Administrative notice
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To: Pharmaceutical Affairs Section, Prefectural Health Department (Bureau)

Evaluation and Licensing Division, Pharmaceutical and
Food Safety Bureau, Ministry of Health, Labour and Welfare

# Notes on the Principles on Bioequivalence Studies of Oral Solid Dosage Forms with Manufacturing Process Changes

"Principles on Bioequivalence Studies of Oral Solid Dosage Forms with Manufacturing Process Changes" and "Q&As on the Principles on Bioequivalence Studies of Oral Solid Dosage Forms with Manufacturing Process Changes," which were recently issued under a Health and Labour Sciences Research Grants (multidisciplinary research project on regulatory science for drugs, medical devices, etc.)-funded project entitled "A Study on Quality Assurance in Response to Changes in the Manufacturing Process of Oral Solid Dosage Forms (FY 2008 to 2010)" (responsible researcher: Yomota Chikako, Division of Drugs, National Institute of Health Sciences), are provided for your reference in Attachments 1 and 2.

(Attachment 1)

# Principles on Bioequivalence Studies of Oral Solid Dosage Forms with Manufacturing Process Changes

## Contents

## Chapter 1 Introduction

This material on quality-related studies to be conducted for the change control of post-approval partial changes in the manufacturing process of oral solid immediate-release, enteric-coated, or extended-release formulations is intended to assure bioequivalence between the formulations before and after the manufacturing process change. Manufacturing process changes should be controlled based not only on specification tests but also on the overall assessment of the change itself, as well as any alteration in the product quality before and after the change, in light of how the drug is developed and quality assured. When changing the manufacturing process, a dissolution test or a human bioequivalence study should be performed in accordance with the conditions described herein. However, the test shown here may not be required if it can be demonstrated from the nature of the change, dissolution test or bioavailability data during development, etc., that bioequivalence is maintained after the manufacturing process change.

## Chapter 2 Terminology

Reference product

Three batches of the drug product before the manufacturing process change, selected in accordance with Chapter 3, A.I (Immediate-release or enteric-coated formulations) or B.I (Extended-release formulations) in the Guideline for Bioequivalence Studies of Generic Drugs (hereinafter referred to as the "Guideline for Generic Drugs").

Test product

The formulation after the manufacturing process change. It is desirable to use a formulation manufactured on the same scale as that of commercial batches, but it may be a formulation that is at least 1/10 the commercial scale.

Formulations containing poorly soluble compounds (hereinafter referred to as "poorly soluble drugs")

See Chapter 3, A.V.3.3) in the Guideline for Generic Drugs.

## Chapter 3 Process change levels and required studies

1. Process change levels

   Process change levels are classified as follows, and changes in the corresponding items are shown in the attached table.

   Level 1: Changes that are unlikely to affect the quality of the formulation

   Level 2: Changes that may affect the quality of the formulation

   Level 3: Changes that may significantly affect the quality of the formulation

2. Required studies

A. Immediate-release or enteric-coated formulations

See Attached Table 1.

Level 1

If a dissolution test has been established in accordance with Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances (PMSB/ELD Notification No. 568) or justified, perform the specified dissolution test. If the test product meets the specification, the test and reference products are considered bioequivalent. Otherwise, perform the dissolution test specified in Chapter 3, A.V of the Guideline for Generic Drugs. For drugs having a broad therapeutic index, a dissolution test may be performed with a dissolution medium spiked with a surfactant at a concentration equal to or higher than that specified in the guideline, if justified. Reasonable justification is required if a dissolution test is performed with a dissolution medium spiked with a surfactant for a poorly soluble drug having a narrow therapeutic index. If the dissolution behavior is judged equivalent in accordance with Chapter 5 of the Guideline for Bioequivalence Studies of Formulation Changes of Oral Solid Dosage Forms, the test and reference products are considered bioequivalent. Equivalence may be judged using only the dissolution test conditions of the specification, if the dissolution test conditions established in the specification are excellent in distinguishability.

If dissolution test results do not indicate bioequivalence or if a dissolution test cannot be performed, perform a bioequivalence study according to the Guideline for Generic Drugs. No human studies are necessary, if justified.

Level 2

If a dissolution test has been established in accordance with Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances (PMSB/ELD Notification No. 568) or justified, perform a dissolution test under the specification test conditions. Otherwise, perform the dissolution test specified in Chapter 3, A.V of the Guideline for Generic Drugs. For drugs having a broad therapeutic index, a dissolution test may be performed with a dissolution medium spiked with a surfactant at a concentration equal to or higher than that specified in the guideline, if justified. Reasonable justification is required if a dissolution test is performed with a dissolution medium spiked with a surfactant for a poorly soluble drug having a narrow therapeutic index. If the dissolution behavior is judged equivalent in accordance with Chapter 5 of the Guideline for Bioequivalence Studies of Formulation Changes of Oral Solid Dosage Forms, the test and reference products are considered bioequivalent.

