Appendix 3. Method to evaluate effect of film coating on dissolution

1) When the average dissolution of the reference product reaches 85% in at least one test condition: the dissolution tests of core tablets (or uncoated tablets) and film-coated tablets for before and after the film-coating change should be performed under the conditions shown in Sec. 4. When the dissolution profile of the film-coated tablets before and after the film-coating change is judged to be equivalent to the corresponding core tablets according to the criteria in Sec. 5, it should be considered that the film coating does not affect dissolution. Core tablets (or uncoated tablets) and film-coated tablets manufactured by the same manufacturing method and process as those of the reference and test products can be used.

2) When the average dissolution of the reference product does not reach 85% in any of the test conditions: using a high solubility drug such as acetaminophen etc, core tablets of which the components and composition except the active ingredient are the same and the average dissolution of the core tablets reach 85% in all the test conditions are applied. Using the obtained core tablets, model film-coated tablets before and after the film-coating change are prepared respectively. The dissolution tests of the core tablets and model film-coated tablets before and after the film-coating change should be performed under the conditions shown in Sec. 4. When the dissolution profile of the model film-coated tablets before and after the film-coating changes are judged to be equivalent to the core tablets according to the criteria in Sec. 5, it should be considered that the film coating does not affect dissolution.

In any of the above cases of 1) or 2), when the composition rate is the same in the film-coated tablets before and after the film-coating change, the dissolution comparison can be done only for the thicker-film coated tablets (film-coated tablets of which the amount of film coating is higher).

The above 1) or 2) can be also applied to the changes from plain tablets to film-coated tablets and vice versa.

Attachment 4

Appendix 4. Levels of formulation changes and required tests

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

Level	Immediate/ Extended Release	Therapeutic range [1]	Poorly soluble/Soluble	Rapid [3]/Non-rapid dissolution	Confirmation of bioequivalence
A	Immediate Release	Non-narrow			When the dissolution specification is established: if the dissolution profiles are judged to be equivalent in the dissolution test shown in the specifications, the test and reference products are regarded as bioequivalent. When the dissolution specification is not established: if the dissolution profiles are judged to be equivalent in the dissolution test shown in Sec. 4., they are regarded as bioequivalent.
B	Immediate Release Enteric coated [2] Extended Release				If the dissolution profiles are judged to be equivalent in the dissolution test shown in Sec. 4., they are regarded as bioequivalent. In the case of film coating change where it is demonstrated that film coating does not affect dissolution of products and the average dissolution of the reference product does not reach 85% in any test conditions specified, the dissolution test defined in Level A can be used. If the dissolution profiles are judged to be equivalent, they are regarded as bioequivalent.
C	Immediate Release Enteric coated [2]	Non-narrow	Soluble		If the dissolution profiles are judged to be equivalent in the dissolution test shown in Sec. 4., they are regarded as bioequivalent.
			Poorly soluble		Follow the Guideline for Bioequivalence Studies of Generic Products.
		Narrow	Soluble	Rapid	If the dissolution profiles are judged to be equivalent in the dissolution test shown in Sec. 4., they are regarded as bioequivalent.
				Non-rapid	Follow the Guideline for Bioequivalence Studies of Generic Products.
			Poorly soluble		
	Extended Release	Non-narrow			If the dissolution profiles are judged to be equivalent in the dissolution test shown in Sec. 4., they are regarded as bioequivalent.
		Narrow			Follow the Guideline for Bioequivalence Studies of Generic Products.
D	Immediate Release	Non-narrow	Soluble	Rapid	If the dissolution profiles are judged to be equivalent in the dissolution test shown in Sec. 4., they are regarded as bioequivalent.
				Non-rapid	Follow the Guideline for Bioequivalence Studies of Generic Products.
			Poorly soluble		
		Narrow			
	Enteric coated [2] Extended Release				
E	Immediate Release Enteric coated [2] Extended Release				Follow the Guideline for Bioequivalence Studies of Generic Products.

1) Non-narrow: Drugs that are not listed in Table 3 Narrow: Drugs that are listed in Table 3

2) In the change of the diameter of the units having substantial enteric function from less than 4 mm to 4 mm or more, or vice versa, the formulation change of the level is E, and bioequivalence studies at fed state should be additionally performed.

3) Average dissolutions of the reference and test products reach 85% at 30 min under all the testing conditions in Sec.4.

English translation of **Attachment 2 of Clerical Notification** of the Pharmaceutical and Food Safety Bureau, dated February 29, 2012

Guideline for Bioequivalence Studies for Different Strengths of Oral Solid Dosage Forms
Guideline for Bioequivalence Studies for Formulation Changes of Oral Solid Dosage Forms
Q&A

General matters

Q-1 In the guideline (formulation changes), why are test products after change regarded as bioequivalent to reference products before change with dissolution equivalence? In the Guideline for Bioequivalence Studies of Generic Products, why are generic products not regarded as bioequivalent to innovator products with dissolution equivalence?

(A) This guideline applies to products before and after component and composition changes. The concept is that in small formulation ranges where changes should not significantly alter the bioavailability, confirming the equivalence in dissolution under several test conditions, including the physiological pH range test solution, should make a human bioequivalence study unnecessary. However, formulation components, compositions, and manufacturing methods of new generic products may be quite different from innovator products, and therefore it is impossible to ensure bioequivalence by confirming dissolution equivalence. In generic product applications, it is necessary to confirm bioequivalence in a human study.

