Sakura Bloom Tablets P2 Mock

Disclaimer

This mock provides an example of the contents to be included in CTD 2.3.P.2 "Pharmaceutical Development" section for a drug product that had been developed by using the Quality by Design (QbD) methodology presented in ICH Q8, Q9, Q10 and Q11. It is supposed to be into CTD Module 2.3 (Quality Overall Summary). In addition, in order to help readers' better understanding, some additional contents corresponding to 2.3.P.3"Manufacture" and 2.3.P.5"Control of Drug Product" are also included in this mock.

The purpose of this mock is to envision development of drug product (more specifically, film-coated tablets containing new chemical entity) using the Enhanced Approach methodology (whose definition is the same as advanced methodology or QbD approach). Note that we are not intending to create any new regulatory requirement or eliminate any existing regulatory requirement. Also, note that this mock may not cover all the items to be required for 2.3.P.2 or CTD Module 2.

While there was an expectation that a QOS normally should not exceed 40 pages of text excluding tablets and figures as the CTD guideline (June 21st, 2009, Iyakuhin #899, appendix 3) was implemented, we didn't adhere to this point in authoring this mock because we believe that we should show the reviewers not only data but additional background for understanding of the product and process. Thus, this mock was prepared without taking account of page restriction. Note that this P2 mock is intended for JNDA (New Drug Application in Japan) but not for US NDA or EU MAA. It is also noted that while a QOS is considered a primary review document to reviewers in Japan, its role may be different in review of the US NDA or the EU MAA. In Japan, the CMC contents provided in the Application Form (Module 1) will only be considered regulatory commitments.

Sakura Bloom Tablets Mock Sub-group

MHLW sponsored QbD Drug Product Study Group

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Permeable

International conference on harmonization of technical requirements for registration of pharmaceuticals for human use (ICH) has developed the policy that "enhanced QbD (Quality by Design) approach" based on pharmaceutical science and quality risk management concept in pharmaceutical development and quality control enables pharmaceutical industries to obtain regulatory flexibility [ICH Q8(R2)]. Indicating the example of enhanced QbD approach in pharmaceutical development has been considered to promote the effective evaluation of the product development study on the basis of common understanding between regulatory authorities and industries.

One of the advantages to employ "enhanced QbD approach" defined in ICH Q8(R2) is application of Real Time Release Testing (RTRT) with comprehensive process understanding and Process Analytical Technology (PAT). Although the RTRT has a potential advantage for pharmaceutical industry, there are very limited practical examples to apply RTRT with enhanced QbD approach, especially in Japanese domestic companies. The potential reason is considered complicated relationship between design space and RTRT defined in ICH Q8(R2), and practical difficulty in establishing the "design space" described in the mock-up or case study at the public domain. "Material attribute" and "process parameter" become the keywords in considering relations of design space and RTRT. In "Sakura tablets" of quality overall summary P2 mock-up (description example) concerning the public welfare labor science research, not only "material attributes" like the particle size of drug substance, but also "process parameter" like the lubricant blending time or compression pressure are included in the factor that composes the design space of Sakura tablets. These material attribute and process parameters in addition to the lubricant specific surface area are included as the factor of dissolution RTRT prediction model, and this equation is described in justification of specification and test methods in the mock-up application form.

However, for example, the possibility that so-called major change as a regulatory action occurs is very high when commercial manufacturing blender is changed leading to changes in the blending time to obtain suitable blending state as before, if the design space is constructed using process parameters. This shows that the enhanced QbD approach to which regulatory flexibility is sure to improve may have a critical issue with less regulatory flexibility if the process parameter is employed for the factor that composes the design space and RTRT like Sakura tablets. So we decided to create a mock-up CTD P2 "Sakura Bloom Tablets" in which critical material attributes (CMAs) are used as the factors for not only RTRT model calculation but also design space construction in order to solve the issue where the process parameters were excluded from the design space factor as much as possible, and the factors for RTRT are connected directly to those of design space. This approach is intentional since the resultant design space factors to be also used for RTRT are not linked to equipment or process parameters and therefore are site, scale, and equipment independent. In this mock-up, CMAs are controlled with PAT tools within the appropriate range adjusting process parameters. Also, the fluidized bed granulation method that is one of the typical manufacturing methods in the Japanese domestic companies is adopted, and the concept of Large-N standard examined in our sectional committee and advanced control strategy examples are included for content uniformity of RTRT.