If dissolution test results do not indicate bioequivalence or if a dissolution test cannot be performed, perform a bioequivalence study according to the Guideline for Generic Drugs. No human studies are necessary, if justified.

Level 3

For drugs with a broad therapeutic index, the test and reference products are considered bioequivalent if both the test product and the reference product show a mean percent dissolved of ≥ 85% in 30 minutes

under all conditions in the dissolution test specified in Chapter 3, A.V of the Guideline for Generic Drugs and their dissolution behaviors are judged equivalent in accordance with Chapter 5 of the Guideline for Bioequivalence Studies of Formulation Changes of Oral Solid Dosage Forms.

Otherwise, perform a bioequivalence study according to the Guideline for Generic Drugs. No human studies are necessary, if justified.

Attached Table 1. Process change levels and required studies for immediate-release and enteric-coated formulations

| Change level | Item | Change | Required studies[b)] |
|---|---|---|---|
| Level 1 (Minor change) | Component properties | Change to the crystalline form, particle size, etc. of the drug substance or to the grade, etc. of excipients that has little impact on quality | 1) If a dissolution test has been established in accordance with "Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances" (PMSB/ELD Notification No. 568): Conformity to the specification<br>2) If the specified dissolution test is excellent in distinguishability: Equivalence of the dissolution behavior under the specification test conditions<br>3) Other: Equivalence of the dissolution behavior under all conditions specified in the Guideline for Generic Drugs[c)] |
| | Manufacturing scale | Change to the manufacturing scale that has little impact on quality (Apparatus having the same mode and operating principle; similar SOP) | |
| | Location | Transfer to a manufacturing location having the same education and training system for workers (Same SOP, environment, and management) | |
| | Apparatuses | Change to another apparatus having the same mode and operating principle | |
| | Manufacturing process | Change to operating parameters, such as blending time and operating speed, within the scope of application or validation | |
| Level 2[a)] (Moderate change) | Component properties | Change to the crystalline form, particle size, etc. of the drug substance or to the grade, etc. of excipients that may have an impact on quality | 1) If a dissolution test has been established in accordance with "Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances" (PMSB/ELD Notification No. 568): Equivalence of the dissolution behavior under the specification test conditions<br>2) Other: Equivalence of the dissolution behavior under all conditions specified in the Guideline for Generic Drugs[c)] |
| | Manufacturing scale | Change to the manufacturing scale that may have an impact on quality (Apparatus having the same mode and operating principle; similar SOP) | |
| | Location | Transfer to a manufacturing location having a different education and training system for workers (Apparatus having the same mode and operating principle; same SOP, environment, and management) | |
| | Apparatuses | Change to an apparatus having a different mode and operating principle | |
| | Manufacturing process | Change to operating parameters, such as blending time and operating speed, outside the scope of application or validation | |
| Level 3 (Major change) | Manufacturing process | Change beyond the scope shown above that may have a significant impact on quality. An example is a change in the type of the manufacturing process from wet granulation to dry direct compression. | 1) If the drug has a broad therapeutic index and dissolves 85% or more in 30 minutes under all the conditions specified in the Guideline for Generic Drugs: Equivalence of the dissolution behavior<br>2) Other: Bioequivalence study according to the Guideline for Generic Drugs |

a) Level 1 test may be applied if there is a reasonable ground for the absence of impact on quality.
b) If dissolution test results do not indicate bioequivalence, perform a bioequivalence study according to the Guideline for Generic Drugs. No human studies are necessary, if justified.
c) For drugs having a broad therapeutic index, a dissolution test may be performed with a dissolution medium spiked with a surfactant at a concentration equal to or higher than that specified in the guideline, if justified. Reasonable justification is required if a dissolution test is performed with a dissolution medium spiked with a surfactant for a poorly soluble drug having a narrow therapeutic index.

B. Extended-release formulations

See Attached Table 2.

Level 1

If a dissolution test has been established in accordance with Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances (PMSB/ELD Notification No. 568) or justified, perform the specified dissolution test. If the test product meets the specification, the test and reference products are considered bioequivalent. Otherwise, perform the dissolution test specified in Chapter 3, B.IV of the Guideline for Generic Drugs (paddle method, only the test at 50 rpm and 100 rpm). If the dissolution behavior is judged equivalent in accordance with Chapter 5 of the Guideline for Bioequivalence Studies of Formulation Changes of Oral Solid Dosage Forms, the test and reference products are considered bioequivalent.

