Approval Application Form for Sakura Bloom Tablets

Mock-up for Columns of Manufacturing Methods and Specifications & Test Methods for Drug Products (sample description)

Study project for regulatory harmonization & evaluation of drugs etc.
Studies on quality control approach to new development and change in manufacturing of drugs
"Studies on quality assurance throughout the drug product lifecycle"
Sakura Bloom Tablets Mock Sub-group
MHLW sponsored QbD Drug Product Study Group
December 2016

[Manufacturing methods] Critical steps
<First Step> Granulation Process
<Third Step> Tablet Compression Process

<First Step> Granulation Process
Charge 『20 kg』 of prunus, 『136 kg』 of lactose hydrate, 『20 kg』 of microcrystalline cellulose and 『10 kg』 of croscarmellose sodium into a fluid bed granulator, and blend. After blending, granulate with spraying binder solution at the rate of "900 – 1100 g/min." During granulation, monitor the granule particle size on a real-time basis, and determine the particle size at the endpoint of granulation [In-process control 1].
After the completion of spraying, dry, and obtain granules. Screen the dried granules using a screening mill.

<Second Step> Blending Process
Charge the screened granules obtained in Frist Step with 『2 kg』 of magnesium stearate, and blend using a diffusion mixer (tumble).

<Third Step> Tableting Process
Compress the blend obtained in Second Step at "6 - 14 kN" using a rotary-type tablet press [In-process control 2].

<Fourth Step> Coating Process
Charge the uncoated tablets obtained in Third Step into a pan coating machine, and spray coating suspension.

<Fifth Step> Inspection Process
Conduct visual inspection on the coated tablets obtained in Fourth Step. After finishing Inspection Process, take a sample of the coated tablets [In-process control 3].

<Sixth Step> Packaging/Labeling/Storage Process
Using a blister packaging machine, fill a "polypropylene film" with the coated tablets, place an "aluminum foil" on it and seal it by heating. Cut the sealed products to make PTP sheets, transfer them into a "carton box," perform labeling appropriately, and store these labeled boxes.

[In-process control 1]
Granule particle size: 90 to 210 μm (FBRM method)
Determine the granule particle size as an in-process control test of the dissolution (RTRT), and the result is applied and assessed as a release specification (the attached Annex: Design

Space). During granulation, monitor the granule particle size on a real-time basis, and determine the particle size at the endpoint of granulation: Granule particle size is 90 to 210 μm.
The above control range is established based on a design space for the dissolution.

[FBRM method]
Operating conditions—
Diameter of the measurement probe: "ϕ35 mm"
Measurement interval: "5 s"

System suitability—
System performance: When the test of system performance possessed by FBRM equipment as a function is performed using the standard particles, it complies with the acceptance criteria.

[In-process control 2]
Weight (mean value) of uncoated tablets: "188.2 to 199.8 mg"
Determine the weight (mean value) of uncoated tablets regarding "200 tablets" of in-process samples to be used for assessment of Uniformity of Dosage Units: Its value is "188.2 to 199.8 mg."

Uniformity of Dosage Units test on uncoated tablets: When "200 tablets" of uncoated tablets are assessed, those 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."
Perform the test of Uniformity of Dosage Units (RTRT) as an in-process control test, and the result is applied and assessed as a release specification. Regarding "200 tablets (10 tablets × 20 time points)" of uncoated tablets collected periodically while tableting, determine the drug substance concentration in uncoated tablets by an NIR method. Regarding "200 tablets" of different samples, uncoated tablets, measure once each uncoated tablet by an NIR method, analyze the obtained spectra using the calibration model, and determine the drug substance concentration in uncoated tablets. Concerning the operating conditions, proceed as directed in the operating conditions in the following In-process control test method for the drug substance concentration in uncoated tablets [NIR method]. For individual tablets, calculate the contents in individual tablets according to Formula 1 in the attached Annex using the drug substance concentration in uncoated tablets measured by an NIR method and the weight of uncoated tablets, and make a judgment by the acceptance criteria in Table 1: In case of assessing "200 tablets," 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."

