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Guideline for Bioequivalence Studies of Generic Products

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Section 1: Introduction

This guideline describes the principles of procedures of bioequivalence studies of generic products. The objective of the study is to assure therapeutic equivalence of generic products to innovator products. In the bioequivalence study, bioavailability should be compared for innovator and generic products. If this is not feasible, pharmacological effects supporting therapeutic efficacy or therapeutic effectiveness in major indications should be compared (These comparative tests are hereafter called pharmacodynamic studies and clinical studies, respectively). For oral products, dissolution tests should be performed, since they provide important information concerning bioequivalence.

Section 2: Terminology

Terms used in the guideline are defined as follows:

Bioavailability: The rate and extent of absorption of active ingredients or active metabolites from a product into the systemic circulation.

Bioequivalent products: Drug products having the equivalent bioavailability.

Therapeutically equivalent products: Drug products having the equivalent therapeutic efficacies.

Innovator products: A drug products that have been approved as a new drug, or a drug that corresponds to one.

Generic products: Products of which active ingredients, strengths, dosage forms, and dosage regimens are the same as those of innovator products.

Section 3: Tests

A. Oral immediate release products

I. Reference and test products

In principle, dissolution tests (Sec. 3.A.V.) should be performed using the following dissolution media 1) or 2), using 6 vessels or more for three lots of innovator products by the paddle method at 50 rpm. Among the three lots, the one which shows intermediate dissolution should be selected as the reference product. When the average dissolutions of the three lots reach 85% within 15 minutes, any lots can be used as the reference product.

1) The specification test medium when the dissolution specifications are established in the specifications and test procedures.
2) Among the dissolution media described in the dissolution conditions in Sec. 3 A.V., when the average dissolution of at least one lot reaches 85%, the dissolution medium providing the slowest dissolution should be selected. When the average dissolution of any of the lots does not reach 85%, the dissolution medium providing the fastest

dissolution should be used.

If a reference product cannot be appropriately selected for the drug product by dissolution testing as described above, the reference product should be the innovator product lot that shows intermediate characteristics when either a dissolution (release) test appropriate for the characteristics of the drug product or a substitute physicochemical test is performed. If the drug is administered as a liquid where the active ingredient dissolves, an appropriate lot can be used as a reference product without performing dissolution tests.

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. If the product is a homogeneous liquid where the active ingredient dissolves, a lot of which manufacturing scale is less than the 1/10 can be used. Manufacturing method of the test product and commercial products should be similar and quality and bioavailability of both products should be equivalent.

A reference product whose content or potency is as close as possible to the labelled claim should be used. Furthermore, it is preferable that the difference between the content or potency of the test product and that of the reference product be within 5% of the labelled claim.

II. Bioequivalence studies

1. Test methods

Appropriate study protocol including the required number of subjects and sampling intervals should be determined according to pilot studies and previously reported data. The rationale of the protocol should be described.

1) Design

In principle, crossover studies should be employed with random assignment of individual subjects to each group. Parallel designs can be employed for drugs with extremely long half-lives.

2) Number of subjects

A study should be conducted with a sufficient number of subjects for the bioequivalence analysis.

Multiple dose studies or studies with stable isotopes may be useful for highly variable drugs that require large sample sizes.

3) Selection of subjects

In principle, healthy adult volunteers should be employed.

If the use of the drug is limited to a specific population and test and reference products show a significant difference in dissolution*[a] under one or more of conditions of the dissolution test (Sec.3 A.V), the bioequivalent studies should be performed using subjects from the specific population.

If the use of the drug is not limited to a specific population and test and reference products showed a specific significant difference in dissolution*[b] at around pH 6.8 by the

dissolution test (Sec.3 A.V) or between pH 3.0 and 6.8 for products containing basic drugs, subjects with low gastric acidity (achlorhydric subjects) should be employed unless the application of the drug is limited to a specific population.

When it is unfavorable to use healthy subjects because of potent pharmacological action or adverse (side) effects, patients receiving the medication should be employed. If the clearance of drug differs to a large extent among subjects due to genetic polymorphism, subjects with higher clearance should be employed.

Before, during and after studies, subjects' health condition should be monitored with close attention, especially, to adverse (side) effects.

*a) Significant difference in dissolution means the following 2 cases;

1) The average dissolution of the slower-dissolution product is 50% or less at the time when the average dissolution of the faster-dissolution product reaches 80%. Also when the average dissolution of the faster product is 85% or more within 15 minutes, the average dissolution of the slower product is not more than 60% of that of the faster product. However, this rule is not applied when the average dissolution of both products is 85% or more within 15 minutes after lag time (defined as the time when 5% of the drug dissolves) and the difference in the mean lag time in dissolution between test and reference products is within 10 minutes.

2) The average dissolution of the slower product is not more than 60% that of the faster product at the final testing time when the average dissolution of either product does not reach 80% within the specified testing time. The rule is also not applied when the average dissolution of both products at the final testing time specified in Sec. 3 A.V.3 (2 hours in pH 1.2 medium and 6 hours in others) is 20% or less, because of difficulty of appropriate comparison of their dissolution.

*b) Specific significant difference in dissolution means when test and reference products showed a significant difference in dissolution around pH 6.8 (between pH 3.0 and 6.8 for products containing basic drugs), and they do not show a significant difference in other test conditions. This rule is not applied when test and reference products show a significant difference in dissolution around pH 6.8 (between pH 3.0 and 6.8 for products containing basic drugs), and also they show the same degree of or more significant difference in at least one other pH conditions. If the significant difference is observed only at 100 rpm in the dissolution test (Sec. 3 A.V) due to the susceptibility of the product to physical stress, the result is not concluded to be a specific significant difference.

4) Drug administration

a. Dose: One dose unit or a clinical usual dose should generally be employed. A higher dose which does not exceed the maximal dose of the dosage regimen may be employed when analytical difficulties exist, such as high detection limit.

b. Single vs. multiple dose studies: In principle, bioequivalence studies should be performed by single dose studies. Multiple dose studies may be employed for drugs which are repeatedly administered to patients.

i. Single dose studies: Drugs are usually given to subjects with 100–200 ml water

(normally 150 ml) after fasting for more than 10 hours. Fasting lasts for at least 4 hours post-dose. If the postprandial dose is specified in the dosage regimen, and if the bioavailability in fasting state is very poor, or high incidence of severe adverse events is anticipated, drugs may be given after food. In the fed study, a low fat diet of 700 kcal or less containing not more than 20% by energy of the lipid should be employed. The meal should be eaten within 20 minutes, and drugs are administered according to the dosing regimen or 30 minutes after the meal, if the dosing time is not indicated in the regimen.

Bioequivalence studies of solubility-enhanced products should be performed by single dose studies in both the fasted and fed states. In the case of postprandial administration, a high fat diet of 900 kcal or more containing 35% lipid content should be used. The meal should be eaten within 20 minutes, and drugs administered within 10 minutes thereafter. When a high incidence of severe adverse events is indicated after dosing in the fasting state, the fasting dose studies can be replaced with postprandial dose studies with the low fat meal.

ii. Multiple dose studies: Drugs should, in principle, be administered to subjects under fasting conditions as in the single dose studies when biological fluids are sampled for the assessment of bioavailability. In the time period before fluids are sampled, drugs should repeatedly be given between meals (drugs should be administered more than 2 hours after a meal) at constant intervals.