If dissolution test results do not indicate bioequivalence, perform a bioequivalence study according to the Guideline for Generic Drugs. No human studies are necessary, if justified.

Level 2

If a dissolution test has been established in accordance with Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances (PMSB/ELD Notification No. 568) or justified, perform a dissolution test under the specification test conditions. Otherwise, perform the dissolution test specified in Chapter 3. B.IV of the Guideline for Generic Drugs (if the property of a release-controlling excipient is to be changed, perform the test by the paddle method and the rotating basket method; if the property of a non-release controlling excipient is to be changed, perform the test by the paddle method at 50 rpm and 100 rpm only). If the dissolution behavior is judged equivalent in accordance with Chapter 5 of the Guideline for Bioequivalence Studies of Formulation Changes of Oral Solid Dosage Forms, the test and reference products are considered bioequivalent.

If dissolution test results do not indicate bioequivalence, perform a bioequivalence study according to the Guideline for Generic Drugs. No human studies are necessary, if justified.

Level 3

Perform a bioequivalence study according to the Guideline for Generic Drugs. No human studies are necessary, if justified.

Attached Table 2. Process change levels and required studies for extended-release formulations

| Change level | Item | Change | Required studies[b)] |
|---|---|---|---|
| Level 1<br>(Minor change) | Component properties | Change to the crystalline form, particle size, etc. of the drug substance or to the grade, etc. of excipients that has little impact on quality | 1) If a dissolution test has been established in accordance with "Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances" (PMSB/ELD Notification No. 568): Conformity to the specification<br>2) Other: Equivalence of the dissolution behavior under multiple conditions[c)] specified in the Guideline for Generic Drugs |
| | Manufacturing scale | Change to the manufacturing scale that has little impact on quality<br>(Apparatus having the same mode and operating principle; similar SOP) | |
| | Location | Transfer to a manufacturing location having the same education and training system for workers<br>(Same SOP, environment, and management) | |
| | Apparatuses | Change to another apparatus having the same mode and operating principle | |
| | Manufacturing process | Change to operating parameters, such as blending time and operating speed, within the scope of application or validation | |
| Level 2[a)]<br>(Moderate change) | Component properties | Change to the crystalline form, particle size, etc. of the drug substance or to the grade, etc. of excipients that may have an impact on quality | 1) If a dissolution test has been established in accordance with "Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances" (PMSB/ELD Notification No. 568): Equivalence of the dissolution behavior under the specification test conditions<br>2) Other: Equivalence of the dissolution behavior under multiple conditions[d)] specified in the Guideline for Generic Drugs |
| | Manufacturing scale | Change to the manufacturing scale that may have an impact on quality<br>(Apparatus having the same mode and operating principle; similar SOP) | |
| | Location | Transfer to a manufacturing location having a different education and training system for workers<br>(Apparatus having the same mode and operating principle; same SOP, environment, and management) | |
| | Apparatuses | Change to an apparatus having a different mode and operating principle | |
| | Manufacturing process | Change to operating parameters, such as blending time and operating speed, outside the scope of application or validation | |
| Level 3<br>(Major change) | Manufacturing process | Change beyond the scope shown above that may have a significant impact on quality. An example is a change in the type of the manufacturing process from wet granulation to dry direct compression. | Bioequivalence study according to the Guideline for Generic Drugs |

a) Level 1 test may be applied if there is a reasonable ground for the absence of impact on quality.

b) If dissolution test results do not indicate bioequivalence, perform a bioequivalence study according to the Guideline for Generic Drugs. No human studies are necessary, if justified.

c) Among the dissolution test conditions listed in Chapter 3, B.IV of the Guideline for Generic Drugs, the paddle method at 50 rpm with 5 conditions and at 100 rpm should be used.

d) If the property of a release-controlling excipient is to be changed, the paddle method at 50 rpm with 5 conditions, at 100 rpm, at 200 rpm, and the rotating basket method at 100 rpm and 200 rpm should be used among the dissolution test conditions listed in Chapter 3, B.IV of the Guideline for Generic Drugs. For other changes, the paddle method at 50 rpm with 5 conditions and at 100 rpm should be used among the dissolution test conditions.

# Q&As on the Principles on Bioequivalence Studies of Oral Solid Dosage Forms with Manufacturing Process Changes

## <<Introduction>>

Q-1 What are the characteristics of and precautions to apply this material?