In-process control test method

[NIR method]

Operating conditions—

Measuring method: Transmittance method of near infrared absorption spectrometry

Measuring equipment: FT-NIR

Scan range: "12,500 - 3,600 cm^{-1}"

Number of scans: "64 times"

Resolution power: "8 cm^{-1}"

Calibration model—

Spectrum pre-treatment conditions: "First derivative"

Analysis method: PLS regression analysis

Calibration

Prepare the calibration model using granules for compression having at least 5 levels of different drug substance concentrations, in which the dispensing quantity of drug substance is in the range of "approximately 60 to 140%" of the labeled amount, as well as other material properties and/or a variation range of in-process parameters in the daily production are included.

Validation

Perform validation using uncoated tablets having at least 5 levels of different drug substance concentrations, in which the dispensing quantity of drug substance is in the range of "approximately 70 to 130%" of the labeled amount, as well as other material properties and/or a variation range of in-process parameters in the daily production are included.

System suitability—

System performance: When the test of system performance possessed by NIR equipment as a function is performed in accordance with "Control of equipment performance" under JP's General Information "Near Infrared Spectrometry," it complies with the acceptance criteria.

System repeatability: Measure 10 times each of uncoated tablets for system suitability assessment by an on-line NIR method. When the obtained spectra are analyzed using the calibration model and the measured values by the on-line NIR method are obtained, RSD of these percent recoveries (values obtained by dividing the on-line NIR method's measured values by the conventional test method's HPLC measured values) is not more than 2.0%.

Use the lot of uncoated tablets for system suitability assessment having the conventional test method's measured values of 98.0 to 102.0%. When assessing the system suitability using the relevant lot of uncoated tablets, determine the percent recovery using the HPLC measured value previously obtained by the conventional test method.

In this testing, perform the following calibration and validation, and use the calibration model having performed the periodical verification.

Periodical verification
Perform verification of the calibration model (a direct comparison between HPLC measured values by the conventional test method, a reference method, and drug substance contents obtained based on the calibration model) using commercial lots at appropriately predetermined intervals. Where necessary, renew the library reference, and perform validation of the calibration model.
As the reference assessment method used for system suitability, calibration and validation, follow the test of Uniformity of Dosage Units (conventional test).

Revalidation
When a renewal of the calibration model is required, perform the appropriate level of validation on the re-established model using commercial lots or small-scale production lots.

Content in uncoated tablets: The mean of Uniformity of Dosage Units (RTRT) test results is 95.0 to 105.0% of the labeled amount.
Perform the test of Content in uncoated tablets (RTRT) as an in-process control test, and the result is applied and assessed as a release specification. When the mean of the contents in individual tablets ("200 tablets") is calculated according to Uniformity of Dosage Units (RTRT) test on uncoated tablets, its value is 95.0 to 105.0%.

Hardness of uncoated tablets (mean value): 3 to 11.5 kp.
Perform the hardness test of uncoated tablets as an in-process control test, and the result is applied and assessed as a release specification for dissolution (RTRT) (the attached Annex: Design Space). When the hardness of 30 uncoated tablets is measured and the mean hardness is calculated, its value is 3 to 11.5 kp.
The above control range is established based on a design space for the dissolution.

[In-process control 3]

Description: Light red film-coated tablets.
Place Sakura Bloom Tablets on a white paper, and observe their color and shape.

Perform the test of Identification (RTRT) as an in-process control test, and the result is applied and assessed as a release specification. When the test is performed by an at-line NIR method, it conforms to the specification. By means of an at-line NIR method, measure once each film-coated tablet by an NIR method, and analyze the obtained spectra using a discriminating model. When the samples, 3 tablets, are measured once for each tablet, all of the 3 tablets are identified as Sakura Bloom Tablets.
Concerning the operating conditions, proceed as directed in the operating conditions in the following In-process control test method for Identification [at-line NIR method].