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Attachment

"Justification of Specifications when the Real Time Release Testing is Employed for Uniformity of Dosage Units"

MODULE 2: COMMON TECHNICAL DOCUMENT SUMMARIES
Generic name: Prunus

2.3 QUALITY OVERALL SUMMARY

Sakura Bloom Tablets

2.3.P.1 Description and Composition of the Drug Product (Sakura Bloom Tablets, Film-coated Tablet)

The composition of Sakura Bloom Tablets is shown in Table 2.3.P.1-1.

Table 2.3.P.1-1 Composition of Sakura Bloom Tablets

Function	Specification	Ingredient	Amount
Drug substance	In-house specification	Prunus	20 mg
Diluent	JP [e)]	Lactose Hydrate	q.s.
Diluent	JP [e)]	Microcrystalline Cellulose [a)]	20 mg
Binder	JP [e)]	Hydroxypropylcellulose	6 mg
Disintegrant	JP [e)]	Croscarmellose Sodium	10 mg
Sub-total granule			192 mg
Lubricant	JP [e)]	Magnesium Stearate	2 mg
Sub-total uncoated tablet			194 mg
Coating agent	JP [e)]	Hypromellose [b)]	4.8 mg
Polishing agent	JP [e)]	Macrogol 6000	0.6 mg
Coloring agent	JP [e)]	Titanium Oxide	0.6 mg
Coloring agent	JPE [f)]	Red Ferric Oxide	Trace amount
Sub-total coating layer			6 mg
Total			200 mg
Container Closure System			PTP/Al [c)] 500 tablets/bottled [d)]

a) Mean degree of polymerization, 100 to 350; loss on drying, 7.0% or less; bulk density, 0.10 to 0.46 g/cm^3
b) Substitution type, 2910; viscosity, 6 mPa•s
c) Polypropylene on one side and aluminum foil on the other side
d) Polyethylene bottle + plastic cap
e) Japanese Pharmacopoeia
f) Japanese Pharmaceutical Excipients

2.3.P.2 Pharmaceutical Development (Sakura Bloom Tablets, Film-coated Tablet)

2.3.P.2.1 Components of the Drug Product

2.3.P.2.1.1 Drug substance

The physicochemical properties of prunus, the drug substance of Sakura Bloom Tablets, are shown in Section 2.3.S.1.3. General Properties. Prunus is a basic compound with a molecular weight of 450, having poor wettability and a metal adherability. The solubility decreases with increasing pH, with a low solubility in an alkaline solution at 37°C. Sakura Bloom Tablets contain 20 mg of prunus, which is classified as a low solubility compound according to the Biopharmaceutical Classification System (BCS). The 1-octanol/water partition coefficient (log D) of prunus is 2.6 at 25°C, and based on the measured permeability across Caco-2 cell membranes, prunus is classified as a high permeability compound according to BCS. From these results, prunus is classified as a BCS class 2 compounds (low solubility and high permeability).

