Approval Application Form for Sakura Bloom Tablets: Mock-up for Columns of Manufacturing Methods and Specifications & Test Methods for Drug Products (sample description) **—explanation & comments document**

Description in Mock-up	Explanation & comments
Overall structure	[Order of description in the column of Manufacturing methods] This mock-up adopts a structure in which all the unit Processes (1 to 6) are described first, and then In-process control tests (1 to 3) related to these Processes are described. Although another method to describe In-process control tests in each corresponding unit Process was discussed as a candidate, this order of description is adopted based on the judgment that because the description of In-process control tests will increase in volume under the real-time release testing (hereinafter referred to as "RTRT"), it is more understandable to describe them by collecting together. [Description of In-process control tests] There is an opinion that since In-process control tests used for RTRT are given substantially the same position as specification testing, they should be described in the column of "Specifications & test methods." However, "Specifications & test methods" in the approval application form are currently regarded as the matters of "a partial change approval in approved matters (hereinafter referred to as "partial change") in principle; therefore, once RTRT itself is moved to the column of "Specifications & test methods," any factor acceptable to a minor partial change in approved matters (hereinafter referred to as "minor change") by a so-called double-quotation-marks (" ") description is unable to be included. For example, in the analytical technology making the most of chemometrics such as NIR frequently used as a PAT tool, there are many test methods assuming to conduct maintenance through its life cycle including an update of the library reference; therefore, to make all the measuring / analysis conditions treated as "partial change" uniformly becomes a factor to hinder the recommended continuous improvement. Based on the above discussion, our Sub-group has judged a structure adequate in which these In-process control tests are described in the column of "Manufacturing methods," and any corresponding In-process control test is "referred to" in the column of "Specifications & test methods." The Japanese Pharmacopoeia 17th Edition introduces the heading "Manufacture" and specifies in the paragraph 12 under General Notices that "From the point of view of quality assurance, requirements that should be noted on manufacturing processes, if appropriate in addition to the specifications, are shown in the heading "Manufacture" in monograph." Therefore, it is considered adequate to regard RTRT as "requirements that should be noted on manufacturing processes." As described later, however, in case of making part of test method parameters acceptable for "minor change," the reason why it may be a

	"minor change" should be described in Module 2 (on the contrary, an adoption of a double-quotation-marks (" ") easily without good reason may cause unnecessary matters of inquiry). Meanwhile, it is judged impossible to introduce a concept of minor change in the current column of Specifications & test methods because the current Law on Assuring Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices etc. (ministerial ordinance) specifies that "a change in specification is a partial change." [Calculation formulae for RTRT] To facilitate the continuous improvement, the location to describe the calculation formulae for RTRT is selected into the position of "Annex in the column of Manufacturing methods," the same as the location selected in the above Description of In-process control tests, which makes the minor change (e.g. coefficient of a dissolution model formula) acceptable. After discussing the definition of "Annex" and "Attachment" within our Sub-group, it is ascertained that whether or not it is referred to in the approval application form itself is critical and that based on the above, "Annex referred to in the text" is the approval items, while "Attachment not referred to" is the reference information in the approval application form.
Manufacturing methods	
Critical steps	[Reasons for selecting Critical steps] As described in Section 2.3.P.3.3 of Sakura Bloom Tablets P2 Mock, the manufacturing processes having CMA and CPP that should be controlled to assure the CQAs, i.e. First Step (Granulation Process) and Third Step (Tableting Process), are considered as Critical steps for Sakura Bloom Tablets.
<First Step> Granulation Process	[Description of charge-in quantity] Mock-up (Sample Description) for Application Form for Sakura Tablet, a predecessor of Sakura Bloom Tablets, described the charge-in quantity as <<○%>>; however, Sakura Bloom Tablets describes it as "○ kg" in accordance with the description example (hereinafter referred to as "Description Example") in "Guideline on Matters to be described in Application for Marketing Approval of Pharmaceuticals, etc. under Revised Pharmaceutical Affairs Law" (PFSB/ELD Notification No.0210001 dated February 10, 2005). [Description of parameters] Parameters are described in accordance with the principle described in Section 2.3.P.3.3. In Description Example, a screen size of a screen machine is described; however, in case of Sakura Bloom Tablets, this