In-process control test method

[At-line NIR method]

Operating conditions—

Measuring method:	Diffuse transmittance method
Measuring equipment:	FT-NIR
Scan range:	"12,500 - 3,600 cm^{-1}"
Number of scans:	"64 times"
Resolution power:	"8 cm^{-1}"
Analysis method:	"Principal Component Analysis (PCA)"

System suitability—

System performance: When the test of system performance possessed by NIR equipment as a function is performed in accordance with "Control of equipment performance" under JP's General Information "Near Infrared Spectrometry," it complies with the acceptance criteria.

In this testing, perform the following calibration and validation, and use a discriminating model having performed the periodical verification.

Calibration

Prepare a discriminating model using the active tablets identified as Sakura Bloom Tablets by the test of Identification (conventional test), the reference assessment method, and the placebo tablets identified not as Sakura Bloom Tablets.

Validation

Regarding the discriminating model obtained, perform validation using the active tablets identified as Sakura Bloom Tablets by the test of Identification (conventional test), the reference assessment method, and the placebo tablets identified not as Sakura Bloom

Tablets. For this validation, use test specimens different from the test specimens used for calibration.

Periodical verification

Perform verification of the discriminating model (a direct comparison of results obtained by the conventional test method, a reference method, and those obtained on the basis of a discriminating model) using commercial lots at appropriately predetermined intervals. Where necessary, renew the library reference, and perform validation of the discriminating model.

As the reference assessment method used for system suitability, calibration and validation, follow the test of identification (conventional test).

Revalidation

When a renewal of the calibration model is required, perform the appropriate level of validation on the re-established model using commercial lots or small-scale production lots.

Glossary of terms

- Binder solution

  Add『6 kg』of Hydroxypropylcellulose to『94 kg』of purified water, and dissolve with stirring.
- Coating suspension

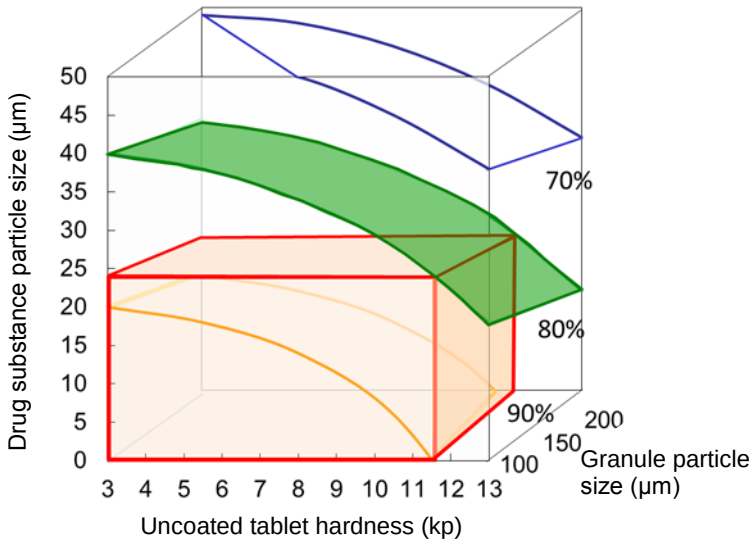
  Add 『4.8 kg』of Hypromellose, 『0.6 kg』 of Macrogol 6000, 『0.6 kg』 of Titanium Oxide and 『0.01 kg』 of Red Ferric Oxide to 『54 kg』 of purified water, and disperse with stirring. (the theoretical amount of 『1 lot content』)

Table 1. Acceptance criteria for Uniformity of Dosage Units on uncoated tablets

Sample size (n)	**Acceptable number ***	
	C1 (±15.0%)	**C2 (±25.0%)**
Less than 100	Acceptance criteria under JP's General Test <6.02> Uniformity of Dosage Units	
Not less than 100 and less than 150	3	0
Not less than 150 and less than 200	4	0
Not less than 200 and less than 300	6	1
Not less than 300 and less than 500	8	2
Not less than 500 and less than 1000	13	4
Not less than 1000 and less than 2000	25	8
Not less than 2000 and less than 5000	47	18
Not less than 5000 and less than 10,000	112	47
Not less than 10,000	217	94

* Carry out an assay on a representative sample of the lot using an appropriate analytical method, and calculate the content of API as a percentage of the label claim. The requirements for dosage form uniformity are met when the number of individual dosage units with a content outside 15.0% and 25.0% is not more than C1 and C2, respectively. The label claim is treated as the standard point of deviation.