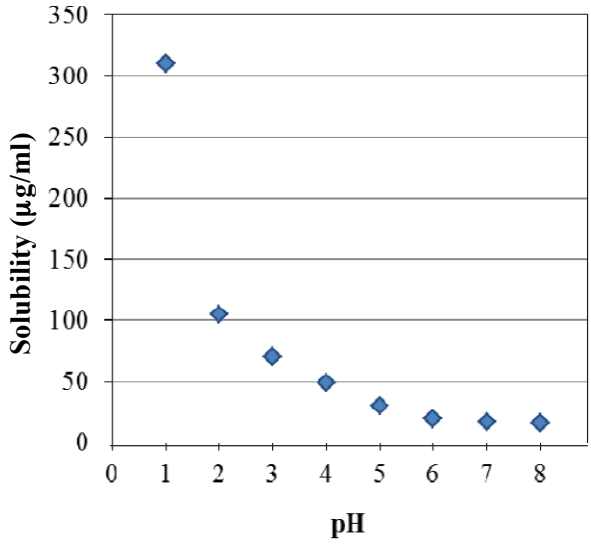

Figure 2.3.P.2.1-1 Solubility of prunus in buffers at various pH

2.3.P.2.1.2 Excipients

Excipients used in Sakura Bloom Tablets have good compatibility with drug substance and the compatibility test results showed neither a change in appearance, an increase in related substances nor a decrease in assay. To select a diluent, uncoated tablets were prepared with lactose hydrate, D- mannitol, or microcrystalline cellulose, and evaluated for dissolution and hardness. The results showed that a combination of lactose hydrate and microcrystalline cellulose produced a formulation with the highest dissolution rate and appropriate hardness, therefore lactose hydrate and microcrystalline cellulose were selected as diluents. To select a disintegrant, uncoated tablets were prepared with croscarmellose sodium, crospovidone, carmellose calcium or low substituted hydroxypropylcellulose, and evaluated for dissolution. As a result, croscarmellose sodium was selected because of its rapid dissolution. Hydroxypropylcellulose was selected as a binder and magnesium stearate as a lubricant, both of which are widely used.

Prunus drug substance is photosensitive, therefore Sakura Bloom Tablets are film-coated tablet to protect from light. Hypromellose, titanium oxide, and macrogol 6000 are commonly used coating agents which have been shown not to interfere with the stability of the drug substance, To give an appearance of a pale red color, red ferric oxide was added to the coating agent.

2.3.P.2.2 Drug Product

1) Formulation Development Strategy

A systematic approach (Quality by Design: QbD or Enhanced Approach) was employed for formulation development of Sakura Bloom Tablets, building on prior knowledge. In addition to prior knowledge and manufacturing experiences, Design of Experiments (DoE) and quality risk management were also used. This enhanced approach to formulation and process development, enabled identification of Critical Quality Attributes (CQAs) and Critical Process Parameters (CPPs) of the drug substance and the drug product, establishment of a design space, and Real Time Release Testing (RTRT), supporting continual improvement throughout the product lifecycle.

To support definition of the control strategy for the final manufacturing process and quality assurance of Sakura Bloom Tablets, the following approaches were employed.

1. Establishment of the Quality Target Product Profile (QTPP) and initial risk assessment
2. Identification of the product CQAs that ensure desired quality, safety and efficacy
3. Assessment of the effects of the following Potential Critical Material Attributes (p-CMA) on CQAs, and identification of Critical Material Attributes (CMA)*
   - Drug substance particle size
   - Granule particle size
   - Blend uniformity
   - Lubricant surface area
   - Lubricity of lubricant
   - Granule segregation
   - Uncoated tablet weight
   - Uncoated tablet weight variation
   - Uncoated tablet hardness
4. Assessment of the effects of the following Potential Critical Process Parameter (p-CPP) on Critical Material Attribute (CMA), and identification of Critical Process Parameter (CPP)
   - Inlet air volume
   - Inlet air temperature
   - Spray rate
   - Tableting rotation speed – Compression force
4. Construction of the control strategy
5. Review of the risk assessment after implementation of the control strategy
6. Overall evaluation of risk assessment

According to the approach described above, Preliminary Hazard Analysis (PHA) was used in the initial risk assessment, and Failure Mode and Effects Analysis (FMEA) was used in the risk assessment of the manufacturing process and in the risk assessment after implementation of the control strategy.

A risk assessment based on the results of formulation development with Sakura Bloom Tablets indicated that drug substance particle size, granule particle size, uncoated tablet hardness, uncoated tablet weight, uncoated tablet weight variation, and granule segregation impacted the drug product CQAs of dissolution, uniformity of dosage units, and assay. These attributes were therefore identified as CMAs. In the final control strategy, drug substance particle size was included in the specifications of the drug substance, granule particle size and uncoated tablet hardness were to be controlled within the design space to ensure the dissolution, and uncoated tablet weight and the weight variation were to be controlled by in-process control. To confirm that the granule segregation is within the acceptable range, the drug substance concentrations in uncoated tablets are periodically monitored with near infrared spectrophotometry (NIR). CPPs in each unit operation were to be feedback-controlled with Process Analytical Technology (PAT) for granule particle size in the granulation process, and for uncoated tablet hardness, uncoated tablet weight, uncoated tablet weight variation and drug substance concentrations in uncoated tablets in the tableting process. Application of the above control strategy, including supporting models enables real time release testing for the drug product CQAs of dissolution, uniformity of dosage units, and assay.