Q-2 In these guidelines, what is the reason that the required tests are different depending on change level, dissolution rate, and therapeutic ranges of drugs?

(A) The guidelines set the range of formulation change for which it is unnecessary to confirm bioequivalence of the products by human study.

The ranges are limited to situations where the changes are so small that bioavailability does not change beyond the bioequivalent range and changes in drug product properties can be evaluated by dissolution tests before and after the changes. Dissolutions of drug products before and after changes should be similar when the formulation change is small and the drug products demonstrate rapid equivalent dissolution behavior under all the multi-dissolution test conditions. The slower the drug product dissolution is, the larger are the interactions between dissolution of drugs and physiological factors in the gastrointestinal tract; in this situation, it becomes difficult to evaluate *in vivo* dissolution equivalence (in the gastrointestinal tract) between drug products by an *in vitro* dissolution study. Therefore, drug products with a slow dissolution, the range of formulation change for which bioequivalence can be confirmed only by dissolution tests is narrow compared to drug products with a rapid dissolution. The ranges of formulation change where bioequivalence can be confirmed by dissolution tests are also

narrower for products containing narrow therapeutic range drugs, taking the risk of an error in evaluating bioequivalence by the dissolution tests into consideration.

Changes of excipients of which composition is described as "trace use" and excipients categorized as "Others" within the range of not more than 1.0% (sum of absolute values of difference of content) are classified as level A. Since those changes are considered not to affect pH-dependence of the dissolution properties, the test product is then regarded as bioequivalent to the reference product when their dissolution is judged to be equivalent under the dissolution specification conditions.

In level B changes, where formulation changes are small, dissolution equivalence under multi-dissolution conditions indicates that there is no significant difference in bioavailability between the drug products. Therefore irrespective of the drugs' therapeutic ranges, the dissolution rates, and the release category (immediate, enteric, or extended), the test product is regarded as bioequivalent to the reference product when their dissolution is judged to be equivalent.

In level C changes, where formulation changes are relatively large, the formulation change ranges for which bioequivalence is confirmed by dissolution tests, are limited. It is difficult to confirm bioequivalence by dissolution only in "Products containing poorly soluble drugs" when dissolution does not reach 85% in any of the test fluids without surfactants. In level C and higher changes for "Products containing poorly soluble drugs," bioequivalence should be confirmed by a human study.

For products containing narrow therapeutic range drugs, unless bioequivalence is certainly confirmed, there is a possibility that efficacy and safety issues may occur. Therefore, in level C and higher changes, bioequivalence should be confirmed by a human study; however, when dissolutions of the reference and test products reach 85% within 30 minutes under all the test conditions and dissolution behavior is equivalent, possibility of inbioequivalence is considered low and it is unnecessary to confirm bioequivalence by a human study.

In level D and higher changes, it is difficult to confirm bioequivalence by dissolution equivalence, and in principle, bioequivalence should be confirmed by a human study. However, when dissolution of the reference and test products reach 85% within 30 minutes under all the test conditions and dissolution behavior is equivalent, it is speculated that possibility of inbioequivalence is low. Therefore, in such cases, except for products containing narrow therapeutic range drugs, it is unnecessary to confirm bioequivalence by a human study.

Q-3 This guideline (formulation changes) corresponds to a part of the FDA guidances, SUPAC-IR and SUPAC-MR *. What points are different or similar?

* SUPAC-IR: Immediate Release Solid Oral Dosage Forms; Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo

Bioequivalence Documentation, November 1995.

SUPAC-MR: Modified Release Solid Oral Dosage Forms; Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation, September 1997.

(A) Points of similarity

Both this guideline and the SUPAC guidance are based on the concept that taking into consideration formulation change ranges, dissolution rates, and therapeutic ranges of the drugs, in the case that the changes are so small that bioavailability does not change beyond the bioequivalent range, bioequivalence can be confirmed if dissolution tests can appropriately demonstrate that there is no difference in the performance of the drug product before and after the formulation changes. Other similarity is that the range of the formulation change, where bioequivalence is confirmed by dissolution tests, is narrower for products containing narrow therapeutic range drugs. Both guidelines have similar dissolution equivalence criteria that the difference of average dissolution of the reference and test products should be within 10%.

Points of difference

(1) A key difference is that the guideline does not adapt the Biopharmaceutics Classification System (BCS)*. The SUPAC guidance classifies drugs into 4 categories based on solubility and membrane permeability. This guideline does not adopt the BCS, but rather classifies drug products by dissolution rates. The idea in the SUPAC guidance is that in drugs with low solubility and low permeability, it is difficult to confirm bioequivalence by dissolution tests only due to their low *in vivo-in vitro* correlation. The lower the *in vivo-in vitro* correlation is, the narrower is the range of the formulation changes where bioequivalence is confirmed by dissolution tests. The reason this guideline did not adopt the BCS is that differences in bioavailability between drug products are caused by differences in formulation properties such as the particle size of drug substance, the component compositions, and the manufacturing methods. This guideline adopts the idea that differences in bioavailability do not occur between drug products with equivalent dissolution in the gastrointestinal tract. This guideline requires in level B and higher changes, dissolution equivalence by comparison under multi-dissolution test conditions to confirm dissolution equivalence in the complex and highly diverse gastrointestinal tract.

* Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate Release Solid Oral Dosage Forms Containing Certain Active Moieties/Active Ingredients Based on a Biopharmaceutics Classification System, August 2000, FDA.

(2) In this guideline, the change levels for coated products, including sugar-coated products, are determined by calculations separate from those in the tablet core and in the coating layer. However, in the SUPAC guidance, calculations of change in the excipient levels in the coating layer are done in the same way as those in tablet core. In this guideline, excipients in the coating layer are handled separately from those in the tablet core because, in some cases, the

coating layer can affect the dissolution profile of drug products; thus the thickness of the coating layer should be considered rather than the weight of coating layer.

(3) The scope of this guideline includes only components and composition changes, while the scope of the SUPAC guidance includes site changes, changes in batch size, and manufacturing equipment/processes. This difference is because of the historical differences in the approval and licensing system between the USA and Japan. These matters are outside of the scope of the guideline because they were not included in the product approval system before the revision of Pharmaceutical Affairs Law (effective in April 2005). However, the revision of the Law enforces the descriptions of manufacturing methods in the Application Form, and GMP compliance is required for product approval. Therefore, confirmation of bioequivalence by appropriate methods is necessary for manufacturing changes.

Scope

Q-4 Is it acceptable to apply this guideline to formulation changes during drug development?

(A) This guideline should be applied to post-approval formulation changes and is not intended to be applied to changes during drug development. Judgement to use the principles of this guideline in formulation changes during development should be done under responsibility of the pharmaceutical company based on scientific considerations of the phases of clinical studies, extent of formulation changes, and efficacy and safety of the drug.

Q-5 What is the reason for setting a "Standard formulation"?

(A) The reason for setting a "Standard formulation" is to prevent the component and composition change range where bioequivalence is confirmed by dissolution tests only form changed from the formulations of which therapeutic efficacy and safety were established by clinical trials, or bioequivalence was demonstrated by human studies, by repeated changes by dissolution tests only. Change levels are calculated by comparing to a standard formulation. The standard formulation is not always available commercially, and therefore, commercially available drug product can be used as a reference product in a bioequivalence study.

Q-6 The "Standard formulation" is defined as the formulation for which therapeutic efficacy and safety were established by clinical trials or for which bioequivalence was demonstrated by human studies. The formulation of a drug product that has had its formulation change approved by dissolution equivalence only is not eligible to be "Standard formulation". Is a human study always required after the formulation change?

(A) It is not desirable but permissible to repeat formulation changes by dissolution tests only by using the formulation for which therapeutic efficacy and safety were established by clinical trials or for which bioequivalence was demonstrated by human studies as the "Standard formulation", if the "Standard formulation" is identified.

Q-7 When the "Standard formulation" is not available in the market, is it acceptable to manufacture the "Standard formulation" drug product and use it as reference product?

(A) It is not acceptable. In formulation changes, the product before the change should be used as the reference product.

Q-8 When the formulations of marketed pharmaceutical products are changed by the dissolution test or animal studies according to "Bioequivalence test standards" stipulated in Table 2 attached to the Division-Notification No. 718 issued on May 30, 1980, which tests are required?

(A) When the change level that was calculated compared to the standard formulation is within the range where bioequivalence can be confirmed by dissolution tests only, the dissolution test should be performed according to this guideline using the product before the change as the reference product. However, in many cases of such pharmaceutical products, the level calculated is out of the range where bioequivalence can be confirmed by dissolution tests, according to this guideline. In such cases, a bioequivalence study is conducted according to the Guideline for Bioequivalence Studies of Generic Products by using the product before change and the innovator product as reference product in the case of innovator product and generic product, respectively.

Q-9 In the case of generic products for which bioequivalence was demonstrated by human studies, is it acceptable to use the own generic product as the reference product according to the Guideline for Bioequivalence Studies for Different Strengths of Oral Solid Dosage Forms, even if there is no innovator product of the same strength?

(A) Bioequivalence of different strengths can be evaluated using the generic product for which bioequivalence was demonstrated by human studies, as reference product even if there is no innovator product of the same strength as long as within the dose range and the dose regimen.

Q-10 When there are 2 strengths of innovator products (e.g., 10 mg and 20 mg strength tablets), and when bioequivalence of one strength formulation (either 10 mg or 20 mg) is confirmed by a human study, is the same time application of the other strength product performed according to the Guideline for Bioequivalence Studies for Different Oral Solid Dosage Forms acceptable?

(A) Yes, it is possible. In principle, application of multi-strength products at the same time is possible by conducting a bioequivalence study with the higher strength (e.g., 20 mg strength), according to the Guideline for Bioequivalence Studies of Generic Products, and a bioequivalence study of the other strength (e.g., 10 mg strength) according to the Guideline for Bioequivalence Studies for Different Oral Solid Dosage Forms. Bioequivalence of the

reference product used in the Guideline for Bioequivalence Studies for Different Oral Solid Dosage Forms must be confirmed by comparing to innovator products.