Figure 1. Design space to assure dissolution CQA (red cuboid)



A design space to assure the dissolution of Sakura Bloom Tablets: The cuboid consisting of straight lines within an area that satisfies 80% or more of dissolution rate (predicted value), the specification, in the response aspect of dissolution based on the formula for dissolution prediction (Formula 2).

Formula 1 (Uniformity of Dosage Units: Real-time release testing)

Content of each drug product (%) = drug substance concentrations in uncoated tablets (%) × uncoated tablet weight (mg)/194 (theoretical uncoated tablet weight, mg)

Formula 2 (Dissolution: Real-time release testing)

Dissolution rate = "A – B × particle size of drug substance– C × granule particle size – D × uncoated tablet hardness – E × particle size of drug substance × uncoated tablet hardness"

Periodical verification
Perform verification of the dissolution model using commercial lots at appropriately predetermined intervals (a direct comparison between the values calculated by the model and those obtained by the conventional test method for dissolution). Where necessary, renew the library reference, and perform validation of the dissolution model.

Revalidation
When a renewal of the model is required, perform the appropriate level of validation on the re-established model using commercial lots or small-scale production lots.

[Specifications & test methods]
[Test name]: Content
[Specifications & test methods]
Sakura Bloom Tablets contain not less than 95.0% and not more than 105.0% of the labeled amount of prunus ($C_{XX}H_{XX}N_XO_X$: XXX.XX).

[Specifications & test methods]
[Test name]: Description
[Specifications & test methods]
Perform the test of Description (RTRT) as an in-process control test, and the result is applied and assessed against a release specification. Sakura Bloom Tablets occur as light red film-coated tablets.

[Specifications & test methods]
[Test name]: Identification
[Specifications & test methods]
Perform the test of Identification (RTRT) as an in-process control test, and the results is applied and assessed against a release specification. Regarding (1) Identification (RTRT), proceed as directed in [In-process control 3]: the In-process control test method for Identification [at-line NIR method]. When impossible to perform an adequate testing by (1), perform the test according to (2) Identification (conventional test). A case impossible to perform an adequate testing should be limited only to the case impossible to obtain measurement results due to measuring equipment and an NIR discriminating model. When impossible to obtain measurement results due to an NIR discriminating model, the test is allowed to be performed according to (2) Identification (conventional test) based on the risk assessment results making a judgment, after investigating a fault of the discriminating model used, that the conventional test is acceptable.

(1) Identification (RTRT)
Proceed as directed in [In-process control 3]: In-process control test method for Identification [at-line NIR method].

(2) Identification (conventional test)
Determine the ultraviolet absorption spectrum of the sample solution and standard solution obtained in Assay or Uniformity of Dosage Units under the same conditions as Assay or Uniformity of Dosage Units setting the spectrum range of measurement for a photodiode array detector at XXX to XXX nm: the retention time of the main peak and the shape of the ultraviolet absorption spectrum obtained from the sample solution coincide with those from the standard solution.

[Specifications & test methods]

[Test name]: Uniformity of Dosage Units

[Specifications & test methods]

Perform the test of Uniformity of Dosage Units (RTRT) as an in-process control test, and the result is applied and assessed against a release specification. Regarding (1) Uniformity of Dosage Units (RTRT), proceed as directed in [In-process control 2]: Content in uncoated tablets [NIR method] and Formula 1 (Annex), and assess the drug substance content in uncoated tablets in Tableting Process using the number of tablets according to Acceptance criteria for Uniformity of Dosage Units (Annex): Uncoated tablets exceeding the range of 85.0 to 115.0% are not more than the corresponding number of tablets described in Acceptance criteria for Uniformity of Dosage Units (Annex), and those exceeding the range of 75.0 to 125.0% are not more than the corresponding number of tablets described in Acceptance criteria for Uniformity of Dosage Units (Annex). When impossible to perform an adequate testing by (1), perform the test according to (2) Uniformity of Dosage Units (conventional test). A case impossible to perform an adequate testing should be limited only to the case impossible to obtain measurement results due to measuring equipment and an NIR model.