(A) Manufacturing process changes are various and include changes in the apparatus, process, manufacturing scale, manufacturing environment, etc. The nature of change is also diverse, and the impact of change also differs from drug to drug. Furthermore, a change to a single factor often interacts with other factors. It is thus difficult to handle manufacturing process changes on a uniform manner, and the level, nature, and scope of change shown herein are just principles.

The Guideline for Bioequivalence Studies of Formulation Changes, which clearly specifies change levels, required studies, acceptance criteria for test results, and data to be submitted to regulatory authorities, is regarded as "standards" that must be adhered to. On the other hand, this material on manufacturing process changes prompts pharmaceutical companies to appropriately judge the change level and required studies for each formulation to ensure the bioequivalence and quality in terms of efficacy and safety, while assessing the degree of impact of each change on quality. This material significantly differs in this point from the "Guideline for Bioequivalence Studies," and to clarify this, it is entitled "Principles on Bioequivalence Studies."

Q-2 Under Introduction, it is stated that “manufacturing process changes should be controlled based not only on specification tests but also ... in light of how the drug is developed and quality assured.” Could you explain how change control should be?

(A) Drug manufacturing implies manufacture and clinical supply of formulations having equivalent efficacy and safety to those whose efficacy and safety have been confirmed in clinical trials. From this point of view, the key in the change control of manufacturing process changes of oral solid dosage forms is to confirm that the bioavailability, content uniformity, and stability remain unchanged. In order to confirm that these three aspects remain unchanged, not only specification tests to examine conformity to the specification that represents only a part of quality, but also a study to understand the factors of the manufacturing process affecting quality (especially efficacy and safety) and evaluate the impact of these factors on the quality or confirm that the quality remains unchanged should be conducted for change control. "Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances" (PMSB/ELD Notification No. 568 dated May 1, 2001) states, "Specifications are one part of a total control strategy for the drug substance and drug product designed to ensure product quality and consistency. Other parts of this strategy include thorough product characterization during development, upon which specifications are based, and adherence to Good Manufacturing Practices: e.g., suitable facilities, a validated manufacturing process, validated test procedure, raw material testing, in-process testing, stability testing, etc." In order to ensure consistent manufacture of high-quality drugs even after manufacturing process changes, it is important to manufacture drugs with the three pillars, thorough product characterization during development, subsequent establishment of appropriate specifications and implementation of quality tests, and GMP-based validation and control of the commercial production process, combined in an organic manner.

Q-3 What regulatory procedure should be followed to change the manufacturing process described in the approval document?

(A) Regulatory change control of drug manufacturing processes is managed based on the descriptions in the approval document. Depending on the characteristics of each product, the marketing authorization holder

should determine which should be followed, a partial change application, a minor change notification, or in-house GMP control. According to "Handling of Data to be Attached to Applications for Approval of Prescription Drugs" (PFSB/ELD Notification No. 0109005 dated January 9, 2008), attached data are not required in a partial change application and are to be submitted if required in the review, if changes are made to the manufacturing process only. The results of studies obtained according to the approach presented herein are applicable as review data.

Q-4 This material assumes cases where the manufacturing process of a drug product is changed after approval. What should be done if the manufacturing process is changed from the "formulation whose efficacy and safety have been confirmed in clinical trials or whose equivalence to the original drug has been confirmed in a human bioequivalence study" before approval?

(A) It is desirable to regard the product before the change as the reference product and demonstrate the bioequivalence of the product after the manufacturing process change according to the approach presented herein. Basically, it is sufficient to perform an appropriate dissolution test like the one shown in this material to confirm the equivalence of dissolution behavior, but in some cases, bioequivalence should be confirmed in a human study. Scale-up may be tested in accordance with Q-6 (A) of "Q&As on the Guideline for Bioequivalence Studies of Generic Drugs" in Appendix 1 to the Administrative Notice from the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare dated November 24, 2006.

<<Manufacturing process change>>

Q-5 If the application comes with a design space as specified in ICH-Q8, how should changes within the design space be considered?

(A) If a design space has been proposed and approved in the manufacturing process, changes within the design space are not regarded as changes because the relationship between the process variables and the dissolution behavior in the dissolution test has been analyzed and established within a range that would not alter bioavailability.

Q-6 How should the manufacturing scale be considered in continuous processing?

(A) In the case of continuous processing, the manufacturing scale is not subject to change because there is no concept of batch.

Q-7 Why is there an item on component properties herein?

(A) Component properties are specified herein because they may affect the quality of the formulation.

Q-8 "Changes to the crystalline form, particle size, etc. of the drug substance or to the grade, etc. of excipients that may have an impact on quality" are specified as Level 2 changes. What are "changes that may have an impact on quality"?