5) Measurement of biological samples

a. Biological fluids to be sampled: Blood samples should generally be employed. Urine samples may be used if there is a rationale.

b. Sampling schedule: Blood samples should be taken at a frequency sufficient for assessing C_{max}, AUC and other parameters. Sampling points should be at least 7, including zero time, 1 point before C_{max}, 2 points around C_{max} and 3 points during the elimination phase. Sampling should be continued until AUC_t is over 80% of AUC_∞ (normally more than 3 times the elimination half-life after t_{max}). However, when the elimination half-life of unchanged active ingredient or active metabolites to be measured is extremely long, blood samples should be collected for at least 72 hours. When urine samples are used, they should be collected in the same manner as blood samples. When F is evaluated by deconvolution, body fluid must be collected until completion of absorption, but collection of body fluid over a long period of time is not necessarily required.

c. Substances to be measured: As a general rule, the unchanged active ingredient should be measured. Major active metabolites may be measured instead of the unchanged active ingredient, if it is rational. Stereoselective assay is not generally required. However, when it is indicated that there exist stereoisomers with different activities for the main pharmacological effect, and stereoselective absorption or elimination, dependent on the absorption rate is noticeable, the enantiomer with higher activity should be measured.

d. Analytical method: Analytical methods should be fully validated regarding specificity, accuracy, precision, linearity, quantitation limit, and stability of substances in samples and so forth.

6) Washout period

Washout periods in crossover studies between administrations of test and reference products should usually be more than 5 times the elimination half-life of the unchanged active ingredient or active metabolites to be measured.

2. Assessment of bioequivalence

1) Parameters to be assessed

If blood is the sampled body fluid, AUC_t and C_{max} should be used as the parameters for evaluation of bioequivalence in a single dose study, and AUC_τ and C_{max} should be used in a multiple dose study. The measured value should be used for C_{max}, and the value calculated by the trapezoidal integration for AUC. If F can be calculated by deconvolution, F may be used instead of AUC.

AUC_∞, t_{max}, MRT, k_{el} and so on should be used as reference parameters. In multiple dose studies, C_τ is also used as a reference parameter. However, if differences in the time required for manifestation of the effect of the drug could affect its clinical usefulness, t_{max} should also be used as a parameter for evaluation of equivalence.

If urine is the sampled body fluid, the parameters Ae_t, Ae_τ, Ae_∞, U_{max} and U_τ should be used instead of AUC_t, AUC_τ, AUC_∞, C_{max} and C_τ. If differences in the time required for manifestation of the effect of the drug could affect its clinical usefulness, urine cannot be used as the sampled body fluid.

2) Bioequivalence range

If AUC and C_{max} are log-normally distributed, the bioequivalence acceptance range for each parameter is 0.80 to 1.25 when expressed as the ratio of the parameter's population means for the test product and reference product. If AUC and C_{max} are normally distributed, the acceptance range for each parameter is –0.20 to +0.20 when expressed as the ratio of the difference between the population mean for the test product and that for the reference product, to the population mean for the reference product. If the drug's effect is not strong, a wider bioequivalence acceptance range than those above is sometimes set for C_{max}. If t_{max} is used as a parameter to evaluate equivalence, an appropriate bioequivalence acceptance range should be set beforehand.

3) Statistical analysis

As a general rule, the parameters other than t_{max} are usually distributed log-normally, so those parameters should be logarithmically transformed before the statistical analysis. The 90% shortest confidence interval or two one-sided *t* tests with the significance level of 5% should be used. Other reasonable statistical methods also can be used.

4) Acceptance criteria

Products are considered to be bioequivalent, if the 90% confidence interval of difference in the average values of logarithmic parameters to be assessed between test and reference products is within the acceptable range of log(0.80) - log(1.25). However, even though the confidence interval is not in the above range, test products are accepted as bioequivalent, if the following three conditions are satisfied; 1) the total sample size of

the bioequivalence study is not less than 20 (n=10/group), 2) the differences in average values of logarithmic parameters to be assessed between two products are between log(0.90) - log(1.11), and 3) dissolution rates of test and reference products are evaluated to be similar under Sec.3 A.V. Reference parameters should be subjected to statistical assessment. If a significant difference is detected in the parameters between reference and test products, effects of this difference on therapeutic equivalence should be explained.

III. Pharmacodynamic studies

A pharmacodynamic study is one in which therapeutic equivalence is demonstrated by using the pharmacological effect in humans as an index. Pharmacodynamic studies are used for drugs whose unchanged active ingredient or active metabolite is difficult to measure in blood or urine, and for drugs whose bioavailability does not indicate their therapeutic effect. In pharmacodynamic studies, it is advisable to compare the pharmacological effect over time. For antacids or digestive enzymes, suitable in vitro efficacy tests can be employed.

The Acceptance criteria of equivalence in pharmacodynamic study should be established by considering the pharmacological activity of each drug.

IV. Clinical studies

Clinical studies are performed to establish the therapeutic equivalence of drugs using clinical effectiveness as an index. If bioequivalence studies and pharmacodynamic studies are impossible or inappropriate, clinical study is applied.

The acceptance criteria of equivalence in clinical study should be established by considering the pharmacological characteristics and activity of respective drug.

V. Dissolution tests

Dissolution tests should be performed, using a suitably validated dissolution system and assay.

1. **Number of vessels**: 12 vessels or more under each testing condition.

2. **Testing time**: 2 hours in pH 1.2 medium and 6 hours in other dissolution media. The test can be stopped at the time when the average dissolution of reference product reaches 85%.

3. **Testing conditions:** The test should be carried out under the following conditions.

Apparatus: JP paddle apparatus.

Volume of dissolution medium: Basically 900 ml.

Temperature: 37±0.5°C

Dissolution medium: The 1st and 2nd Fluids for the dissolution test (JP17) are used as pH 1.2 and 6.8 dissolution media, respectively. Diluted McIlvaine buffers (pH is

adjusted by 0.05 mol/L disodium hydrogen phosphate and 0.025 mol/L citric acid) are used for other pH solutions. If the average dissolution rate of the reference product does not reach 85% by six hours under any of the above-mentioned dissolution test conditions but does reach 85% in another suitable dissolution media, a test using the other dissolution media may be added.

1) Products containing acidic drugs

Agitation （rpm）	pH
50 [a)]	(1) 1.2
	(2) 5.5 - 6.5 [b)]
	(3) 6.8 - 7.5 [b)]
	(4) Water
100 [c)]	(1), (2), or (3) [b)]

a) The paddle method at 75 rpm or the basket method at 100 rpm can be used instead of the paddle method at 50 rpm, when coning phenomenon of disintegrates in the bottom of vessel is observed.
b) In the dissolution media where the average dissolution of reference product reaches 85% within the testing time specified, the dissolution medium where the dissolution is the slowest should be selected. When the average dissolution of the reference product does not reach 85% within the specified time in any of dissolution media, the dissolution medium should be selected where the dissolution is the fastest.
c) If, in a dissolution test by the paddle method at 50 or 75 rpm, both the reference product and the test product dissolve an average of 85% or more within 30 minutes in dissolution medium that could be used with the paddle method at 100 rpm, the dissolution test by the paddle method at 100 rpm may be omitted.