	process aims at milling granules, which was judged not critical without any impact on the particle size, CMA, in the risk assessment, and therefore the particle size is not described as a parameter in the approval application form. [Water content after drying] Although the risk assessment results of Sakura Bloom Tablets led to the judgment that the water content in granules after drying has no impact on CQA, “In-process control for Water content (in-house)” is set up to confirm the process endpoint in Section 2.3.P.3.3, and its control range is to be established in the product master formula, etc. In the approval application form, meanwhile, it is not described as In-process control due to less criticality having no connection with CQA.
<Second Step> Blending Process	[Description of charge-in quantity] Although the charge-in quantity was described as ○ w/w% for Sakura Tablet, it is described as“○ kg” for Sakura Bloom Tablets in accordance with Description Example. [Blending time] Although the blending time was described as <<○ to ○ minutes>> for Sakura Tablet, it is not described for Sakura Bloom Tablets in accordance with Section 2.3.P.3.3.1.
<Third Step> Tableting Process	[Description of parameters] Parameters are described in accordance with the principle described in Sections 2.3.P.3.3.1 and P.3.3.2.
<Fourth Step> Coating Process	[Parameters] As described in Section 2.3.P.3.3, parameters are set up regarding their control ranges in the product master formula, etc.; therefore, they are not described in the approval application form. [Water content after drying] Same as Granulation Process, although the control range of water content is set up as “In-process control for Water content (in-house)” in the product master formula, etc. in order to confirm the process endpoint, it is not described in the approval application form due to less criticality having no connection with CQA.
<Fifth Step> Inspection Process	[Inspection Process] Inspection Process is a process not described in Sakura Tablet nor in Description Example, and usually not described in the column of Manufacturing methods. However, this process is described here due to In-process control 3 being carried out. In case of a product item having no Inspection Process, it is

	adequate for In-process control 3 to be carried out in Fourth Step (Coating Process). Meanwhile, to prevent the content of "Inspection" from being judged as In-process control 3, it is described to "take a sample of coated tablets after finishing Inspection Process.
<Sixth Step> Packaging/Labeling/Storage Process	[Description of storage and testing] Although it was described for Sakura Tablet as "Store these labeled boxes and perform appropriate testing," it is described for Sakura Bloom Tablets as "store these labeled boxes" because conventional tests are not performed in the end, but instead all the specification testing is performed as RTRT.
[In-process control 1]	[Specification for particle size of granules] As described in Section 2.3.P.3.3, the particle size of granules is CMA constructing the design space to assure the dissolution; therefore, its control range, 90 to 210 μm, is subject to In-process control as matters for partial change. [Diameter of the measurement probe] The diameter of the measurement probe was described as the information of instruments used when applying for approval. Meanwhile, it has no impact on the results of measuring the particle size of granules; therefore, its condition is described as "φ35 mm" designating it as matters for minor change. [Measurement interval] The measurement interval has an impact on the frequency of measurement. Measurement results of granules' particle size adopt their particle sizes when drying in which the measurement interval has no impact on their results; therefore, its condition is described as "5 s" designating it as matters for minor change. [System suitability] System suitability can be confirmed by verifying the test of system performance possessed by FBRM equipment as a function using the standard particles. It is not a matter to be confirmed always for every lot because it is possible to be confirmed by periodical maintenance, etc.
[In-process control 2]	**Weight (mean value) of uncoated tablets** [Weight (mean value) of uncoated tablets] As described in Section 2.3.P.3.3, the weight (mean value) of uncoated tablets is CMA for the content specification; therefore, its control standard is subject to In-process control. The specification for content in tablets is "95.0 to 105.0%." As In-process control for weight, therefore, aiming to meet the content