(A) The degree of impact of alteration in the property of the drug substance or excipients on the drug product attributes varies depending on the drug or drug product, and it is not possible to uniformly determine what degree of alteration constitutes a "Level 2 change." Rapidly dissolving drugs have little impact on dissolution even if the particle size of the drug substance or the grade of excipients is slightly different, and changes that do not apparently affect dissolution are regarded as Level 1 changes. In poorly soluble drugs, in contrast, even a slight alteration may have a significant impact, which corresponds to a Level 2 change. Generally, when changing the grade of excipients, grade changes of diluents, colorants, flavoring agents, etc. that are considered not to affect drug product attributes are classified as Level 1, and grade changes of disintegrants, binders, lubricants, etc. that are considered to affect drug product attributes are classified as Level 2.

It is desirable to examine the extent to which changes to the crystalline form or particle size of the drug substance or to the grade, etc. of excipients affect drug product attributes during development, and then, whether or not the change should be classified as Level 2 should be assessed for each drug or drug product. For excipients that affect drug product attributes or poorly soluble drugs, the criteria for judging the change level may be more stringent, but if there is evidence that the impact on quality is small, the change may be classified as Level 1.

Q-9 To what extent are changes to the "manufacturing scale that have little impact on quality" or "manufacturing scale that may have an impact on quality"?

(A) Judgment should be made on an individual basis, taking into account the property (e.g., solubility) of the drug substance, drug product attributes, characteristics of the apparatus, etc. In the context herein, changes to the manufacturing scale in the range of 0.1 to 10 times are generally classified as Level 1, and those of less than 0.1 or more than 10 times are classified as Level 2.

Q-10 "Same SOP, environment, and management" is stated for changes to the manufacturing location, but if manufacturing is outsourced, "same SOP" does not fit the situation at the outsourcing company. At present, product quality can be ensured by separately issuing instructions to outsourcing companies on key items on the GMP. The phrase "same SOP, environment, and management" is also used in the US SUPAC, but what does "same" mean?

(A) "Same SOP, environment, and management" does not mean that everything must exactly be the same. The same SOP for manufacturing operation implies that the operating procedures and conditions for each manufacturing step described in the product master formula are the same, yielding the drug product of the same quality. The phrase "same SOP" is used when the apparatus is the same. For manufacturing scale changes, the phrase "similar SOP" is used because the apparatus may be different even if the mode and operating principle of the apparatus are the same. "Same environment" refers to the same environmental control conditions (temperature, humidity, etc.) for manufacturing, and "same management" refers to the identical in-process test methods and acceptance criteria required for the drug product to meet the specified quality.

Q-11 How should manufacturing process changes be considered when manufacturing is outsourced?

(A) Outsourced manufacturing involves a change to the manufacturing location. In this case, Level 2 is applicable because even if the mode and operating principle of the apparatus, SOP for manufacturing operation, manufacturing environment, and management method of manufacturing operation are the same, the change to workers with a different education and training system may affect the quality of the formulation. However, if the apparatus and manufacturing scale are the same, Level 1 test may be applied. Level 1 test may also be applied if knowledge gained from manufacturing experience or product knowledge gained during development has been transferred.

Q-12 What are the levels of the following changes?

[1] Change to the screen size of the mill

[2] Change to the granulation fluid volume

[3] Change from agitated granulation to fluidized bed granulation

[4] Change to the solvent in the wet granulation process

(A) Which changes are critical or non-critical depends on the drug or drug product. Each pharmaceutical company involved in the development and manufacture of the drug should make individual judgments because they have the best information on the manufacturing process. General answers would be:

[1] If the purpose of milling is to change the particle size distribution, it may affect dissolution of the drug product. Therefore, a change to the screen size is classified as Level 2. However, if data showing that the change to the screen size does not alter dissolution are available, the change is classified as Level 1. If the change is merely to facilitate powder flow and does not alter the particle size distribution of the sieved raw material or intermediate product, it is classified as Level 1 because there may be little impact on the quality of the formulation.

[2] Changes to the granulation fluid volume may affect dissolution of the drug product in general. Therefore, it is necessary, prior to production using the conditions after the change, to conduct a study at production scale or small scale, or to confirm from the data available during development that dissolution would remain unchanged. Changes to the granulation fluid volume is outside the scope herein.

[3] Changes from agitated granulation to fluidized bed granulation are classified as Level 2 because the mode and operating principle are different.