2) Products containing neutral or basic drugs, and coated products

Agitation （rpm）	pH
50 [a)]	(1) 1.2
	(2) 3.0 - 5.0 [b)]
	(3) 6.8
	(4) Water
100 [c)]	(1), (2), or (3) [b)]

a) The paddle method at 75 rpm or the basket method at 100 rpm can be used instead of the paddle method at 50 rpm, when coning phenomenon of disintegrates in the bottom of vessel is observed.
b) In the dissolution media where the average dissolution of reference product reaches 85% within the testing time specified, the dissolution medium where the dissolution is the slowest should be selected. When the average dissolution of the reference product does not reach 85% within the specified time in any of dissolution media, the dissolution medium should be selected where the dissolution is the

fastest.

c) If, in a dissolution test by the paddle method at 50 or 75 rpm, both the reference product and the test product dissolve an average of 85% or more within 30 minutes in dissolution medium that could be used with the paddle method at 100 rpm, the dissolution test by the paddle method at 100 rpm may be omitted.

3) Products containing poorly soluble drugs

A drug product containing a poorly soluble drug is a drug product for which, when the test is performed at 50 rpm, the average dissolution rate of the reference product does not reach 85% within the designated test time in any of the dissolution media specified in 1) or in 2) above with no surfactant in the medium.

Agitation（rpm）	pH	Surfactant
50[a)]	(1) 1.2	Non
	(2) 4.0	Non
	(3) 6.8	Non
	(4) Water	Non
	(5) 1.2	Polysorbate 80 [b)]
	(6) 4.0	Polysorbate 80 [b)]
	(7) 6.8	Polysorbate 80 [b)]
100[c)]	(5), (6), or (7) [d)]	Polysorbate 80 [e)]

a) The paddle method at 75 rpm or the basket method at 100 rpm can be used instead of the paddle method at 50 rpm, when coning phenomenon of disintegrates in the bottom of vessel is observed.

b) Investigate polysorbate 80 concentrations of 0.01%, 0.1%, 0.5% and 1.0% (W/V). Determine the lowest polysorbate 80 concentration necessary for the reference product to dissolve an average of 85% or more in at least one of dissolution media (5), (6) and (7) within the designated test time, and add that concentration of polysorbate 80 to dissolution medium (5), (6) or (7). If the reference product does not dissolve an average of 85% in any of the dissolution media within the designated test time, choose the polysorbate 80 concentration at which dissolution is fastest.

In the event that polysorbate 80 affects the dissolution behaviour of the drug by interacting with the drug or with excipients, or in another such event, it is permissible to replace potassium dihydrogen phosphate with sodium dihydrogen phosphate as the buffering agent and use sodium lauryl sulfate. However, if sodium lauryl sulfate is used, the solubility of the drug may not exceed the solubility maximum concentration specified for polysorbate 80.

c) If, in a dissolution test by the paddle method at 50 or 75 rpm, both the reference product and the test product dissolve an average of 85% or more within 30 minutes in dissolution medium that could be used with the paddle method at 100 rpm, the dissolution test by the paddle method at 100 rpm may be omitted.

d) In the dissolution media where the average dissolution of reference product reaches 85% within the testing time specified, the dissolution medium where the dissolution is the slowest should be selected. When the average dissolution of the reference product does not reach 85% within the specified time in any of dissolution media, the dissolution medium should be selected where the dissolution is the fastest.

e) The same concentration as that in the case of 50 rpm.

4) Solubility-enhanced products

Dissolution tests of the reference drug should be performed under the test conditions of 1) or 2). Perform the test under the test conditions of 1) or 2) if the average dissolution by the paddle method at 50 rpm reaches 85% or more within the designated test time under at least three sets of dissolution test conditions.

In other cases, the testing conditions should follow.

Agitation（rpm）	pH	e
50[a)]	(1) 1.2	Non
	(2) 4.0	Non
	(3) 6.8	Non
	(4) Water	Non
	(5) 1.2	Polysorbate 80 [b)]
	(6) 4.0	Polysorbate 80 [b)]
	(7) 6.8	Polysorbate 80 [b)]
100[c)]	any of the media except (4) [d)]	

a) The paddle method at 75 rpm or the basket method at 100 rpm can be used instead of the paddle method at 50 rpm when the disintegrates form corn in the bottom of vessel.

b) The concentration of polysorbate 80 should be determined after performing the dissolution test in the dissolution media (5), (6) and (7) containing three (0.01%, 0.1%, 0.5% and 1.0%) concentrations (W/V) of polysorbate 80. Use the media with the lowest polysorbate 80 concentration necessary for the reference product to dissolve an average of 85% or more in at least one of the dissolution media (5), (6) and (7) within the designated test time. If the reference product does not dissolve an average of 85% in any of the dissolution media within the designated test time, choose the polysorbate 80 concentration at which dissolution is the fastest. If the reference product dissolves an average of 85% or more in any of the dissolution media (1), (2), or (3) within the designated test time, the dissolution test in the corresponding pH media including polysorbate 80 ((5), (6) or (7)) may be omitted.

In the event that polysorbate 80 affects the dissolution behaviour of the drug by interacting with the drug or with excipients, or in another such event, it is

permissible to replace potassium dihydrogen phosphate with sodium dihydrogen phosphate as the buffering agent and use sodium lauryl sulfate. However, if sodium lauryl sulfate is used, the solubility of the drug may not exceed the solubility maximum concentration specified for polysorbate 80.

c) If, in a dissolution test by the paddle method at 50 or 75 rpm, both the reference product and the test product dissolve an average of 85% or more within 30 minutes in dissolution medium that could be used with the paddle method at 100 rpm, the dissolution test by the paddle method at 100 rpm may be omitted.

d) If the average dissolution of the reference product reaches 85% within the designated test time other than the particular media (4), the dissolution medium where the dissolution is the slowest should be selected. When the average dissolution of the reference product does not reach 85% within the designated test time in any of the test media, the dissolution medium should be selected where the dissolution is the fastest.

The concentration of polysorbate 80 used in the test at 100 rpm should be the same as that of the test at 50 rpm.

4. Acceptance criteria for Similarity of dissolution profiles

The average dissolution rate of the test product is compared with the average dissolution rate of the reference product. If dissolution of the reference product or test product has a lag time, the dissolution curve can be adjusted with the dissolution lag time (Appendix 2). Criteria (1) to (3) below are applied after the lag time. However, when dissolution curves are corrected, the difference between the average dissolution lag times of the test product and reference product must be not more than 10 minutes. The time points for comparing dissolution rates when assessment is performed by the f_2 function are specified in Appendix 1. 2).

When any of the criteria below are met under all the sets of dissolution test conditions, the dissolution behaviour is judged as similar. However, the average dissolution rate of the reference product must reach 85% or more within the designated test time under at least one set of dissolution test conditions.

If the comparison time point is to be less than 15 minutes, dissolution behaviour may be evaluated using a comparison time point of 15 minutes. If correction for lag time is performed, the comparison time point of 15 minutes is the time before correction.

Dissolution behaviour of enteric-coated products in the test medium at pH 1.2 may be evaluated using only the dissolution rate at the designated test time (after 2 hours).

A judgement of similarity in dissolution does not mean bioequivalence.

(1) When the average dissolution of the reference product reaches 85% within 15 minutes: the average dissolution of the test product reaches 85% within 15 minutes or is within that of the reference product ±15% at 15 minutes.

(2) When the average dissolution of the reference product reaches 85% at between 15 and 30 minutes: the average dissolution of the test product are within that of the reference product ±15% at two appropriate time points when the average dissolution of the

reference product are around 60% and 85%. Or f_2 value is not less than 42.