	specification sufficiently, its control range, the central weight 194 mg ± 3%, is established making the control range smaller than the assay specification's. This weight control with ± 3% is given a sufficient restriction than the content specification with ± 5%; therefore, it is designated as matters for minor change. **<u>Uniformity of Dosage Units test on uncoated tablets</u>** [Measurement tablet numbers and counting specification] Acceptance criteria for Uniformity of Dosage Units test on uncoated tablets are described in the attached Annex. The number of measurement tablets is "200 tablets" as the tablet numbers when applying, and designated as a matter for minor change. Even in case where the number of measurement tablets is changed, the counting specification depending on the measurement tablet numbers is established according to the acceptance criteria in the Annex; therefore, it is judged acceptable to change by minor change notification. Examples to change the measurement tablet numbers are following cases where: "owing to the development of instruments, the quality assurance of a higher level is available by increasing the number of measurement tablets," "owing to the satisfactory stability of data in the actual production, the quality assurance of the same level is available even if the number of tablets is reduced," etc. Accordingly, the counting specification — uncoated tablets exceeding the range of 85.0 to 115.0% are not more than "6 tablets," and those exceeding the range of 75.0 to 125.0% are not more than "1 tablet." — is also designated as matters for minor change. [Operating conditions for NIR method] The measuring method (Transmittance method of near infrared absorption spectrometry) is a critical item related to the measurement principle; therefore, it is designated as a matter for partial change. The measuring equipment (FT-NIR) is a critical item related to the measurement principle; therefore, it is designated as matters for partial change. Meanwhile, the name of measuring equipment and the name of vendor are described in M2/3. The scan range ("12,500 - 3,600 cm^{-1}") means the range of wavelength when measuring, and is designated as matters for minor change in order to make it possible to improve the model precision positively by decreasing the estimated error associated with improving the knowledge and acquiring more experienced values in the model maintenance. Meanwhile, the scan range used for preparing the initial model is described in M2/3. The number of scans ("64 times") is the item related to the measurement precision, and is designated as matters for minor change in order to make it possible to improve the model precision positively by decreasing the estimated error associated with improving the knowledge and acquiring more experienced

	values in the model maintenance. The resolution power ("8 cm^{-1}") is the item related to the measurement precision, and is designated as matters for minor change in order to make it possible to improve the model precision positively by decreasing the estimated error associated with improving the knowledge and acquiring more experienced values in the model maintenance. The spectrum pre-treatment conditions ("First derivative") are expected to have an effect to improve the model precision by means of erasing an impact from variation of a baseline or making the API's peak emphasized, while they have some approaches. The spectrum pre-treatment conditions are designated as matters for minor change in order to make it possible to improve the model precision positively by decreasing the estimated error associated with improving the knowledge and acquiring more experienced values in the model maintenance. The analysis method (PLS regression analysis) is a critical item related to the analysis principle; therefore, it is designated as matters for partial change. [Measurement ranges for calibration / validation] Taking into account the specification for Uniformity of Dosage Units, it is required to cover the range of 75 to 125%; therefore, it is set to cover the range of "about 70 to 130%" of the labeled amount for validation, while "about 60 to 140%" of the labeled amount for calibration. These ranges are satisfactory when set up wider than the range of 75 to 125%, and their small revision is possible when improving the model precision positively associated with improving the knowledge and acquiring more experienced values in the model maintenance; therefore, they are designated as matters to change. [System suitability] System performance specifies that the test of system performance possessed by NIR equipment as a function should be performed in accordance with JP's General Information. The verification using a sample (standard test specimen) is set to be described, where necessary, within the Decision tree in Attachment. [Periodical verification and revalidation] The periodical verification means to confirm periodically that there is little difference between the prospective value by NIR method and the measured value by HPLC, the conventional test method. Although the word "periodical revalidation" was used in the mock-up for Sakura Tablet, the term "periodical verification" is adopted here meaning to verify periodically. When a renewal of the model is required as a result of the periodical verification, it is necessary to

	perform the validation anew, the action of which is nominated as “revalidation.” **<u>Content in uncoated tablets</u>** [Content in uncoated tablets] As described in Section 2.3.P.3.3, the content in uncoated tablets is CMA for the content specification; therefore, its control standard is subject to In-process control. **<u>Hardness of uncoated tablets</u>** [Hardness of uncoated tablets] As described in Section 2.3.P.3.3, the hardness of uncoated tablets is CMA constructing the design space to assure the dissolution; therefore, its control range, 3 to 11.5 kp, is subject to In-process control as matters for partial change. [Control by the mean value] Based on the assumption that these uncoated tablets have hardness the variation of whose individual values is small, the hardness is set to be controlled by the mean value not further controlling the variation of individual hardness values.
[In-process control 3]	[Operating conditions for at-line NIR method] The measuring method (Diffuse transmittance method) is a critical item related to the measurement principle; therefore, it is designated as matters for partial change. The measuring equipment (FT-NIR) is a critical item related to the measurement principle; therefore, it is designated as matters for partial change. Meanwhile, the name of measuring equipment and the name of vendor are described in M2/3. The scan range (“12,500 - 3,600 cm^{-1}”) means the range of wavelength when measuring, and is designated as matters for minor change in order to make it possible to improve the model precision positively associated with improving the knowledge and acquiring more experienced values in the model maintenance. Meanwhile, the scan range used for preparing the initial model is described in M2/3. The number of scans (“64 times”) is the item related to the measurement precision, and is designated as matters for minor change in order to make it possible to improve the precision of a discriminating model positively associated with improving the knowledge and acquiring more experienced values in the model maintenance. The resolution power (“8 cm^{-1}”) is the item related to the measurement precision, and is designated as matters for minor change in order to make it possible to improve the precision of a discriminating model

