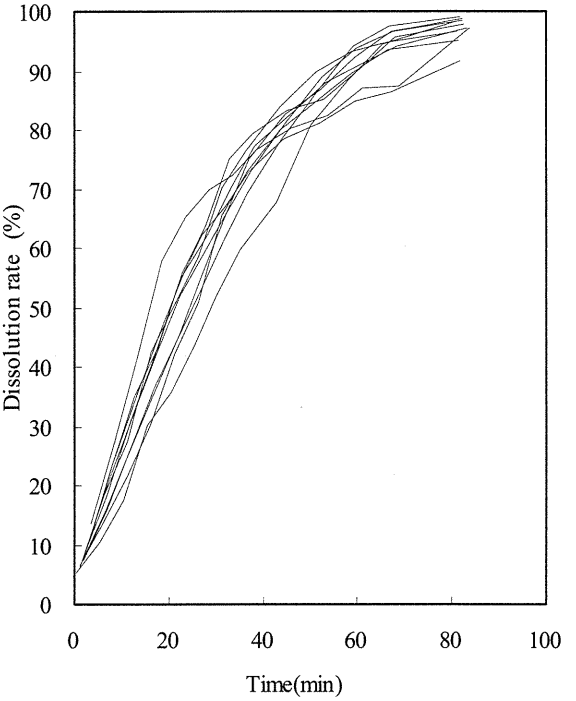

Figure 2: Lag-time adjusted dissolution curves of each product

Table 2 Adjusted time-points and dissolution rate for each reference product

Products	Time (min)	t_L	10	15	20	25	30	35	40	45	52.5	60	67.5	75	90
①	Adjusted time(min)	7.7	2.3	7.3	12.3	17.3	22.3	27.3	32.3	37.3	44.8	52.3	59.8	67.3	82.3
	Dissolution rate(%)		8.1	17.8	29.3	41.6	51.6	60.1	68.3	75.2	81.8	84.1	91.2	97.2	100.0
②	Adjusted time(min)	7.6	2.4	7.4	12.4	17.4	22.4	27.4	32.4	37.4	44.9	52.4	59.9	67.4	82.4
	Dissolution rate(%)		8.9	20.9	31.8	42.2	52.0	59.1	66.3	72.9	81.3	88.9	93.7	96.7	98.5
③	Adjusted time(min)	6.7	3.3	8.3	13.3	18.3	23.3	28.3	33.3	38.3	45.8	53.3	60.8	68.3	83.3
	Dissolution rate(%)		11.3	23.7	35.0	45.8	55.7	62.2	70.3	77.3	82.8	88.1	91.0	94.1	97.2
④	Adjusted time(min)	7.9	2.1	7.1	12.1	17.1	22.1	27.1	32.1	37.1	44.6	52.1	59.6	67.1	82.1
	Dissolution rate(%)		7.4	16.1	26.4	36.5	44.9	55.5	65.5	75.1	82.9	86.7	92.3	96.5	98.9
⑤	Adjusted time(min)	8.3	1.7	6.7	11.7	16.7	21.7	26.7	31.7	36.7	44.2	51.7	59.2	66.7	81.7
	Dissolution rate(%)		7.1	15.6	25.5	35.0	44.3	52.6	61.3	69.3	78.4	86.7	94.2	97.5	99.1
⑥	Adjusted time(min)	8.7	1.3	6.3	11.3	16.3	21.3	26.3	31.3	36.3	43.8	51.3	58.8	66.3	81.3
	Dissolution rate(%)		6.6	16.0	26.0	36.8	44.7	54.1	61.4	70.4	77.5	88.0	90.5	97.8	100.0
⑦	Adjusted time(min)	7.2	2.8	7.8	12.8	17.8	22.8	27.8	32.8	37.8	45.3	52.8	60.3	67.8	82.8
	Dissolution rate(%)		9.5	22.7	35.1	43.3	55.8	63.8	75.0	79.3	83.3	85.3	90.2	95.8	97.7
⑧	Adjusted time(min)	8.0	2.0	7.0	12.0	17.0	22.0	27.0	32.0	37.0	44.5	52.0	59.5	67.0	82.0
	Dissolution rate(%)		8.1	18.6	31.0	42.0	53.7	62.1	67.1	72.9	78.4	81.2	85.0	86.5	91.7
⑨	Adjusted time(min)	8.7	1.3	6.3	11.3	16.3	21.3	26.3	31.3	36.3	43.8	51.3	58.8	66.3	81.3
	Dissolution rate(%)		6.6	13.8	21.5	30.4	42.3	50.8	65.4	73.0	80.1	84.9	89.4	93.6	95.2
⑩	Adjusted time(min)	9.7	0.3	5.3	10.3	15.3	20.3	25.3	30.3	35.3	42.8	50.3	57.8	65.3	80.3
	Dissolution rate(%)		5.3	10.5	17.5	30.2	35.6	43.6	52.0	59.6	67.8	80.9	88.2	94.6	98.1
⑪	Adjusted time(min)	8.8	1.2	6.2	11.2	16.2	21.2	26.2	31.2	36.2	43.7	51.2	58.7	66.2	81.2
	Dissolution rate(%)		6.3	18.2	27.3	42.5	50.5	58.4	70.3	76.4	84.1	89.9	93.3	94.9	96.5
⑫	Adjusted time(min)	6.4	3.6	8.6	13.6	18.6	23.6	28.6	33.6	38.6	46.1	53.6	61.1	68.6	83.6
	Dissolution rate(%)		13.6	27.5	42.1	57.8	65.3	70.0	72.4	76.5	80.4	82.6	87.1	87.3	97.2