(3) When the average dissolution of the reference product does not reach 85% within 30 minutes: the results meet one of the following criteria.

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 ±15% at two appropriate time points when the average dissolution of the reference product are around 40% and 85%. Or f_2 value is not less than 42.

b. When the average dissolution of the reference products reaches 50% and does not reaches 85% within the testing time specified: the average dissolution of the test product are within that of the reference product ±12% 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 f_2 value is not less than 46.

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 ±9% 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 f_2 value is not less than 53. However, when the average dissolution of the reference product is not more than 10% at the stipulated dissolution time, the average dissolution of the test product is within that of the reference product ±9% at the testing time specified only.

VI. Reporting of test results

1. Samples

1) Brand name and lot No. of the reference product. Code No. or name, lot No. and lot size of the test product
2) Type of dosage form
3) Name of drug substances
4) Labeled claims or potencies
5) Measured contents or potencies and assay procedures
6) Solubility of drugs at different pHs and in water used for dissolution tests
7) Particle size or specific surface area for poorly soluble drugs and their measurement procedures
8) Types of polymorph and solubility
9) Others (for example, pKa and physicochemical stability)

2. Results

1) Summary

2) Dissolution tests:

a. List of test conditions (apparatus, stirring speed, types and volumes of dissolution media)

b. Assay: method and summary of validation

c. Summary of validation of dissolution tests

d. Results

i. Results of preliminary tests performed to select a reference product.

Tables listing dissolution rate of individual sample under each testing condition, average dissolutions and standard deviations of each lot.

Figures comparing average dissolution curves of each lot under each testing condition

ii. Results of preliminary tests performed to select test media.

iii. Comparison of reference and test products

Tables listing dissolved% of individual sample under each testing condition, the average dissolutions and standard deviations of test and reference products.

Figures comparing average dissolution curves of test and reference products under each testing condition.

3) Bioequivalence studies

Following should be described. Pilot study items should also be reported.

a. Experimental conditions

i. Subjects:

Age, sex, body weight and other data obtained by laboratory tests are described. Individual gastric acidity should be reported if necessary or otherwise available.

ii. Drug administration

Duration of fasting, co-administered water volume, and time of food ingestion after drug administration are described. In the case of postprandial administration, menu, content of meal (protein, fat, carbohydrate, calories and others), and time from food ingestion to drug administration are described.

iii. Assay: procedure and summary of validation.

b. Results

i. Individual subject data

Tables showing drug concentration in biological fluids at each sampling time, C_{max}, C_τ, AUCt, AUC_τ, AUC_∞, k_{el}, t_{max}, and MRT. For all items, provide the untransformed data. The correlation coefficient for determining k_{el} should be reported together with time points used.

The ratios of C_{max} and AUC_t of test product to those of reference product in each individual should be reported.

Figures comparing individual drug concentration-time profiles of the two products drawn on a linear/linear scale.

ii. Averages and standard deviations

Tables showing averages and standard deviations of raw data of drug levels in biological fluids at each time point, C_{max}, C_τ, AUCt, AUC_τ, AUC_∞, k_{el}, t_{max}, and

MRT.

The ratios of average of C_{max} and AUC_t of test product to those of reference product should be reported.

Figures comparing average drug level-time profiles of the two products drawn on a linear/linear scale.

iii. Statistical analysis and equivalence assessment

Analysis of variance tables for C_{max}, C_τ, AUCt, AUC_τ, AUC_∞, k_{el}, t_{max}, and MRT which are logarithmically transformed when required. The statistical results for C_{max}, AUC_t, and AUC_τ. For other parameters, statistical testing results of the null-hypotheses should be reported where the average values of test and reference products are assumed to be equivalent.

iv. Analysis of pharmacokinetic parameters

If deconvolution is used, the program, algorithm, pharmacokinetic models and fitting information should be listed.

v. Others

Information on dropouts (data, reasons), monitoring records of health status of subjects.

4) Pharmacodynamic studies

Reporting of results should follow the description of bioequivalence studies.

5) Clinical studies

Reporting of results should follow the description of bioequivalence studies.

B. Oral extended release products

I. Reference and test products

In principle, dissolution tests (Sec. 3 B. IV.) should be performed using the following dissolution medium 1) or 2), using 6 vessels or more for three lots of innovator products by the paddle method at 50 rpm. Among the three lots, the one which shows intermediate dissolution should be selected as the reference product.

1) The specification test medium when the dissolution specifications are established in the specifications and test procedures.
2) Among the dissolution media described in the dissolution conditions in Sec. 3 B. IV., when the average dissolution of at least one lot reaches 85%, the dissolution medium providing the slowest dissolution should be selected. When the average dissolution of any of the lots does not reach 85%, the dissolution medium providing the fastest dissolution should be used.

If a reference product cannot be appropriately selected for the drug product by dissolution testing as described above, the reference product should be the innovator product lot that shows intermediate characteristics when either a dissolution (release) test appropriate for the characteristics of the drug product or a substitute physicochemical test is performed.

The test generic product must not differ markedly from the innovator product in size, shape, specific gravity or release mechanism. For the test product lot size, and content or potency, follow Sec. 3 A. “Oral immediate release products”. The dissolution behaviour of the test product must be similar to that of the reference product. Assess the similarity of dissolution behaviour according to Sec. 3 B. IV. 4.

II. Bioequivalence studies

1. Test Method

Bioequivalence studies should be performed by single dose studies in both the fasted and fed states. In the case of postprandial administration, a high fat diet of 900 kcal or more containing 35% lipid content should be used. The meal should be eaten within 20 minutes, and drugs administered within 10 minutes thereafter.

When a high incidence of severe adverse events is indicated after dosing in the fasting state, the fasting dose studies can be replaced with postprandial dose studies with the low fat meal employed in the study for oral immediate release products. Other testing conditions should follow those of oral immediate release products.

2. Assessment of bioequivalence

1) Bioequivalence range, parameters to be assessed, data transformation and statistical analysis

These are the same as those of oral immediate release products.

2) Acceptance criteria

Products are considered to be bioequivalent, if the 90% confidence interval of difference in the average values of logarithmic parameters to be assessed between test and reference products is within the acceptable range of log(0.80) - log(1.25).

However, even though the confidence interval is not in the above range, test products are accepted as bioequivalent, if the following three conditions are satisfied; 1) the total sample size of the bioequivalence study is not less than 20 (n=10/group), 2) the difference in average values of logarithmic AUC and C_{max} between two products is between log(0.90) - log(1.11), and 3) the dissolution characteristics of the test product are equivalent to those of the reference product. The dissolution profiles are judged to be equivalent following the Sec. 3.B. IV.4. The assessment of reference parameters follows that of oral immediate release products.

III. Pharmacodynamic and clinical studies

If bioequivalence studies cannot be performed, pharmacodynamic or clinical studies should be carried out to evaluate therapeutic equivalence according to the studies for oral immediate release products.

IV. Dissolution tests

1. Number of vessels: 12 vessels or more under each testing conditions.

2. Testing time: The testing time is normally 24 hours, but at pH 1.2, the test may be concluded after two hours. The test can be stopped at the time when the average dissolution of reference product reaches 85%.

3. Test conditions: The test should be carried out under the following conditions.

Apparatus: Paddle apparatus, rotating basket and disintegration testing apparatus can be selected, the reason for which should be stated.