Q-11 When an innovator product has a 20 mg strength formulation only, can this guideline be applied for the application of a 10 mg strength generic product formulation?

(A) The above case refers to the application of different dosage forms, and in this case, the Guideline for Bioequivalence Studies for Different Oral Solid Dosage Forms is applicable.

Q-12 Is it acceptable to conduct an animal study instead of a human study in the cases where formulation changes and the addition of different strength products have strong pharmacological actions or adverse effects and it may be unfavorable to use healthy volunteers?

(A) As in the answer for Q-15 in the Guideline for Bioequivalence Studies of Generic Products Q&A, it is not acceptable to conduct an animal study instead of a human study.

Q-13 Are dry syrup products within the scope of this guideline?

(A) Dry syrup products are within the scope of this guideline since the dissolution test in this guideline can evaluate their dissolution profile. For products intended to be dissolved when used, dissolution tests can be done after the product is dissolved. When an active ingredient is completely dissolved, the product is regarded as a medicinal product of which the reference and the test products dissolve not less than 85% within 15 minutes in the test solutions (Refer to Q-44 in the Guideline for Bioequivalence Studies of Generic Products Q&A).

Q-14 Is it possible to evaluate bioequivalence of oral dosage forms according to the dissolution tests in this guideline, when the active ingredient is not expected to exert therapeutic efficacy by entering the systemic circulation?

(A) When it is justified to perform the dissolution tests, it is possible to evaluate bioequivalence by conducting the dissolution tests described in this guideline. When not justified, or if it is impossible to perform dissolution testing, pharmacodynamic studies or clinical studies, as described in the Guideline for Bioequivalence Studies of Generic Products, should be conducted.

Q-15 Is it possible to evaluate bioequivalence of soft capsules according to this guideline?

(A) Bioequivalence studies of readily soluble, soft capsule drugs, whose reference product dissolution reaches 85% within 15 min under all the dissolution test conditions, can be conducted according to this guideline. Refer to Appendix B for definitions of such terms as readily soluble drugs and formulation change levels.

Glossary

Q-16 What is the definition of extended-release products?

(A) Extended-release products are defined as drug products where drug release is intentionally extended to exert clinical effects and/or where usability is improved to an extent that cannot be achieved by immediate-release products. Enteric products are not categorized as extended-release products.

Q-17 When generic product makers conduct human bioequivalence studies according to the Guideline for Bioequivalence Studies of Generic Products, which product should be used for the reference drug: its own product or the innovator product?

(A) Since formulation change levels are calculated by comparing to the product before the change, the reference product should be its own product before the change and not the innovator product.

Q-18 For extended-release products, it is required that test products should not significantly differ from that of reference product in shape, size, and specific gravity, and release mechanism. When the release mechanism is the same, why is the similarity of shape and size required?

(A) The shape, size, and specific gravity of the dosage form are considered to affect the gastrointestinal transit and the resulting drug release rate of extended-release formulations since most of them should transit through the gastrointestinal tract retaining their dosage forms for a relatively long time. In addition, the transition rate of dosage forms cannot be evaluated by *in vitro* dissolution tests. Therefore, similarity of the dosage form shapes, sizes, densities, and release mechanisms between the reference and test products is required.

Q-19 What are the ranges for similarity of shape, size, specific gravity of the dosage form, and release mechanism in extended-release products?

(A) Shape: similar form

Size: for tablets, the diameter of the punch should be within 25%. For capsules filled with extended-release granules, there is no capsule size requirement.

Specific gravity: The percentage of floating granules on the dissolution test fluid, mounted granules on the bottom of the vessel, and floating granules in the fluid should be similar.

Release mechanism: The concept of the formulation design should be the same and dissolution behavior should be similar.

Q-20 What is the range of "the same in dosage form" described in the introduction of the Guideline for Bioequivalence Studies for Different Strengths of Oral Solid Dosage Forms?

(A) The range of "the same in dosage form" is the range in applications where partial change

of the approved items is possible.

Formulation change levels and required tests

Q-21 According to the Guideline for Bioequivalence Studies for Different Strengths of Oral Solid Dosage Forms, formulation changes are classified as level B when the ratios of all compositions between the test product and the reference product are the same for products containg narrow therapeutic range drugs, extended-release products, and enteric-coated products. What is the change level for different strength capsules where the same granules are filled, corresponding to the strengths?

(A) For hard capsules where the same granules are filled by disc method (without a press), a bioequivalence study is not required for capsules of different strengths except the case that the capsule shell is not modified with a special treatment. However, it must be confirmed that there is no difference properties checked by tests such as proper disintegration tests and dissolution tests.between strengths.

Q-22 What are the grounds to select narrow therapeutic range drugs in Table 3?

(A) The narrow therapeutic range drugs are those having less than a 2-fold difference in the minimum toxic concentrations and minimum effective concentrations in the blood, and those for which specific drug treatment control fees are approved as remuneration for treatment.
*21 CFR 320.33 (c)

Q-23 In the case that 1 excipient is used for 2 functions in the composition, is the formulation change level calculated for 1 of the 2 functions, or for both the functions?