[4] Changes to the solvent type or solvent composition in the wet granulation process may affect the dissolution or stability of the drug product in general. Therefore, prior to production under the conditions after the change, a study at production scale or small scale should be conducted, or it should be confirmed from the data available during development that the dissolution and stability of the drug product would remain unchanged. Changes to the solvent type or solvent composition in the wet granulation process is outside the scope herein.

Q-13 Is it appropriate to interpret that "application" in "within the scope of application or validation" for changes to the manufacturing process refers to marketing approval? Also, Level 1 or 2 is based on "within or outside the scope of validation." What is the scope of validation? The "scope of validation" is an already verified range. Is it necessary to regard this as the subject of "change"? Also, how should the manufacturing scale be defined for validation (will results at small scale also be acceptable)?

(A) Application in this context refers to marketing approval.

The scope of validation is the range of manufacturing operation that has been demonstrated to result in the specified quality in a manufacturing step affecting drug product attributes. An example is blending time in the blending of powder. It is the range of blending time that has been demonstrated to achieve appropriate blending of the powder.

In the context of manufacturing process changes, changes to manufacturing factors or parameters that are critical to the dissolution or stability of the drug product should be treated as Level 1, even if they are within the validated range, to confirm that quality remains unchanged. Some changes to non-critical manufacturing factors or parameter may not necessarily be classified as Level 1 (for example, changes within the scope of maintenance are not classified as Level 1 changes). All changes should be recorded in accordance with GMP change control procedures, in the manufacturing instruction record, or by other appropriate means.

For the manufacturing scale of validation, small-scale results may be used if they reflect the commercial scale.

Q-14 How should it be handled when two or more items corresponding to Level 1 or 2 are changed simultaneously?

(A) When two or more items are changed simultaneously, each change affects each other and can be significant in some cases. The level should be assessed for each change, and the highest level evaluated is usually

selected, except when factorial interactions are concerned. The determination of change level 1, 2, or 3 depends on the extent of potential impact of the change on bioavailability or the expected risk of the change, which also depends on the attributes (e.g., dissolution) of the drug. Level 1 or 2 test may be applied to changes in multiple items if they may alter bioavailability but the alteration can be adequately checked in the dissolution test, but a problem arises when the alteration cannot be adequately checked. This is the case for poorly soluble drugs that require the addition of surfactants in the dissolution test. Under conditions where surfactants are added, the distinguishing ability of the dissolution test decreases, making it difficult to declare biological equivalence even if the dissolution behavior is equivalent. Therefore, it is necessary to appropriately justify the assessment in the dissolution test when simultaneously changing multiple items in the manufacturing process of a poorly soluble drug and applying Level 1 or Level 2 test.

Q-15 Is it acceptable to repeatedly change the manufacturing process?

(A) Repeated changes to the manufacturing process should be avoided as much as possible because they may result in a divergence of quality from that of the drug product described in the application form at the time of approval. When manufacturing process changes are repeated, it is necessary to evaluate all the data related to the series of previous manufacturing process changes (nature of manufacturing process changes and equivalence study data) in chronological order to determine whether the quality is not diverted from that of the drug product described in the application form at the time of approval.

Based on the Q&As on manufacturing process changes above, examples of changes corresponding to change items of each change level are shown in the attached table. These are just examples, and individual changes are not necessarily bound by these examples.

<<Dissolution test>>

Q-16 For the statement "if a dissolution test is justified," how should this be justified?

(A) See the approach stated in "Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances" (PMSB/ELD Notification No. 568 dated May 1, 2001).

Q-17 For immediate-release and enteric-coated formulations, "if the dissolution test conditions established in the specification are excellent in distinguishability" is stated. Of what distinguishability does this mean?

(A) Distinguishability in this context is the distinguishability described in Flowchart #7(2) of "Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances" (PMSB/ELD Notification No. 568 dated May 1, 2001), and here refers to the distinguishability for manufacturing process changes.

Q-18 Why is the confirmation of conformity to the specification, which is the sole requisite when the dissolution test established in the specification has been justified, limited to Level 1?

(A) The guarantee of bioequivalence by dissolution test specifications is usually effective for a limited range of manufacturing process changes and is not applicable to significant manufacturing process changes. If confirmation of conformity to the dissolution test specification is set as the sole requisite for a broad manufacturing process change, a reasonable ground to guarantee bioequivalence should be provided.

Q-19 If the dissolution rate increases rapidly in the assessment of equivalence using f2 function in the dissolution test, equivalence cannot sometimes be determined due to a large variability of dissolution rate. In this case, can this be treated as equivalent if the absence of significant difference in dissolution can be shown by an appropriate statistical method?