Volume of dissolution medium, Temperature and Dissolution medium should follow the description of oral immediate release products.

Apparatus	Agitation (rpm)	pH	Other conditions
Paddle		(1) 1.2	
		(2) 3.0 - 5.0 [a)]	
		(3) 6.8 - 7.5 [a)]	
		(4) Water	
		(3)	Polysorbate 80 (1.0%W/V)
	100	(3)	
	200	(3)	
Basket	100	(3)	
	200	(3)	
Disintegration	30 [b)]	(3)	Without disk
	30 [b)]	(3)	With disk

a) In the dissolution media where the average dissolution of reference product reaches 80% within 24 hours, the dissolution medium where the dissolution is the slowest should be selected. When the average dissolution of the reference product does not reach 80% within 24 hours in any of dissolution media, the test solution where the dissolution is the fastest should be selected.

b) Strokes/minutes.

4. Acceptance criteria for similarity and equivalence of dissolution profiles

If the results meet one of the following criteria shown in 1) under all testing conditions, the dissolution profile of the test product is judged to be similar to that of the reference product.

If the average dissolution of the reference product reaches 80% within the testing time point specified in at least one test condition, and the results meet one of the following criteria shown in 2) under all testing conditions, the dissolution profile of the test product is judged to be equivalent to that of the reference product.

When similarity factor, f_2, is used, Appendix 1 (2) Time points for f_2 should be employed. A judgement of similarity or equivalence in dissolution does not mean bioequivalence.

1) Similarity

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 ±15% at three appropriate time points when the average dissolution of the reference product are around 30%, 50% and 80%. Or f_2 value is not less than 42.

b. When the average dissolution of the reference product reaches 50% and does not reach 80% within the testing time point specified: the average dissolution of the test product are within that of the reference product ±12% 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 f_2 value is not less than 46.

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 ±9% 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 f_2 value is not less than 53. However, when the average dissolution of the reference product is not more than 10% within the testing time specified, the average dissolution of the test product is within that of the reference product ±9% at the testing time specified only.

2) Equivalence

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 f_2 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 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 f_2 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 f_2 value is not less than 61. However, when the average dissolution of the reference product 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.

V. Reporting of test results

The shape, specific gravity and release mechanism of the test product should be described which do not differ significantly from those of the innovator product. The description of other results is the same as that for oral immediate products.

C. Oral enteric-coated products

I. Reference and test products

Follow the description of the oral immediate release products.

II. Bioequivalence studies

1. Test Method

Bioequivalence studies should be performed by single dose studies in both the fasted and fed states. In the case of postprandial administration, a high fat diet of 900 kcal or more containing 35% lipid content should be used. The meal should be eaten within 20 minutes, and drugs administered within 10 minutes thereafter.

When a high incidence of severe adverse events is indicated after dosing in the fasting state, the fasting dose studies can be replaced with postprandial dose studies with the low fat meal employed in the study for oral immediate release products.

This product doesn't require test to subjects with low gastric acidity (achlorhydric subjects).

Other testing conditions should follow those of oral immediate release products.

2. Assessment of bioequivalence

1) Bioequivalence range, parameters to be assessed, data transformation and statistical analysis

Follow the description of the oral immediate release products.

2) Acceptance criteria

Products are considered to be bioequivalent, if the 90% confidence interval of difference in the average values of logarithmic parameters to be assessed between test and reference products is within the acceptable range of log(0.80) - log(1.25).

However, even though the confidence interval is not in the above range, test products are accepted as bioequivalent, if the following three conditions are satisfied; 1) the total sample size of the bioequivalence study is not less than 20 (n=10/group), 2) the differences in average values of logarithmic parameters to be assessed between two products are between log(0.90) - log(1.11), and 3) dissolution rates of test and reference products are evaluated to be similar under Sec.3 C.IV.

The assessment of reference parameters follows that of oral immediate release products.

III. Pharmacodynamic and clinical studies

If bioequivalence studies cannot be performed, pharmacodynamic or clinical studies should be carried out to evaluate therapeutic equivalence according to the studies for oral immediate release products.

IV. Dissolution tests

1. Number of vessels: Follow the description of the oral immediate release products.

2. Testing time: Follow the description of the oral immediate release products.

3. Testing conditions: The test should be carried out under the following conditions.

Apparatus: JP paddle apparatus.

Volume of dissolution medium: Basically 900 ml.

Temperature: 37±0.5 °C

Dissolution medium: The 1st and 2nd fluids for the dissolution test (JP17) are used as pH 1.2 and 6.8 dissolution media, respectively. Diluted McIlvaine buffers (pH is adjusted by 0.05 mol/L disodium hydrogen phosphate and 0.025 mol/L citric acid) are used for other pH solutions. If the average dissolution rate of the reference product does not reach 85% by six hours under any of the above-mentioned dissolution test conditions but does reach 85% in another suitable dissolution media, a test using the other dissolution media may be added.

Agitation (rpm)	pH
50[a)]	(1) 1.2
	(2) 6.0
	(3) 6.8
100[b)]	(2)

a) The paddle method at 75 rpm or the basket method at 100 rpm can be used instead of the paddle method at 50 rpm, when coning phenomenon of disintegrates in the bottom of vessel is observed.

b) If, in a dissolution test by the paddle method at 50 or 75 rpm, both the reference product and the test product dissolve an average of 85% or more within 30 minutes in dissolution medium that could be used with the paddle method at 100 rpm, the dissolution test by the paddle method at 100 rpm may be omitted.

Enteric-coated products containing poorly soluble drugs should be tested by adding polysorbate 80 to the dissolution media (2) and (3) according to the dissolution test method for products containing poorly soluble drugs as described above.

4. Acceptance criteria for Similarity of dissolution profiles

Follow the description of the oral immediate release products.

If the pH of the dissolution test medium is 1.2, dissolution behaviour may be evaluated using only the dissolution rate at the designated test time (after 2 hours).

V. Reporting of test results

Follow the description of the oral immediate release products.

D. Non-oral dosage forms

The test for the products for topical use should be following the Guideline for Bioequivalence Studies of Generic Products for Topical Use an attachment of Division-Notification No. 1124004 of the Pharmaceutical and Food Safety Bureau, Amendments to the Guideline for Bioequivalence Studies of Generic Products and Other Guidelines, dated November 24, 2006.

For other non-oral dosage forms, the test should be performed following the description below.

I. Reference and test products

Suitable release tests or alternative physicochemical tests should be performed for three lots of an innovator product from which one lot providing intermediate characteristics should be selected as a reference product. If the drug is administered as a liquid where the active ingredient dissolves, an appropriate lot can be used as a reference product. The lot size and drug content or potency follows the description for oral immediate release products and enteric-coated products.

II. Bioequivalence studies

The test should follow the bioequivalence test for oral immediate release products but the results of release or physicochemical tests are not used as supportive data for the assessment of bioequivalence.

III. Pharmacodynamic and clinical studies

Follow the description of the oral immediate release products. In pharmacodynamic study, it is desirable to compare the efficacy-time profiles. Appropriate animal studies will be allowed for products for topical use (skin, etc.) of which pharmacological effects on the surface of the skin and can be evaluated appropriately, for example, hemostatic agent, disinfecting agent, intention promotors, which do not need to penetrate the stratum

corneum for exerting their pharmacological effects. For bactericides for external use, appropriate in vitro efficacy tests can be employed.