The dissolution rate (d_B) at a particular time (t_{si}) for calculating an average dissolution rate is determined using the following formula:

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$$d_B = d_1 + (d_2 - d_1) \times (t_{si} - t_1) / (t_2 - t_1) \quad (2)$$

Here, t_1: adjusted measurement time just before t_{si}.

t_2: adjusted measurement time just after t_{si}.

d_1: dissolution rate at t_1.

d_2: dissolution rate at t_2.

Table 3 shows the times for calculating the average dissolution rates and the dissolution rates calculated by interpolation for each product. Figure 3 shows the average dissolution curves before and after adjustment.

Table 3 Time-points used to calculate mean dissolution rate obtained by interpolation.

Products	tsi												
	4	7	12	17	22	27	32	37	44.5	52	59.5	67	80
①	11.4	17.2	28.6	40.9	51.0	59.6	67.8	74.8	81.5	84.0	90.9	97.0	99.6
②	12.7	19.9	30.9	41.4	51.2	58.5	65.7	72.4	80.9	88.5	93.4	96.5	98.2
③	13.0	20.5	32.1	43.0	53.1	60.5	68.2	75.5	80.9	87.2	90.5	93.6	96.5
④	10.7	15.9	26.2	36.3	44.7	55.3	65.3	74.9	82.8	86.6	92.2	96.5	98.6
⑤	11.0	16.2	26.1	35.6	44.8	53.1	61.8	69.7	78.7	87.0	94.3	97.5	98.9
⑥	11.7	17.4	27.5	37.9	46.0	55.1	62.7	71.1	78.5	88.2	91.2	97.9	99.8
⑦	12.7	20.6	33.1	42.0	53.8	62.5	73.2	78.6	82.9	85.1	89.7	95.2	97.3
⑧	12.3	18.6	31.0	42.0	53.7	62.1	67.1	72.9	78.4	81.2	85.0	86.5	91.0
⑨	10.5	14.9	22.7	32.0	43.5	52.8	66.5	73.7	80.5	85.3	89.8	93.7	95.1
⑩	9.1	12.9	21.9	32.1	38.3	46.5	54.6	61.5	70.8	82.6	89.7	95.0	98.0
⑪	13.0	19.7	29.7	43.8	51.8	60.3	71.3	77.2	84.7	90.3	93.5	95.0	96.4
⑫	14.7	23.1	37.4	52.8	62.9	68.5	71.6	75.2	79.6	82.1	86.1	87.3	94.8
Mean	11.9	18.1	28.9	40.0	49.6	57.9	66.3	73.1	80.0	85.7	90.5	94.3	97.0