(A) For f2 function values less than 50, it can be regarded as equivalent if the absence of significant difference can be shown by an appropriate statistical method such as the model dependent confidence region procedure recommended by the FDA (see Guidance for industry: Dissolution testing of immediate release solid oral dosage forms, FDA, 1997).

Q-20 What should be done if the dissolution test specification is not met?

(A) A manufacturing process change that does not meet the dissolution test specification is possible, but this type of change is treated as a partial change in the specification and is out of the scope herein.

Q-21 For immediate-release and enteric-coated formulations, why is the dissolution test under highly distinguishing conditions permitted for Level 1 not permitted for Level 2?

(A) The guarantee of bioequivalence by dissolution test specifications is usually limited to minor manufacturing process changes, although it also depends on the test data that justified the specification, and this does not intend to provide guarantee for major manufacturing process changes. Similarly, a minor manufacturing process change that has little impact on quality is unlikely to cause changes in the pH-dissolution profile, resulting in no change in the highly distinguishing conditions (e.g., pH 6.8), whereas a major manufacturing process change may alter the pH-dissolution profile and also change the highly distinguishing conditions (e.g., pH 6.8). For this reason, the application of a dissolution test under highly distinguishing conditions is limited to Level 1 changes.

Q-22 "Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances" (PMSB/ELD Notification No. 568 dated May 1, 2001) describes cases in which a disintegration test, rather than dissolution test, can be established as a specification test for immediate-release formulations, suggesting that a dissolution test is not always established. How will such formulations be handled?

(A) Drugs that only have a disintegration test specification without a dissolution test specification are special cases. Such drugs will be separately assessed to confirm that their bioavailability remains unchanged after the manufacturing process change, depending on the attributes of each drug product, by following the approach presented herein.

Q-23 "Broad therapeutic index" in the expression "drugs having a broad therapeutic index" is ambiguous. Can examples be provided?

(A) See the Guideline for Bioequivalence Studies of Formulation Changes. This guideline presents a list of and judgment criteria for "drugs having a narrow therapeutic index." Any drugs that do not meet these criteria are considered as drugs having a broad therapeutic index.

Q-24 If the drug hardly dissolves within the specified time when performing a dissolution test for a poorly soluble drug, etc. in a manufacturing process change, is it meaningful to perform a dissolution test under these conditions?

(A) One of the acceptance criteria for equivalence of dissolution behavior is that the mean percent test drug dissolved is within ± 6% of the mean percent reference drug dissolved, if the mean percent reference drug

dissolved does not reach 50%. Comparison of dissolution behavior is not meaningful if neither the reference nor test product obviously dissolves by 6% or more in 6 hours. When component properties are changed, the test product is expected to hardly dissolve if the reference product hardly dissolves due to the low solubility in the dissolution medium in Level 1 or 2 changes, except for changes to an apparatus having a different mode or operating principle. Therefore, if the percent dissolved within the specified time in the dissolution test to select the reference product is 6% or less and the solubility suggests that 6% or more would not dissolve in the dissolution medium, it is not necessary to compare the dissolution behaviors of the reference and test products under these conditions (the dissolution behavior can be regarded as equivalent) when component properties are changed, except for changes to an apparatus having a different mode or operating principle.

Q-25 What specific cases does "No human studies are necessary, if justified" refer to?

(A) This includes cases where it is explained that the manufacturing process change does not affect clinical effects, or cases where, from the viewpoint of bioequivalence, 1) the in vitro/in vivo correlation has been established in appropriate subjects and bioequivalence can be assured from the results of a dissolution test under the relevant test conditions or 2) bioavailability does not alter as much as the alteration of dissolution speed due to the slow gastrointestinal permeability, small clearance, or higher sensitivity of in vitro dissolution than in vivo and bioequivalence can be assured by a dissolution test. These data are often obtained during the development phase.

Q-26 Is there any formulation for which confirmation of equivalence by a dissolution test can be simplified?

(A) For a Level 1 or 2 change, a formulation that shows no alteration in the pH profile of dissolution and dissolves fast can be tested in water alone, for example. Supporting data are needed in this case.

Q-27 For immediate-release and enteric-coated formulations, can bioequivalence be confirmed by the equivalence of the dissolution behavior under the specification test conditions also at Level 3 if the dissolution test specification has been justified?

(A) The justification of dissolution test specifications is applicable to drug products with similar drug product attributes. It is not applicable to largely different drug product attributes, such as those of Level 3. However, this strategy is acceptable if there is a reasonable ground such as rapid dissolution.

Q-28 Should studies be conducted to investigate alteration of the dissolution profile over time?