IV. Dissolution (release) tests or physicochemical tests

Release or physicochemical characteristics should be compared between test and reference products by appropriate tests which will vary depending on the product.

V. Reporting of test results

Follow the description of the oral immediate release products.

E. Dosage forms of which bioequivalence studies are waived

Injections for intravenous administration, administered as an aqueous solution.

Appendix 1. f_2 (similarity factor) and time points for comparisons

(1) Definition of f_2

The following equation defines f_2. Ti and Ri show the average dissolutions 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 f_2

1) When the average dissolution of the reference product reaches 85% (80% for extended release products) between 15 and 30 minutes: 15, 30, 45 minutes.
2) When the average dissolution of the reference product reaches 85% (80% for extended release products) between 30 minutes 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 similarity and equivalence in dissolution curves.

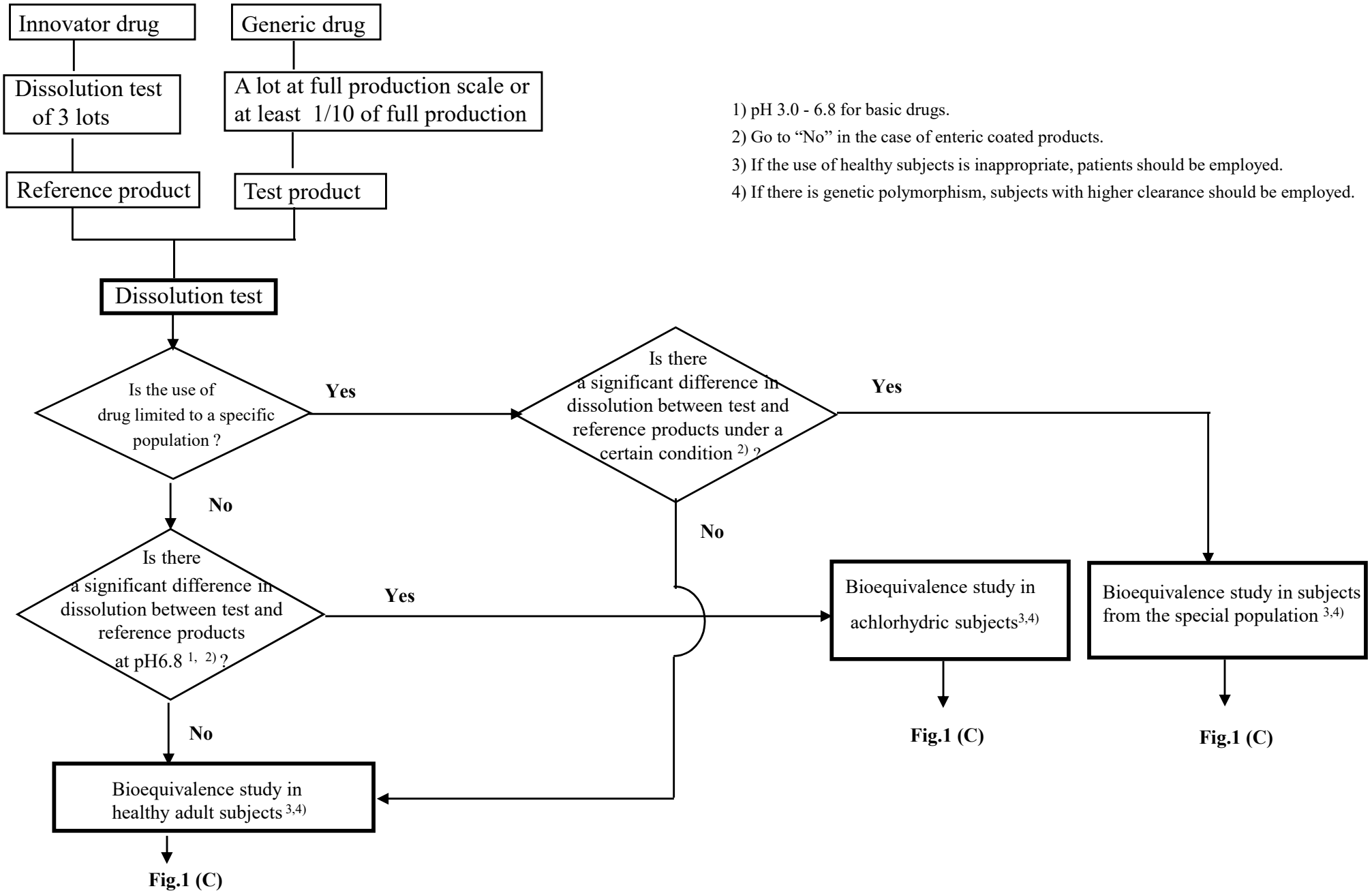
Table

List of abbreviations of parameters

Ae_t	Cumulative amount of drug excreted in the urine from zero to the final sampling time t
Ae	Cumulative amount of drug excreted in the urine from zero to infinity
AUC	Area under drug concentration in blood-time curves
AUC_t	AUC from zero to the final sampling time t
AUC_τ	AUCover one dose interval (τ) at steady-state
AUC_∞	AUC from zero to infinity
Cmax	The maximum drug concentration in blood
C_τ	Drug level in blood at the time τ after dosing at steady-state
F	Ratio of bioavailability of a test product to that of the standard preparation (intravenous dose or oral aqueous dose)
Kel	Elimination rate constant
MRT	Mean residence time
t_{max}	Time to the maximum drug concentration in blood or time to the maximum urinary excretion rate
U_{max}	The maximum urinary excretion rate of drug
U_t	Urinary excretion rate of drug at the final sampling time over one dose interval (t) at steady-state

Fig.1 Bioequivalence study of oral dosage forms

(a) Bioequivalence of oral immediate release products and enteric-coated products



1) pH 3.0 - 6.8 for basic drugs.
2) Go to "No" in the case of enteric coated products.
3) If the use of healthy subjects is inappropriate, patients should be employed.
4) If there is genetic polymorphism, subjects with higher clearance should be employed.