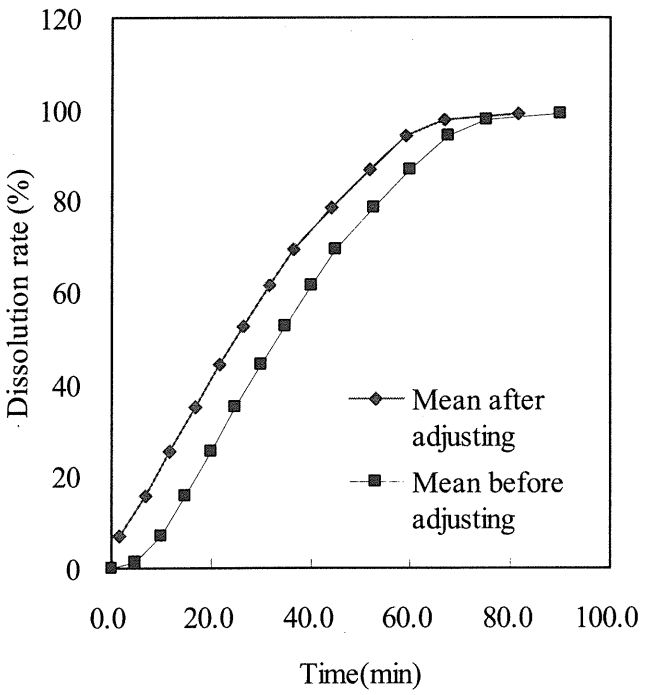

Figure 3: Mean dissolution curves before and after adjustment

Step 4. Determining the times for comparing dissolution profiles and the dissolution rates.

For the reference product in this example, the lag times are observed, and the dissolution rates do not reach 85% after 30 minutes of the lag time but do reach 85% by the specified time. Therefore, this example corresponds to criteria a, under No. 3, Item 4, Section 3-A of the Guideline. The criteria specify that the comparison time, t_{ci}, when the average dissolution rates are compared without f_2 functions, should be the reasonable time at which the reference product dissolution rates reach 40% and 85%. When there is no lag time adjustment, the average dissolution rates at the closest measurement point to 40% or 85% can be compared. When there is a lag time adjustment, the times at which the average reference product dissolution rates reach 40% and 85% are determined by interpolation, and the dissolution rates are then compared at those times. In this example, the time, t_{c1}, at which the reference product dissolution rates reach 40% is 17.0 min, as shown in Table 3. The time, t_{c2}, at which the rates of the reference product reach 85% is determined using formula (1). Data in Table 3 reveal that d_A = 85.0 %, d_1 = 80.1%, d_2 = 85.7%, t_1 = 44.5 min, and t_2 = 52.0 min. Thus, using the following formula, the time at 85% dissolution is calculated to be 51.1 min:

$$t_A = 44.5 + (85.0-80.0) \times (52.0-44.5) / (85.7-80.0) = 51.1$$

When the f_2 function is applied, Ta/4, 2Ta/4, 3Ta/4, and Ta are comparison points if Ta is considered to be a time point at which the average reference product dissolution rates are approximately 85%. t_{c2}, determined above, is Ta, so in this example, the calculation method is not used, and Ta/4, 2 Ta/4, and 3 Ta/4 are calculated as 12.8, 25.5, and 38.3, respectively. The average reference product dissolution rates at each time point are determined using formula (2), and the following results are obtained:

$$= 28.9 + (40.0-28.9) \times (12.8-12.0) / (17.0-12.0) = 30.7\%$$
$$= 49.6 + (57.9-49.6) \times (25.5-22.0) / (27.0-22.0) = 55.4\%$$
$$= 73.1 + (80.0-73.1) \times (38.3-37.0) / (44.5-37.0) = 74.3\%$$

Step 5. Determining the dissolution rates of the test product at the comparison time point.

The average dissolution curves are determined using steps 1) to 3), although the data for the example are not shown. When the average dissolution rates are compared on the basis of those curves without f2 functions, the rates are determined to be 17.0 min and 51.1 min. When f_2 functions are applied, the rates are determined to be 12.8, 25.5, 38.3, and 51.1 min.

A-2 An example of when the average reference product dissolution rates do not reach 85% within the specified time.