(A) When the functions can be separated (for example binder and filler), formulation change levels should be calculated separately. When 1 excipient is described as "used for 2 functions" and it is difficult to separate the formulated amounts for each corresponding function (for example disintegrant and filler), formulation change levels should be calculated for the narrower change level function.

For example, when cornstarch is used as the filler and disintegrant, it is difficult to distinguish what amount is used separately for each of the 2 functions. Therefore, formulation change levels should be calculated for the narrower change level function, disintegrant. In coated products, for example, when hydroxypropylcellulose is used as a binder in core tablets and as a coating agent in the coating layer, it is possible to distinguish each function and then the formulation change levels should be calculated for each function separately.

Q-24 Is it possible to confirm bioequivalence using only dissolution tests when an entire excipient is replaced and the formulation change level is the level where bioequivalence can be confirmed by dissolution tests only?

(A) It is possible for lactose, white soft sugar, sucrose, potato starch, cornstarch, microcrystalline cellulose, and D-mannitol whose composition can be described as "q.s." The composition of excipients whose composition can be described as "q.s." should be theoretical amounts, and the formulation change level should be determined based on these theoretical amounts. When the formulation change level is the level for which bioequivalence can be confirmed by dissolution tests only, it is possible to confirm bioequivalence by dissolution tests only.

For other excipients, when all of the excipient is replaced, it is necessary to confirm that the excipient does not interact with the active ingredient physicochemically and does not affect the membrane permeability of the active ingredient; this confirmation should be done by e.g., animal studies, *in vitro* tests, and literature reviews.

Q-25 Why is the change level determined as "B," except for products containing narrow therapeutic range drugs, when the amount of the film coating is not more than 7% (w/w) of the core tablet and when the film coating is demonstrated not to affect dissolution?

Further, in the above level B change, why is the required test that for change level A for products containing poorly soluble drugs (the average dissolution of reference products does not reach 85% within the testing time specified in any test condition of this guideline.)?

(A) In many cases, the purposes of film coating are to improve the stability and/or mask the bitter taste, which are not intended for,control of dissolution. The formulation change level for these products was determined as B because the possibility of inbioequivalence should be negligible since the changes in the film coating do not affect dissolution and dissolution equivalence is attained.

According to the dissolution equivalence criteria in Section 5, for a drug product whose reference products do not reach average dissolution of 85% within the testing time specified in any test condition, a human study is required in level B changes. However, dissolution of poorly soluble drug products is relatively slow and the effect of a film coating change on the dissolution is considered smaller compared to drug products with rapid dissolution. Therefore, dissolution tests should be performed under the conditions specified in the registration for the drug product whose reference products do not reach an average dissolution of 85% within the testing time specified in any test condition.

Q-26 Are capsules categorized as coated or uncoated formulations? Can proteases such as trypsin or pepsin be added to dissolution test fluids?

(A) When the formulation changes are limited to the filling in the capsules, the capsules are regarded as uncoated formulations. However, when the capsule shell is coated, the capsules are regarded as coated formulations. (When the ingredients of capsule shell are changed, refer to Q-27.)

Dissolution tests should be performed to determine whether a human study is waived or not, and then the dissolution test methods are limited to those described in this guideline. Proteases such as trypsin or pepsin cannot be added.

Q-27 How are ingredient changes of capsule shells handled?

(A) Ingredient changes of capsule shells correspond to the composition changes of the film-coating layer and the sugar-coating layer. Recently, additions to gelatin such as succinylated gelatin, starch, HPMC, and pullulan, are used as capsule shell ingredients. Changes in the ingredients of the capsule shell may affect bioavailability. Except for products containing narrow therapeutic range drugs, bioavailability should be confirmed according to the following:

(1) When carrageenan is used as a gelling agent in the capsule shell

Dissolution tests should be performed under the conditions shown in Sec. 4 (the JP14 2nd fluid for disintegration should be used as the pH 6.8 dissolution test fluid.) The test product is regarded as bioequivalent to the reference product if its dissolution is judged to be equivalent according to the criteria in Sec. 5. When the dissolution is not equivalent, bioequivalence tests should be performed according to the guideline for bioequivalence studies of generic products. In the case that it is impossible to show dissolution equivalence or this impossibility is clear, when filling is granules and it is demonstrated that ingredient changes of capsule shell does not affect dissolution profile according to Appendix 3 of this guideline, bioequivalence can be confirmed by dissolution equivalence shown in dissolution tests conducted under the conditions specified in the registration.

(2) When a gelling agent other than carrageenan is used in the capsule shell

When a gelling agent other than carrageenan is used in the capsule shell, or when dissolution equivalence is not demonstrated in the above (1), bioequivalence should be confirmed by a human study under both fasted and fed conditions according to the Guideline for Bioequivalence Studies of Generic Products. However, when a literature review or other data reveals that changes in the ingredients of the capsule shell do not affect bioavailability, bioequivalence can be confirmed according to the dissolution tests mentioned in this guideline.

Q-28 Why is the difference in content values (%) of the respective change level in Table 2 the same for a water-soluble coating and for a water-insoluble coating?