Fig.1 Bioequivalence study of oral dosage forms

(b) Bioequivalence for oral extended release products

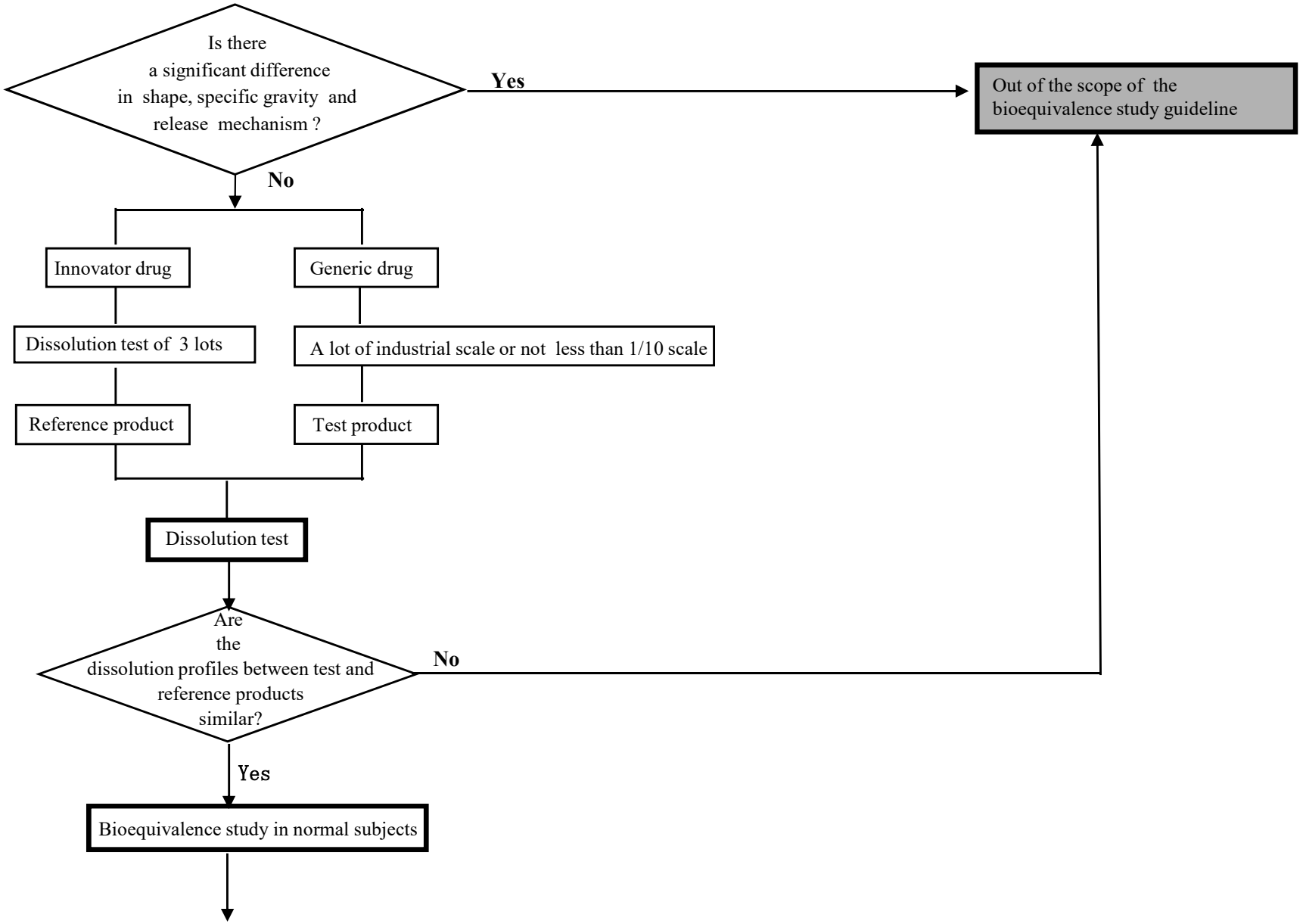
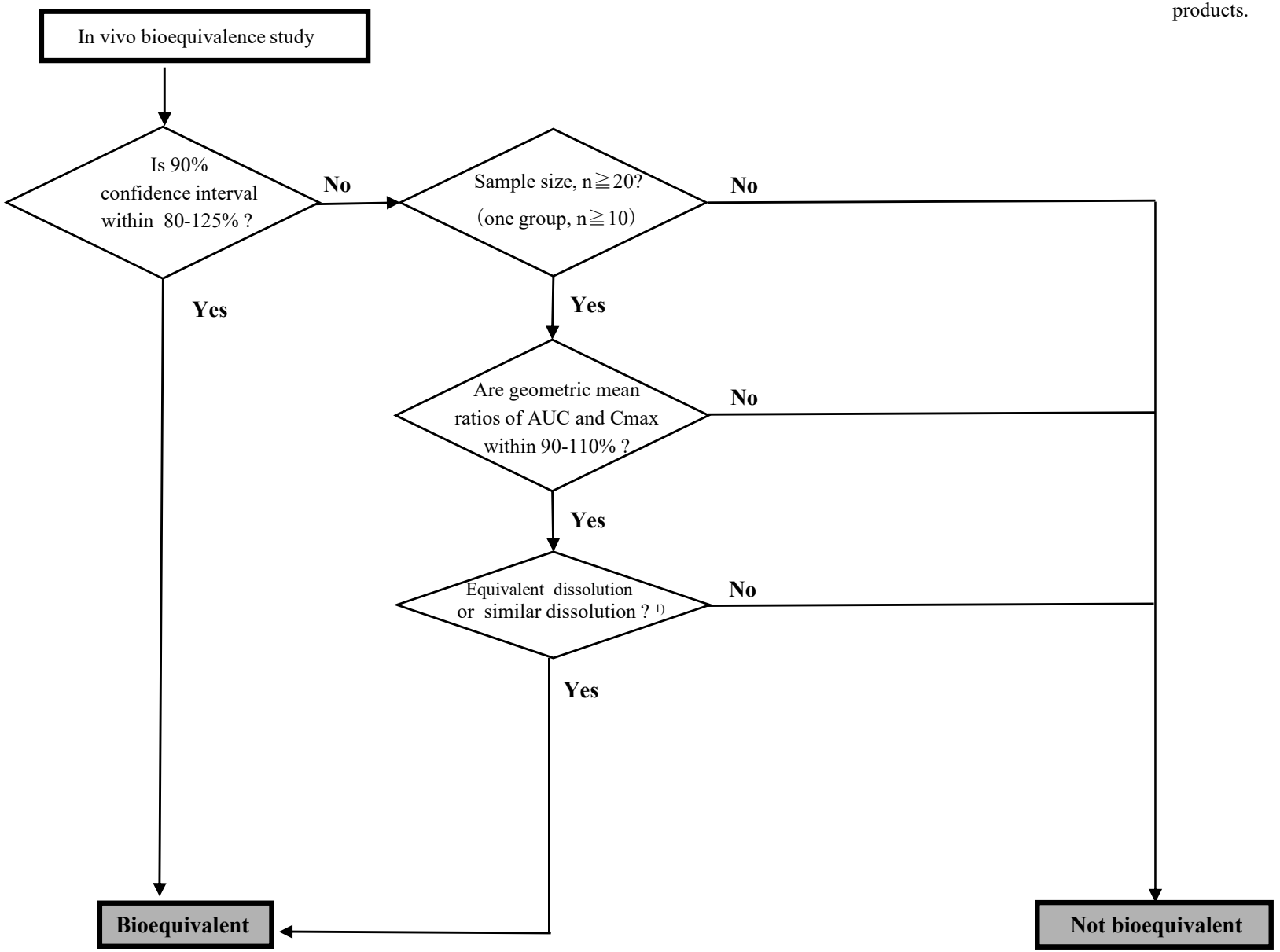


Fig.1 (C)