Assuming that a dissolution test is performed using 12 units of the reference product, the results in Table 4 are obtained:

Table 4: Actual value of dissolution rates (%) of individual reference product

Products	Time (min)													
	0	5	10	15	20	25	30	37.5	45	60	90	120	240	360
①	0.0	0.0	1.6	3.5	12.4	18.9	38.9	46.5	48.1	58.3	65.0	72.3	73.0	75.2
②	0.0	0.0	0.0	7.4	11.1	19.4	29.9	44.7	52.0	60.9	70.2	74.2	72.9	74.9
③	0.0	0.0	0.7	6.0	15.5	24.0	31.9	45.1	52.5	60.3	70.7	72.8	73.6	76.7
④	0.0	0.0	1.1	5.7	16.5	24.5	35.7	43.3	48.4	58.8	71.7	74.4	75.0	77.8
⑤	0.0	0.0	1.3	8.0	10.5	20.9	34.3	47.3	52.4	56.5	65.9	73.8	73.7	74.8
⑥	0.0	0.0	3.0	3.3	12.9	22.3	39.8	41.8	47.8	62.0	69.9	70.7	73.7	75.3
⑦	0.0	0.4	1.3	6.9	10.1	24.8	29.2	41.4	47.0	63.6	73.5	73.5	76.5	77.6
⑧	0.0	0.2	0.2	5.5	12.6	27.4	28.7	43.0	48.9	58.7	70.6	71.4	72.0	76.6
⑨	0.0	0.0	1.8	6.8	18.6	19.4	32.9	37.5	49.1	61.6	69.2	71.8	72.9	78.0
⑩	0.0	0.7	1.0	4.9	14.2	20.2	27.8	41.2	54.9	61.1	71.2	72.5	75.0	75.1
⑪	0.0	0.0	0.1	7.6	16.1	21.5	38.4	38.6	50.0	58.7	66.8	71.0	73.2	74.9
⑫	0.0	0.4	2.8	5.4	10.9	22.5	33.4	45.2	48.4	61.2	66.5	72.4	73.0	73.4
Mean before adjustment	0.0	0.1	1.3	5.9	13.5	22.1	33.4	43.0	50.0	60.2	69.3	72.6	73.7	76.1

Step 1. Calculating a lag time.

The adjusted measurement time obtained from the calculation of the dissolution lag times for each product using formula (1), using the same method as in example A-1, is shown in Table 5. In this example, all values adjusted for lag times are rounded to whole minutes.

Table 5: Adjusted time-points and dissolution rates

Products	t_L (min	Time (min)	20	25	30	37.5	45	60	90	120	240	360
①		Adjusted time(min)	4	9	14	22	29	44	74	104	224	344
	16	Dissolution rate(%)	12.4	18.9	38.9	46.5	48.1	58.3	65.0	72.3	73.0	75.2
②		Adjusted time(min)	7	12	17	24	32	47	77	107	227	347
	13	Dissolution rate(%)	11.1	19.4	29.9	44.7	52.0	60.9	70.2	74.2	72.9	74.8
③		Adjusted time(min)	6	11	16	23	31	46	76	106	226	346
	14	Dissolution rate(%)	15.5	24.0	31.9	45.1	52.5	60.3	70.7	72.8	73.6	76.7
④		Adjusted time(min)	6	11	16	23	31	46	76	106	226	346
	14	Dissolution rate(%)	16.5	24.5	35.7	43.3	48.4	58.8	71.7	74.4	75.0	77.8
⑤		Adjusted time(min)	7	12	17	24	32	47	77	107	227	347
	13	Dissolution rate(%)	10.5	20.9	34.3	47.3	52.4	56.5	65.9	73.8	73.7	74.8
⑥		Adjusted time(min)	4	9	14	22	29	44	74	104	224	344
	16	Dissolution rate(%)	12.9	22.3	39.8	41.8	47.8	62.0	69.9	70.7	73.7	75.3
⑦		Adjusted time(min)	7	12	17	24	32	47	77	107	227	347
	13	Dissolution rate(%)	10.1	24.8	29.2	41.4	47.0	63.6	73.5	73.5	76.5	77.6
⑧		Adjusted time(min)	5	10	15	23	30	45	75	105	225	345
	15	Dissolution rate(%)	12.6	27.4	28.7	43.0	48.9	58.7	70.6	71.4	72.0	76.6
⑨		Adjusted time(min)	7	12	17	24	32	47	77	107	227	347
	13	Dissolution rate(%)	18.6	19.4	32.9	37.5	49.1	61.6	69.2	71.8	72.9	78.0
⑩		Adjusted time(min)	5	10	15	23	30	45	75	105	225	345
	15	Dissolution rate(%)	14.2	20.2	27.8	41.2	54.9	61.1	71.2	72.5	75.0	75.1
⑪		Adjusted time(min)	7	12	17	24	32	47	77	107	227	347
	13	Dissolution rate(%)	16.1	21.5	38.4	38.6	50.0	58.7	66.8	71.0	73.2	74.9
⑫		Adjusted time(min)	6	11	16	23	31	46	76	106	226	346
	14	Dissolution rate(%)	10.9	22.5	33.4	45.2	48.4	61.2	66.5	72.4	73.0	73.4