When impossible to obtain measurement results due to an NIR model, the test is allowed to be performed according to (2) Uniformity of Dosage Units (conventional test) based on the risk assessment results making a judgment, after investigating a fault of the NIR model used, that the conventional test is acceptable.

(1) Uniformity of Dosage Units (RTRT)
Proceed as directed in [In-process control 2]: Content in uncoated tablets [NIR method] and Formula 1 (Annex).

(2) Uniformity of Dosage Units (conventional test)
Perform the Uniformity of Dosage Units test on film-coated tablets according to the following methods: it meets the requirement.
Take 1 tablet of Sakura Bloom Tablets … (hereinafter omitted).

[Specifications & test methods]

[Test name]: Dissolution

[Specifications & test methods]

Perform the test of Dissolution (RTRT) as an in-process control test, and as the result is applied and assessed against a release specification. Regarding (1) Dissolution (RTRT): When the dissolution rate at the test time of 30 minutes is calculated according to Formula 2 (Annex) using the particle size of drug substance, the granule particle size obtained in

[In-process control 1] and the uncoated tablet hardness obtained in Tableting Process, it is not less than 80%. When it is impossible to obtain the dissolution rate by (1) adequately, perform the test according to (2) Dissolution (conventional test). A case impossible to obtain the dissolution rate adequately should be limited to the case impossible to obtain measurement results due to measuring equipment and the case where the dissolution prediction formula has a fault.
When it is impossible to obtain measurement results due to the dissolution prediction formula, the test is allowed to be performed according to (2) Dissolution (conventional test) based on the risk assessment results making a judgment, after investigating a fault of the dissolution prediction formula used, that the conventional test is acceptable.

(1) Dissolution (RTRT)
Using the particle size of drug substance, the granule particle size obtained in [In-process control 1] and the uncoated tablet hardness obtained in Tableting Process, calculate the dissolution rate according to Formula 2 (Annex).

(2) Dissolution (conventional test)
When the test is performed on film-coated tablets at 50 revolutions per minute according to the paddle method, using diluted McIlvaine buffer solution (pH 4.0) as the dissolution medium: Q value in 30 minutes for Sakura Bloom Tablets is 80%. Perform the test with 1 tablet of Sakura Bloom Tablets … (hereinafter omitted).

[Specifications & test methods]

[Test name]: Assay

[Specifications & test methods]

Perform the test of Assay (RTRT) as an in-process control test, and as the result is applied and assessed against a release specification. When the mean of the contents in individual tablets which were calculated according to (1) Uniformity of Dosage Units (RTRT) test on uncoated tablets is calculated, Sakura Bloom Tablets contain not less than 95.0% and not more than 105.0%. When it is impossible to perform the test by (1) adequately, perform the test according to (2) Assay (conventional test). A case impossible to perform the test adequately should be limited to the case impossible to obtain measurement results due to measuring equipment and an NIR model.
When it is impossible to obtain measurement results due to an NIR model, the test is allowed to be performed according to (2) Assay (conventional test) based on the risk assessment results making a judgment, after investigating a fault of the NIR model used, that the conventional test is acceptable.

(1) Assay (RTRT)

Calculate the mean of the contents in individual tablets which were calculated according to Uniformity of Dosage Units (RTRT) test on uncoated tablets.