(A) For water-insoluble polymers such as pH-dependent coating agents (for example, AEA and eudragit E) and ethylcellulose, it is possible to prepare a readily soluble film in water by adding water-soluble plasticizers. For water-soluble coating agents, it is possible to make them water-insoluble by adding water-insoluble plasticizers. These are the reasons for the same requirement.

Q-29 For changes in the film layer, changes in plasticizers are considered not to affect dissolution. Are changes in plasticizers out of the scope of this guideline?

(A) It is difficult to say that changes in plasticizers do not affect dissolution. Some plasticizers are water-soluble, some are lipophilic or amphiphatic, and plasticizers may change the properties of the film layers. Therefore, changes in plasticizers are within the scope of this guideline.

Q-30 When the components and the composition are different between the Application Form and the loading amounts in the actual manufacturing process, what should be used for calculation of the formulation change level?

(A) The components and composition in the approved Application Form should be used for the calculation.

Q-31 What are the grounds to calculate formulation change levels based on changed % of coating layer weight/unit surface area of core?

(A) Formulation changes in coating layer and core have a possibility to change bioavailability, separately. If formulation change levels are not determined separately in coating layer and core, difference of content (%) of changed components in coating layer is calculate as out of total dosage form weight. In this calculation, thickness change in dosage form of which coating layer weight is small, for example, film-coated tablets, is larger compared to that in dosage form of which coating layer weight is large, for example, film-coated granules, when difference of content (%) of changed components in coating layer out of total dosage form weight is the same. When the same formulation changes in core are done both in plain tablets and sugar-coated tablets of which sugar coating weight is high, the formulation change level of the sugar-coated tablets is smaller than that of plain tablets. The above are inconsequence. Further, dissolution times of coating layers generally depend on thickness of the layers in similar property coating layers. There were many cases where changes of coating layers affected bioavailability. Considering the above inconsequence situations, formulation change levels should be determined separately in coating layer and core.

Q-32 Please give examples where calculation of the core surface area is difficult depending on shape of the formulation. In such cases, how should the formulation change levels be calculated?

(A) An example is when formulation shapes are not simple, such as a sphere or a cylinder, where precise calculation of surface area is difficult. In such cases, the calculation can be performed by regarding the shapes before and after the change as a sphere or other similar shape. The surface area ratio before and after the change, S/S_0, is represented as

$((W/D)/(W_0/D_0))^{2/3}$, where S_0, W_0, and D_0 are surface area, weight, and specific gravity of core before the change, respectively, and S, W, and D are those after the change, respectively. The thickness ratio of the coating layers before and after the change, h/h_0, is represented as $((w/d)/(w_0/d_0))\div((W/D)/(W_0/D_0))^{2/3}$, where w_0 and d_0 are weight and specific gravity of the coating layer before the change and w and d are those after the change. For formulation change levels where bioequivalence can be confirmed by dissolution equivalence, as in this example, the difference in densities before and after the change is negligible, and h/h_0 is regarded as the changed % of the coating layer weights per core surface area unit, which is calculated as $(w/w_0) \times (W_0/W)^{2/3}$.

Q-33 When sweetener or glidant is added at the end of the coating process, should these changes be handled as changes in the film- or sugar-coating layer?

(A) Yes, these changes should be handled as changes in film- or sugar-coating layer. When the ingredients are components whose composition is described as "trace use", the changes should be handled as those of component whose composition is described as "trace use."

Dissolution tests, Dissolution equivalence, Bioequivalence studies

Q-34 In different strength dosage forms, when the higher strength is classified as a product containing poorly soluble drugs (as described as in the Guideline for Bioequivalence Studies of Generic Products, Section 3, A.V. 3.3) but the lower strength is not a product containing poorly soluble drugs, which dissolution condition should be applied?

(A) In principle, the dissolution test condition which can discriminate the difference of dissolution more, should be applied. In this case the dissolution condition for products containing poorly soluble drugs for the higher strength should be applied so that dissolution profile can be compared in the same state.

Q-35 In immediate release products and enteric-coated products, the dissolution similarity criteria (representatively ± 15 %) is applied in the Guideline for Bioequivalence Studies of Generic Products, and the dissolution equivalence criteria (representatively ± 10 %) is applied in this guideline. What is the reason for the difference and the setting criteria for variability of individual dissolution in this guideline?

(A) In the Guideline for Bioequivalence Studies of Generic Products, the test results that indicate dissolution similarity (rapid-release or enteric-coated formulations) or equivalence (extended-release formulations) are used as supplemental data to judge bioequivalence in human studies. In this guideline, bioequivalence is confirmed by dissolution equivalence in the range for limited formulation changes. Therefore, the criteria in this guideline are narrower than those in the Guideline for Bioequivalence Studies of Generic Products. The criteria for individual dissolution variability are set to maintain consistent quality before and

after the formulation change.

Q-36 In Section 5 Judgement of equivalence in dissolution, what are the reasons that (1) the criterion ranges for average dissolution are ±8% and ±6%, and (2) the criterion ranges for individual dissolution are ±12% and ±9%, when the average dissolution of the reference products are between 50% to 85% and does not reach 50%, respectively?

(A) These criterion ranges are determined proportionally with regards to the maximum dissolutions as 85% and 50%, respectively, compared to the criteria at 100% dissolution (10% for average dissolution and 15% for individual dissolution).