(A) Although not required as review data, it is desirable to conduct studies on commercial batches after approval. It is not necessary to conduct these studies if the manufacturing process change is unlikely to affect the stability of dissolution (drugs that dissolve fast, changes that do not affect dissolution, etc.).

Q-29 For drugs to which it is not appropriate to apply the dissolution test specified herein, can a dissolution (release) test or physicochemical test be performed instead?

(A) Yes, if there is a reasonable ground such as the ability of the test to guarantee bioequivalence (see Q-16).

The following Q&As are specific to extended-release formulations. Refer to the Q&As above for other issues common to extended-release formulations and immediate-release and enteric-coated formulations.

Q-30 What are extended-release formulations included in the scope of extended-release formulations herein?

(A) An extended-release formulation is a drug product designed to release the drug slowly to maintain its efficacy or to reduce side effects in general. Special cases include time-dependent release formulations and gastrointestinal-limited release formulations. Such drugs should be separately assessed to confirm that their bioavailability remains unchanged after the manufacturing process change, depending on the attributes of each drug product, by following the approach presented herein.

Q-31 Why is the item "Equivalence may be judged using only the dissolution test conditions of the specification, if the dissolution test conditions established in the specification are excellent in distinguishability" specified for immediate-release and enteric-coated formulations not specified for Level 1 changes for extended-release formulations?

(A) For extended-release formulations, it is necessary to evaluate dissolution in more detail than immediate-release or enteric-coated formulations in order to confirm that the release behavior remains unchanged, in particular that dose dumping does not occur. Dissolution cannot be adequately evaluated by the distinguishability of dissolution test conditions alone. If equivalence cannot be ensured by the specified dissolution test, it is necessary to demonstrate equivalent dissolution behaviors under multiple test conditions with different pH levels.

Q-32 Why is the basket method added to changes to excipients or drug substance properties affecting dissolution for extended-release formulations?

(A) To assess dissolution, especially dose dumping, by a mechanically stimulating method.

Attached Table. Process change levels and change examples

| Change level | Item | Change | Change example (proposed) |
|---|---|---|---|
| Level 1 (Minor change) | Component properties | Change to the crystalline form, particle size, etc. of the drug substance or to the grade, etc. of excipients that has little impact on quality | • The solubility of the drug is high, and the change to the crystalline form or particle size does not affect dissolution.<br>• Change to the grade of diluents, colorants, flavoring agents, etc. |
| | Manufacturing scale | Change to the manufacturing scale that has little impact on quality<br>(Apparatus having the same mode and operating principle; similar SOP) | • Change to the manufacturing scale in the range of 0.1 to 10 times |
| | Location | Transfer to a manufacturing location having the same education and training system for workers<br>(Same SOP, environment, and management) | • Change to the manufacturing location within the company |
| | Apparatuses | Change to another apparatus having the same mode and operating principle | • Change of dryer<br>• Change of mixer (mixing vessel shape)<br>• Change from top spray to side spray<br>• Change to the screen size of the mill |
| | Manufacturing process | Change to operating parameters, such as blending time and operating speed, within the scope of application or validation | • Change within the scope of validation<br>• Change to the drying end point (e.g. exhaust temperature → product temperature) |
| Level 2 (Moderate change) | Component properties | Change to the crystalline form, particle size, etc. of the drug substance or to the grade, etc. of excipients that may have an impact on quality | • The solubility of the drug is different depending on the crystalline form. The particle size of the drug substance affects dissolution.<br>• Change to the grade of disintegrants, binders, lubricants, etc. |
| | Manufacturing scale | Change to the manufacturing scale that may have an impact on quality<br>(Apparatus having the same mode and operating principle; similar SOP) | • Change to the manufacturing scale of less than 0.1 or more than 10 times |
| | Location | Transfer to a manufacturing location having a different education and training system for workers<br>(Apparatus having the same mode and operating principle; same SOP, environment, and management) | • Outsourcing of manufacturing to other companies |
| | Apparatuses | Change to an apparatus having a different mode and operating principle | • Change from agitated granulation to fluidized bed granulation<br>• Change from shelf drying to fluidized bed drying<br>• Change from two-step granulation (agitated granulation → sizing) to one-step granulation (fluidized bed granulation)<br>• Change to the screen size of the mill (in the case of changing the particle size distribution) |
| | Manufacturing process | Change to operating parameters, such as blending time and operating speed, outside the scope of application or validation | • Change outside the scope of validation<br>• Change to the granulation end point |
| Level 3 (Major change) | Manufacturing process | Change beyond the scope shown above that may have a significant impact on quality. An example is a change in the type of the manufacturing process from wet granulation to dry direct compression. | • Change from wet granulation to dry direct compression |