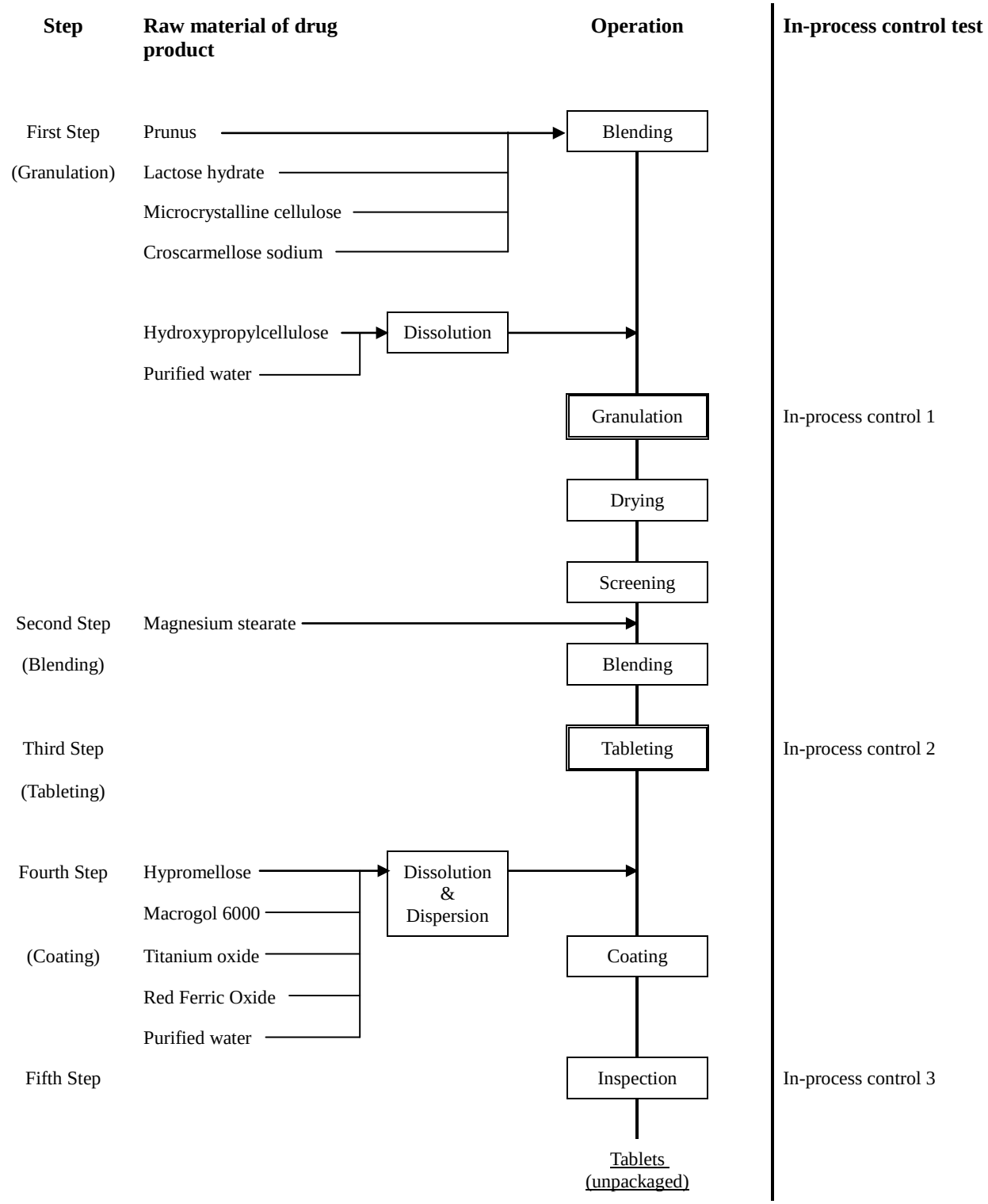
(2) Assay (conventional test)

This test is possible to be substituted with Assay (RTRT) and, therefore, not performed at the time of release.