Step 2. Creating a dissolution curve adjusted for a lag time.

Similar to A-1, the values obtained by subtracting lag times from measurement times are considered

to be an adjusted measurement time. Table 5 shows the dissolution rates and adjusted measurement times of individual product units.

Step 3. Calculating the average dissolution rates from the dissolution data of individual product units where lag times are adjusted.

When the dissolution rates do not reach 85% within the specified time, the time point for comparing average dissolution rates should be determined using the dissolution rate at the final measurement time for a reference product as a criterion. When a lag time is observed, the dissolution testing time for each product unit varies depending on the lag time. The shortest testing time is used as the final measurement time for all product units because the product with the longest lag time has the shortest testing time.

For example, the shortest testing time is 344 minutes in products No. 1 and No. 6, and thus 344 minutes is used as a final time, t_{slast}, for calculating an average dissolution rate. For other time points, most products show the adjusted measurement times, such as 7, 12, 17,...227; those times are then used as the time (t_{si}) for calculating average dissolution times, and the calculation procedure can be skipped. The individual product dissolution rates at t_{si} using formula (2) are calculated, and the results are shown in Table 6. The average dissolution curves before and after the adjustment are also shown in Figure 4.

Table 6: Time tsi for calculating the mean dissolution rate, and dissolution rates(%)

Products	tsi									
	7	12	17	24	32	47	77	107	227	344
①	16.3	30.9	41.8	47.0	51.1	58.9	65.7	72.3	73.0	75.1
②	11.1	19.4	29.9	44.7	52.0	60.9	70.2	74.2	72.9	74.9
③	17.2	25.6	33.7	45.6	53.4	60.7	70.8	72.8	73.6	76.6
④	18.1	26.7	37.0	43.8	49.7	59.3	71.8	74.4	75.0	77.7
⑤	10.5	20.9	34.3	45.7	52.4	56.5	65.9	73.8	73.7	74.8
⑥	18.5	32.8	40.6	43.8	51.6	62.8	70.0	70.8	73.7	75.3
⑦	10.1	24.8	29.2	41.4	47.0	63.6	73.5	73.5	76.5	77.6
⑧	18.5	27.9	32.3	43.8	50.9	59.3	70.7	71.4	72.1	76.6
⑨	18.6	19.4	32.9	37.5	49.1	61.6	69.2	71.8	72.9	77.9
⑩	16.6	23.2	31.4	43.9	56.4	61.8	71.3	72.5	75.0	75.1
⑪	16.1	21.5	38.4	38.6	50.0	58.7	66.8	71.0	73.2	74.9
⑫	13.2	24.7	35.1	45.6	49.6	61.5	66.7	72.4	73.0	73.4
Mean after adjustment	15.4	24.8	34.7	43.5	51.1	60.5	69.4	72.6	73.7	75.8