	positively associated with improving the knowledge and acquiring more experienced values in the model maintenance. The spectrum pre-treatment conditions (“First derivative”) are expected to have an effect to improve the discriminating model precision by means of erasing an impact from variation of a baseline or making the API’s peak emphasized, while they have some approaches. The spectrum pre-treatment conditions are designated as matters for minor change in order to make it possible to improve the precision of a discriminating model positively associated with improving the knowledge and acquiring more experienced values in the model maintenance. The analysis method (“Principal Component Analysis (PCA)”) is an item related to the analysis principle; however, it is designated as matters for minor change in order to make it possible to improve the precision of a discriminating model positively by improving the knowledge, acquiring more experienced values, developing the analysis method, etc.
Glossary of terms	Nothing special
Annex “Acceptance criteria for Uniformity of Dosage Units” in the column of Manufacturing methods	Although the Attachment to Sakura Bloom Tablets P2 Mock describes ALTERNATIVE 2 (the sample size is not less than 100 only) judging from the acceptance criteria for UDU (Uniformity of Dosage Units) test suitable to PAT (Process Analytical Technology) proposed by Ph. Eur., it is modified based on the draft General Information (Acceptance Criteria for Assessment of Content Uniformity in Real Time Release Testing by Process Analytical Technology) scheduled to be listed in the JP. C1 and C2 (critical acceptance number) are the upper limit of sample numbers in which their contents exceed the range of 85 to 115% and 75 to 125%, respectively.
Annex “Calculation formulae” in the column of Manufacturing methods	The Formula 1 is a calculation formula to calculate the content using, as input parameters, the drug substance concentration in uncoated tablets (NIR method) and the weight of uncoated tablets both obtained in [In-process control 2], which is a model based on the first principle (mass balance) reflecting the physical laws; therefore, it is not required to conduct maintenance of this calculation formula through its life cycle. On the other hand, the Formula 2 is to calculate the dissolution rate using, as input parameters, the particle size of drug substance obtained in the manufacturing process for the drug substance and the granule particle size obtained in [In-process control 1] as well as the uncoated tablet hardness obtained in Tablet Compression Process; however, it is a dissolution model of which coefficients were determined to adapt the actual measured values. It is designated as matters for minor change notification because of a necessity of the model maintenance (e.g. a change to reduce the estimated error) through its life cycle associated with the further knowledge and experiences.

Specifications & test methods	
Content	Nothing special
Description	Release judgment is made using the test results of Description obtained as [In-process control 3].
Identification	● Release judgment is made using the test results of Identification [at-line NIR method] obtained as [In-process control 3]. ● "When impossible to perform an adequate testing" — which is described in the conventional test — include not only when instruments are breaking down but also when an NIR discriminating model is unable to be used (e.g. when conducting maintenance of the NIR discriminating model); however, it means verification of the discriminating model according to a decision tree, such as when verifying the adequacy of the discriminating model's calibration. Therefore, it should be taken into account not to perform the conventional test easily. ● An applicant should make a commitment to conduct maintenance of an NIR discriminating model, while it should also be taken into account to make a decision tree to be attached to the approval document not "Attachment" but "Annex (approval items)."
Uniformity of Dosage Units	● In the RTRT (NIR method) specified for Uniformity of Dosage Units, the contents in individual tablets are set to be determined regarding the in-process samples collected periodically during tableting. Therefore, the concrete number of sampling tablets is not described in the Specifications & test methods; instead the number of uncoated tablets, in-process samples, is described in the in-process control test designating it as matters for minor change; and their acceptance criteria are referred to the table in which the acceptance criteria for Uniformity of Dosage Units test on uncoated tablets are described in the attached Annex for [In-process control 3] in table form. ● Although in Sakura Bloom Tablets P2 Mock, the number of sampling tablets is described in the Specifications & test methods, the content value obtained from more in-process samples is able to represent the quality of the corresponding lot more correctly. Therefore, in order to make it possible to change the number of sampling tablets, its mock-up for approval application form adopts a description of referring to the in-process control test. ● Uniformity of Dosage Units is a critical test to guarantee the quality; therefore, "when impossible to perform an adequate testing" — which is described in the conventional test — should be limited only to when instruments are breaking down and when an NIR discriminating model is unable to be used. Procedures for decision-making up to the conventional test are described in the decision tree in Attachment.