Q-37 In the case of a level A formulation change, why can the reference product be selected under the conditions specified in the registration?

(A) In the case of a level A formulation change, the changes are considered to have almost no effect on the dissolution profile, and comparison of the dissolution between the reference and the test products can be performed under the conditions specified in the registration. Therefore, selection of the reference product also can be done under the conditions specified in the registration when the dissolution specifications are established in the specifications and test procedures.

Q-38 For immediate-release products, when the dissolution condition specified in the registration is the paddle method at 50 rpm and dissolution of reference product reaches 85% within 30 min, can a reference product be selected by dissolution at the one point specified in the specification dissolution test?

(A) When the dissolution specification judgement point is within 30 minutes, and when the specification test results confirm that dissolution reaches 85% within 15 minutes by the paddle method at 50 rpm, it is possible to select reference products by using the specification dissolution test data. Also, except for products containing narrow therapeutic range drugs when it is confirmed that dissolution reaches 85% within 30 minutes by the paddle method at 50 rpm, it is possible to select the reference product by specification dissolution test data.

Q-39 When solubility of the active ingredient is extremely low at a specified pH, dissolution comparison at the pH is considered to be futile. Is it acceptable to omit the dissolution test at the pH by showing the solubility at the pH?

(A) Dissolution behavior is not always related to the solubility of the active ingredient. Therefore, it is necessary to conduct the dissolution test at the pH even if the solubility is extremely low.

Q-40 When it is expected that human study is required, is it possible to conduct a bioequivalence

study according to the Guideline for Bioequivalence Studies of Generic Products without judging the dissolution equivalence?

(A) It is possible. In the Guideline for Bioequivalence Studies of Generic Products, before starting human study, it is necessary to conduct dissolution test in order to select subjects for immediate-release products and enteric-coated products and confirmation of the dissolution similarity in the case of extended release products.

Q-41 The guidance says that, "when their dissolution is not equivalent, bioequivalence tests should be performed according to the Guideline for Bioequivalence Studies of Generic Products." In this case, is it possible to use the dissolution data obtained in this guideline as the dissolution data for the Guideline for Bioequivalence Studies of Generic Products?

(A) It is possible.

Q-42 Please explain why a dissolution medium with a low ionic strength at pH 6.0, which is added to the dissolution test condition for enteric-coated products, which is not in the Guideline for Bioequivalence Studies of Generic Products.

(A) In this guideline, bioequivalence is confirmed by dissolution equivalence in the limited ranges of formulation change. When the dissolution of an enteric-coated product depends on ionic strength the dissolution test data obtained only in the test condition mentioned in the Guideline for Bioequivalence Studies of Generic Products leaves some risks of not detecting inbioequivalence Therefore, testing using the low ion strength dissolution medium is required.

Q-43 When there is a dissolution test condition where *in vivo-in vitro* correlation (IVIVC) is demonstrated, can dissolution comparison of reference and test products be done in this dissolution test condition only?

(A) An IVIVC is usually developed between the *in vivo* data and the dissolution test results obtained at one particular test condition. Therefore, bioequivalence is not ensured in subgroups that have other physiological conditions. The dissolution equivalence should be judged by the dissolution tests shown in this guideline.

Q-44 Dissolution tests should be performed according to the conditions shown in the Guideline for Bioequivalence Studies of Generic Products. However, when a pharmaceutical company has a discriminative dissolution test condition based on full knowledge of the reference product, can such a dissolution test condition with a different composition buffer solution or surfactant with the same pH be used?

(A) It is not acceptable to adopt an arbitrary dissolution test condition for an individual case because in this guideline bioequivalence is confirmed by dissolution equivalence in the limited ranges of formulation change.

Q-45 In the paddle method at 50 rpm, dissolution behavior has a high variability owing to the coning phenomena or adhesion of formulation to the bottom of the vessel. In this case, it may be difficult to evaluate the dissolution profile precisely. Is it acceptable to perform the dissolution test at 75 or 100 rpm?

(A) The dissolution equivalence criterion range (representatively ±10%) for average dissolution is used to confirm bioequivalence by dissolution testing using the paddle method at 50 rpm only. It is currently difficult to determine the dissolution equivalence criterion range for 75 or 100 rpm, and therefore, it is not acceptable to change the agitation. When the coning phenomenon occurs or when the formulation adheres to the bottom of the vessel, the basket method at 100 rpm can be used instead of the paddle method at 50 rpm.

Q-46 What is the reason for adopting the similarity factor, f2? How is the dissolution behavior determined by using the results of the average dissolution value comparison (Judgement method 1) and by using f2 (Judgement method 2)?

(A) Judgement method 1 can compare the dissolution profile at meaningful dissolution points of 40%, 60%, and 85% (30%, 50%, and 80% for extended-release products). However, when the result does not meet the criterion at only 1 point, even by a small amount, dissolution equivalence is not obtained. This is inconsequential, and then the similarity factor, f2, is adopted.