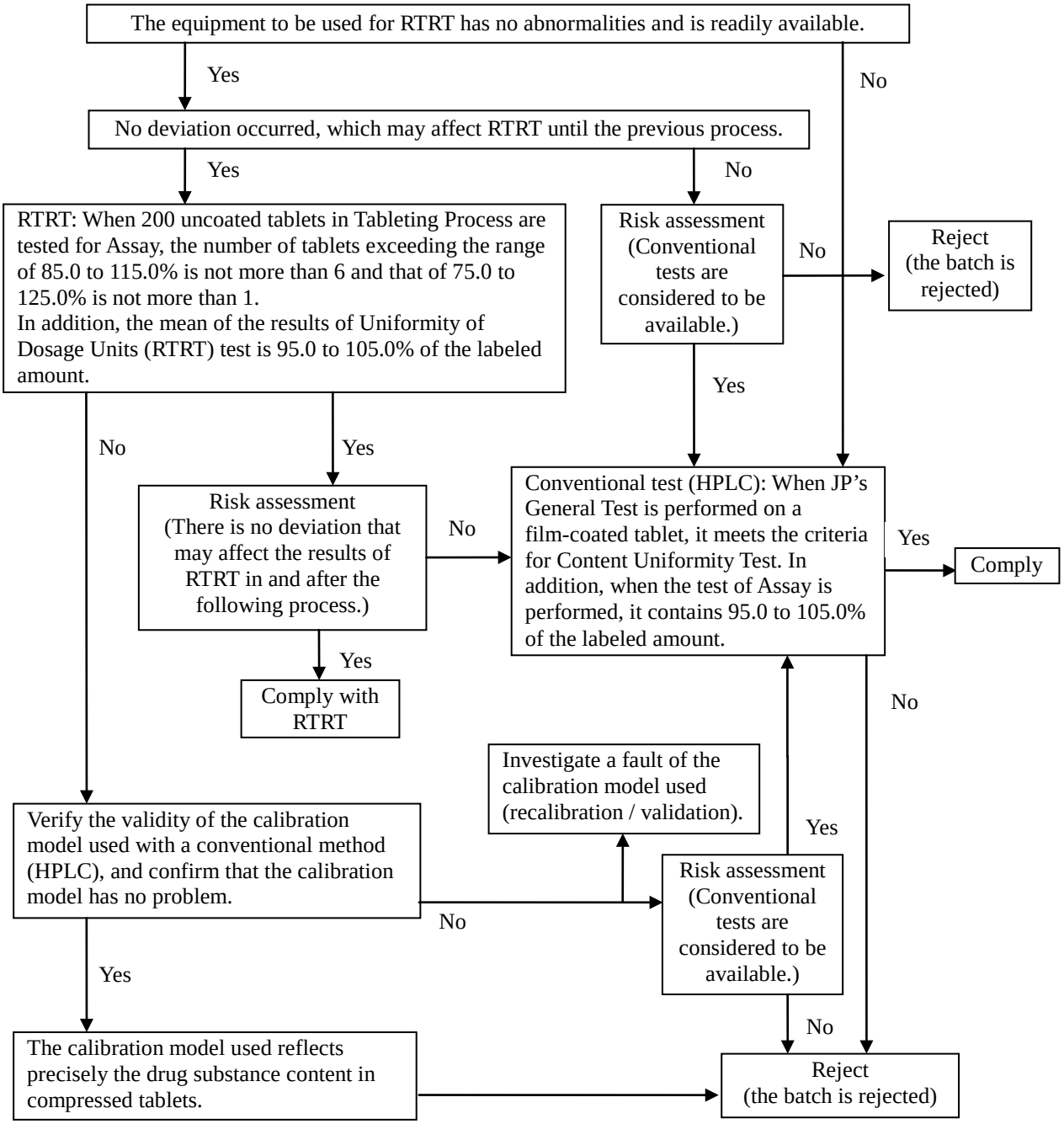
Perform the Assay test on film-coated tablets according to the following methods: It conforms to the specification.

Take 10 tablets of Sakura Bloom Tablets … (hereinafter omitted).

Flow diagram of manufacturing processes (drug product)



Decision tree for Uniformity of Dosage Units / Assay



Decision tree for Dissolution