Dissolution	● In RTRT, the CMA to assure the dissolution (particle size of drug substance, granule particle size and uncoated tablet hardness) should be confirmed being within the design space first, then a risk affecting the RTRT results should be assessed, and finally a judgment of the dissolution rate obtained by RTRT should be made. ● Cases where testing is able to be performed not by RTRT but by the conventional test are limited to the following. Procedures for decision-making up to the conventional test are described in the decision tree in Attachment. ➢ A case where measurement results are not obtained due to measuring equipment: A case where input variables (particle size of drug substance, granule particle size, uncoated tablet hardness, etc.) necessary for calculating the dissolution rate are unable to be measured due to a malfunction of the equipment to perform the RTRT testing. ➢ A case where the dissolution prediction formula has a fault: A case where it is made clear that the dissolution prediction formula itself has a problem as a result of comparing the results obtained by the dissolution prediction formula and the conventional test; and further it is judged possible to perform the conventional test as a result of the risk assessment.
Assay	● In the RTRT (NIR method) specified for Uniformity of Dosage Units, the contents in individual tablets are set to be determined regarding the in-process samples collected periodically during tableting. The content value obtained from more in-process samples is able to represent the quality of the corresponding lot more correctly; therefore, in the test of Assay, the mean of the contents in individual tablets obtained from the in-process samples collected periodically during tableting is set to be used. ● Cases where testing is able to be performed not by RTRT but by the conventional test are limited to the following. Procedures for decision-making up to the conventional test are described in the decision tree in Attachment. ➢ A case where measurement results are not obtained due to measuring equipment: A case where the contents in individual tablets are unable to be measured due to a malfunction of the equipment to perform the RTRT testing. ➢ A case where measurement results are not obtained due to an NIR calibration model: A case where it is made clear that the NIR model itself has a problem as a result of confirming the adequacy of the calibration curve used for comparison with the conventional test; and further it is judged possible to perform the conventional test as a result of the risk assessment.
Attachment	[Decision tree] Positioning of the “Decision tree” was discussed within our Sub-group. In particular, the discussion focused on whether or not a transfer into the conventional test when a PAT tool such as NIR is judged as

	"a case inadequate" should be regarded as "the approval items." Their choices were the following three. 1. Do not describe the decision tree. 2. Describe the decision tree in "Attachment," meaning it is out of the approval items. 3. Describe the decision tree in "Annex," meaning it is the approval items referred to in the text. Our Sub-group has finally concluded that the wording of "risk assessment" in the decision tree is to be directly described in the text (i.e. the approval items) committing administrative authorities and that the whole decision tree itself is to be described in "Attachment" meaning it is out of the approval items. Meanwhile, if it were described, not in "Attachment" but, in "Annex" making it approval items, a probability would be low to be discussed with administrative authorities at every regular GMP compliance investigation, etc. Therefore, as described before, we will make mention of the fact that some companies may apply a strategy to designate the decision tree itself as the approval items by describing it in "Annex." In addition, it is essential for the decision tree to be described in the product master formulae etc., and approved by the GMP organization. The conventional test is an alternate test method to RTRT in the end; therefore, if the policy is changed into using the conventional test constantly, it should be applied for partial change and approved by the authorities. The decision tree for "Identification" is not described in this Mock-up; however, when applying, it is required to prepare the decision tree for "Identification" with reference to the decision trees for "Uniformity of Dosage Units / Assay" and "Dissolution" shown in this Mock-up.