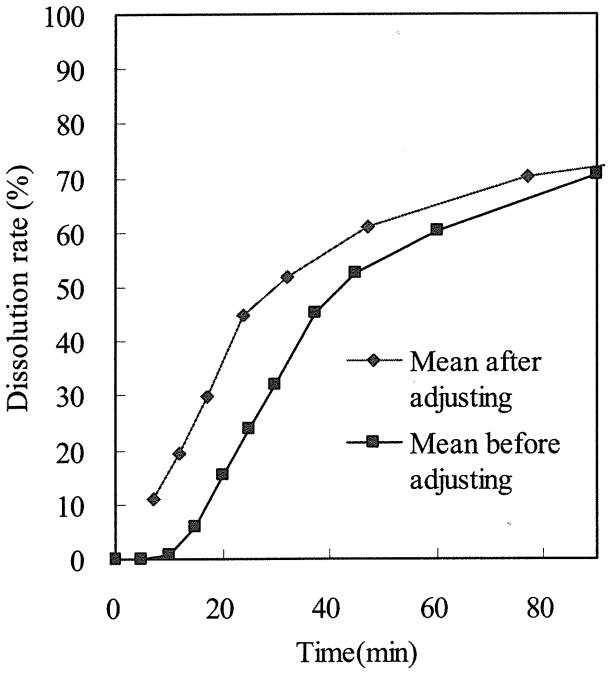

Figure 4: Mean dissolution curves before and after adjustment

Step 4. Determining the times for comparing dissolution profiles and dissolution rates.

When comparing average dissolution rates without f_2 functions, the comparison time point (t_{ci}) is the time showing half of the final average dissolution rate and the final testing time. The average dissolution rate at the final testing time is 75.8%, and half of that is 37.9%. The time, t_{s1}, at which the average dissolution rate is 37.9% is determined using interpolation, and the calculated time is 19 minutes.

When the f_2 function is applied, Ta/4, 2Ta/4, 3Ta/4, and Ta are comparison time points if Ta is considered as a time point at which the final dissolution rate of the reference product is 85%. The average dissolution rate of the reference product at Ta is 64.4% (75.8 × 0.85), and Ta of 46 minutes is calculated using interpolation. Ta/4, 2Ta/4, and 3Ta/4 are calculated to be 12, 23, and 35 minutes, respectively. Since the average dissolution rates at 12 minutes are in shown in Table 6, those at 23 minutes and 35 minutes are calculated using interpolation to be 42.3% and 52.7%, respectively.

Step 5. Determining the dissolution rate of the test product at the comparison time.

The average dissolution curves are determined using steps (1) to (3), but the sample data are not shown. When the average dissolution rates are compared on the basis of the curves without f_2 functions, the rates are determined to be 19 and 344 minutes. Note that when the last measurement time of a test product is shorter than 344 minutes, t_{c1} should be 19 minutes and t_{c2} should be the last test product measurement time. This means that the average test product dissolution rates at t_{c2} should be determined using interpolation. When f_2 functions are applied, the dissolution rates are determined to be 12, 23, 35, and 46 minutes.

Attachment 3

English translation of **Attachment 2 of Division-Notification 0229 No. 10** of the Pharmaceutical and Food Safety Bureau, dated February 29, 2012

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

Index

Section 1: Introduction

This guideline describes the principles of procedures of bioequivalence studies for oral solid dosage forms that contains a different quantity of the active ingredient from an approved medicinal product, but that still maintains the same active ingredient, therapeutic indications, dosage and dose regimen, and dosage form ('a different strength'). The objective of the guideline is to assure the bioequivalence between the products with different strengths when the same doses are administered. The tests required for bioequivalence assessment differ depending on the levels of the formulation changes from the approved product.

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 approved product, 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 test product has a different strength to the reference product. 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 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, the 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.

Except narrow therapeutic range drugs, extended release products and enteric-coated products, the level of the formulation changes of the following 1) - 3) is Level A* irrespective of the levels in Tables 1 and Table 2.

1) Changes where the ratios of all composition are the same, except components of which composition described as "trace use" *.

   * In the case of coated products, ratios of all components in film or sugar coating layers are the same, and the weight of film or sugar coating layers per surface area of the core is the same.

2) Changes of active ingredient 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) 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 s 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[1)] (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

The bioequivalence study should, in principle, be performed at the same dose, not more than the maximum dose shown in the dosage and dose regimen. When the use of different doses is unavoidable, the pharmacokinetic parameters should be normalized by the labeled dose administered (limited to product having linear pharmacokinetics parameters against doses). In principle, the dissolution test should be performed in the condition that the amount of an active ingredient in a vessel should not exceed that of the highest strength product.

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 test, 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 products containing poorly soluble drugs). The test and reference