Fig.1 Bioequivalence study of oral dosage forms

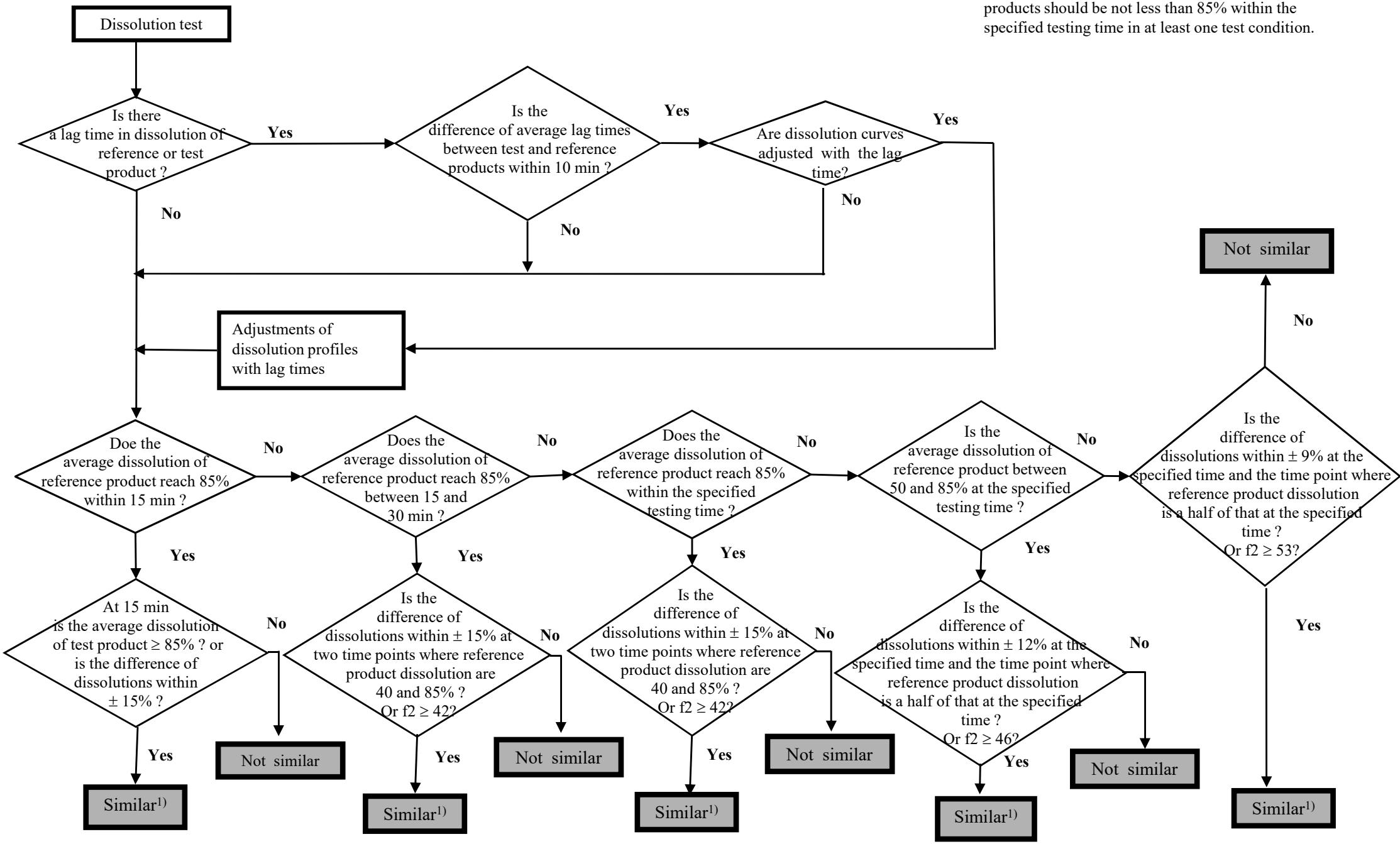
(c) Judgement of bioequivalence



1) Refer to Fig.2 for oral immediate release products and enteric coated products, and refer to Fig.3 for oral extended release products.

Fig.2 Judgement of dissolution similarity

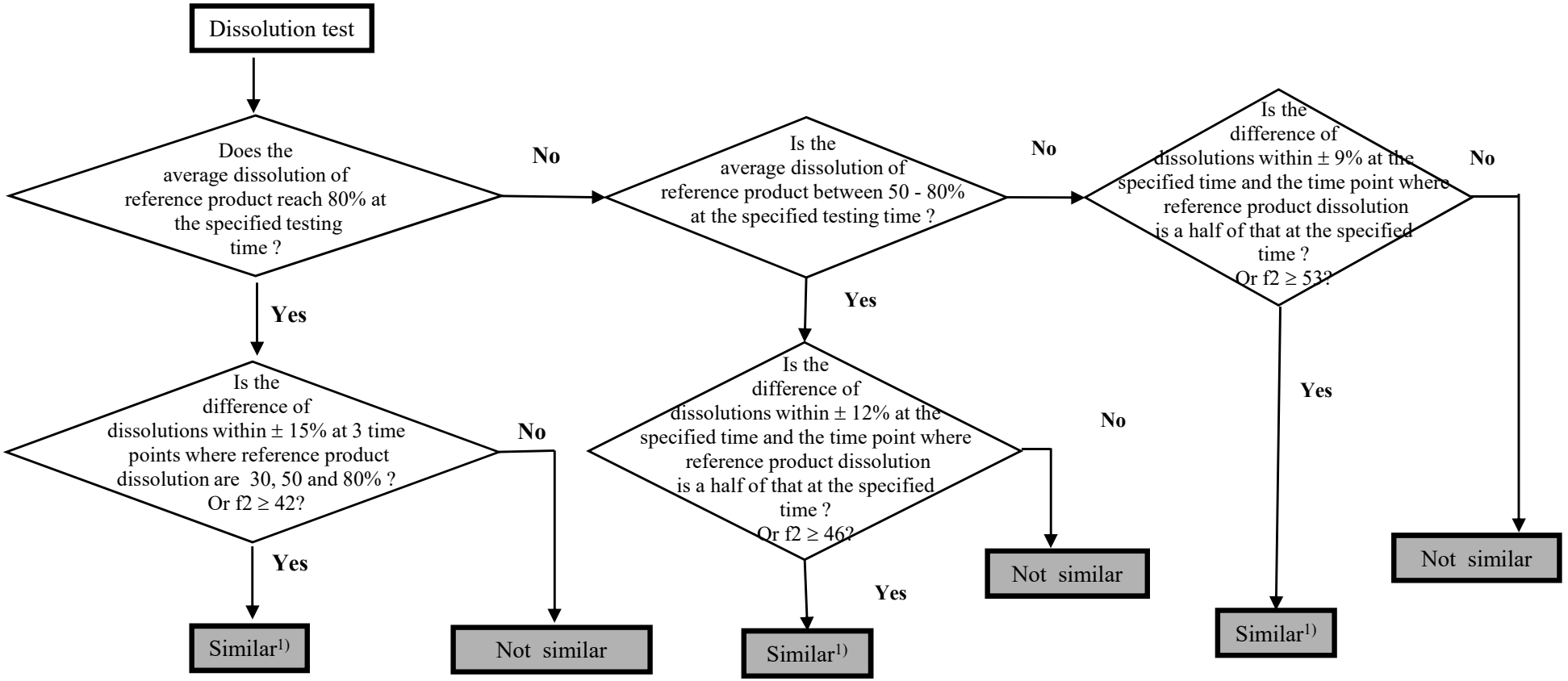
(a) Oral immediate release products and enteric-coated products



1) If the results meet one of the following criteria under all testing conditions. The dissolution from reference products should be not less than 85% within the specified testing time in at least one test condition.

Fig.2 Judgement of dissolution similarity

(b) Oral extended release products



1) If the results meet one of the following criteria under all testing conditions.

Fig.3 Judgement of dissolution equivalence

Oral extended release products

1) If the results meet one of the following criteria under all the testing conditions.

The average dissolution of reference products should be not less than 80% within the specified testing time in at least one test condition.