Judgement method 2 can compare the overall dissolution profile, and the determination of equivalence depends on comparison points. For example, when the points where the dissolution value difference is small, the f2 value becomes large and dissolution equivalence can be obtained. To avoid this tendency, comparison points are specified in Judgement method 2. The meaningful dissolution points are not always included in Judgement method 2, and in this case, Judgement method 1 is adopted.

The two judgement methods may sometimes give different results. Either judgement can be used in comparing the data of each dissolution test, separatetely.

Q-47 Please explain how to adjust a dissolution test for a lag time.

(A) Refer to Appendix A of the Guideline for Bioequivalence Studies of Generic Products Q&A.

Q-48 The guidance states that, "when the use of different doses is unavoidable, the pharmacokinetic parameters should be normalized by the dose administered, but it should be limited to drugs having linear pharmacokinetic parameters against doses." How can the linearity be demonstrated?

(A) Linearity in drug absorption can depend on the particle size of the active ingredient and its

dosage forms. Therefore, in the study to confirm linearity, drug product used in the bioequivalence study or comparable drug product should be used. It is desirable to confirm the linearity by showing that the regression line of dose-AUC is from the origin and that the dose-adjusted pharmacokinetic parameters are equivalent; this can be demonstrated, for example, by comparing to pharmacokinetic parameters of the lower strength. Even in the case that it is difficult to show the linearity by the above method, it is acceptable to judge bioequivalence by dose-adjusted pharmacokinetic parameter values. However, it must be recognized that it is difficult to demonstrate bioequivalence without establishing linearity.

Appendix A. Examples of Change Level Calculations

Calculation of component and composition change levels should be performed as described below. The percentage is calculated to more than one digit, to the number of digits after decimal point required in the guideline, and rounded off at the end.

A-1 : Formulation Change of Oral Dosage Forms

(1) Plain tablets

Change of component and composition

		Standard formulation	Test product
Active ingredient A		40 mg (10.00%)*1)	40 mg (10.00%)
Disintegrant	Cornstarch	40 mg (10.00%)	35 mg (8.75%)
Binder	Povidone	20 mg (5.000%)	23 mg (5.750%)
Lubricant	Mg stearate	4 mg (1.000%)	4 mg (1.000%)
Filler	Lactose monohydrate	100 mg (25.00%)	97 mg (24.25%)
	Microcrystalline cellulose	196 mg (49.00%)	201 mg (50.25%)
Total dosage form weight		400 mg	400 mg

*1) The figure in parentheses is the percent of the each compoment out of the total dosage form weight.

Calculation of difference of % ingredient

Function of excipients and component		Difference of % ingredient	Level
Disintegrant	Cornstarch	−1.25 %	(B)
Binder	Povidone	0.75 %	(C)
Filler	Lactose monohydrate	−0.75%	
	Microcrystalline cellulose	1.25%	
Sum of absolute values of filler differences		2.00%	(B)
Sum of absolute values of changed component differences (1.25 +0.75 + 2.00)		4.00%	(B)

The highest change level for fillers is C, so the level of change in the example is C.

(2) Film-coated tablets

Change of component and composition

・Core tablets

		Standard formulation	Test product
Active ingredient	A	40 mg (10.00%) *1)	40 mg (9.52%)
Disintegrant	Cornstarch	40 mg (10.00%)	45 mg (10.71%)
Binder	Povidone	20 mg (5.000%)	23 mg (5.476%)
Lubricant	Mg stearate	4 mg (1.000%)	4 mg (0.952%)
Filler	Lactose monohydrate	100 mg (25.00%)	108 mg (25.71%)
	Microcrystalline cellulose	196 mg (49.00%)	200 mg (47.62%)
Total weight of core tablet		400 mg	420 mg

*1) The figure in parentheses is % of respective ingredient out of the weight of the core tablet.

・Film layer

	Standard formulation	Test product
Ingredient A	7.5 mg (75.00%)*2)	8.0 mg (74.07%)*2)
Ingredient B	2.5 mg (25.00%)*2)	2.8 mg (25.93%)*2)
Total weight of film layer	10.0 mg	10.8 mg
Surface area of core tablet	2.51 cm^2	2.56 cm^2
Film layer weight/cm^2	3.98 mg/cm^2	4.22 mg/cm^2 (106.03%)

*3)

*2) The figure in parentheses is the % of respective ingredient out of the total weight of the film layer.

*3) The figure in parentheses is the % of test product/Standard formulation.

Calculation of Difference of % ingredient and % changed

・Core tablets

Function of excipients and components		Difference of % ingredient	Level
Disintegrant	Cornstarch	0.71%	(B)
Binder	Povidone	0.476%	(B)
Lubricant	Ca stearate	−0.048%	(B)
Filler	Lactose monohydrate	0.71%	
	Microcrystalline cellulose	−1.38%	
Sum of absolute values of difference of fillers		2.09%	(B)
Sum of absolute values of changed component differences in the core tablet (0.71 + 0.48 + 0.05 + 2.09)		3.33%	(B)

・Film layer

Ingredient	Difference of % ingredient	Level
Ingredient A	−0.93%	
Ingredient B	0.93%	
Sum of absolute values of changed component differences in the film layer	1.86%	(B)

	% Changed	Level
% changed weight of film layer/cm^2	6.03%	(B)

All the change levels are B, so in the example, the change level is B.