For identification, we considered it possible to apply RTRT, by applying NIR spectrophotometry as an in-process control in the inspection process, and by using a discriminating model constructed by a spectrum in

wavenumber region including the drug substance specific peaks. Furthermore, for the description (appearance) we also considered it possible to apply RTRT as an in-process control in the inspection process.

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*CMA (Critical Material Attribute) is not ICH term. As described in permeable, we defined the term of CMA in order to solve the issue where the process parameters were excluded from the design space factor as much as possible, and the factors for RTRT are connected directly to those of design space. When we want to use non-ICH term, we have to clarify the definition in CTD.

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2) QTPP

QTPP of Sakura Bloom Tablets is shown in Table 2.3.P.2.2-1.

Table 2.3.P.2.2-1 QTPPs of Sakura Bloom Tablets

	Target	Related Evaluation Item
Content and Dosage Form	Film coated tablets containing 20 mg of prunus	Description (appearance), identification, uniformity of dosage units, and assay
Specification	Comply with criteria of each evaluation item	Description (appearance), identification, impurity [a)], uniformity of dosage units, dissolution, and assay
Stability	To ensure a shelf-life of 3 years or more at room temperature	Description (appearance), impurity [a)], dissolution, and assay

a: Finally, not to be included in the specifications based on the study results

2.3.P.2.2.1 Formulation Development

As discussed in 2.3.P.2.1.1 Drug Substance, since prunus has properties of high metal adherability and poor flowability, therefore Sakura Bloom Tablets used for clinical studies were manufactured using a fluid bed granulation process (one of the wet granulation methods).

The formulation was optimized using excipients described in 2.3.P.2.1.2 Excipient. A part of a DoE, uncoated tablets were prepared containing 3 levels of each of disintegrant, binder, and lubricant, and were assessed for dissolution and hardness to determine the final formula. Based on the output of the DoE, disintegrant was set at 5%, binder at 3w/w%, and lubricant at 1w/w%. The dissolution and uncoated tablet hardness (CQA and CMA discussed later) were found to be met with a wide range of excipient levels, including the optimum solution levels chosen, thus the chosen formulation was confirmed to be robust for drug product CQAs. The amount of coating agent was set at 3w/w% of the formulation, based on the relationship between the amount of coating agent and photostability.

Table 2.3.P.2.2-2 shows the formulas of 5 mg tablet, 10 mg tablet, and 20 mg tablet used for clinical studies, as well as the formula for the 20 mg tablet for the Japanese New Drug Application (NDA). For the proposed 20 mg tablet included in the NDA, the uncoated tablets had the same formula from the clinical development stage through to commercial supply. However, the coating agent was white during the clinical development stage, but was changed to pale red at the NDA stage.

Table 2.3.P.2.2-2 Formulations used in the clinical studies and the commercial formulation

Batch number		Clinical study 1	Clinical study 2	Clinical study 3	NDA 1, 2, 3
Labeled amount		5 mg	10 mg	20 mg	20 mg
Production scale		500,000 tablets	500,000 tablets	500,000 tablets	100,000 tablets*
Manufacturing date		April 20XX	April 20XX	April 20XX	April 20XX
Manufacturing facility		Investigational drug manufacturing facility, XX Co., Ltd.			
Manufacturing process		Granulation → Blending → Tableting → Coating			
Ingredient/amount (mg/tablet)	Prunus	5.0	10.0	20.0	20.0
	Lactose Hydrate	151.0	146.0	136.0	136.0
	Microcrystalline Cellulose	20.0	20.0	20.0	20.0
	Croscarmellose Sodium	10.0	10.0	10.0	10.0
	Hydroxypropylcellulose	6.0	6.0	6.0	6.0
	Magnesium Stearate	2.0	2.0	2.0	2.0
Sub-total for an uncoated tablet (mg)		194.0	194.0	194.0	194.0
Ingredient/amount (mg/tablet)	Hypromellose	4.8	4.8	4.8	4.8
	Macrogol 6000	0.6	0.6	0.6	0.6
	Titanium Oxide	0.6	0.6	0.6	0.6
	Red Ferric Oxide	-	-	-	0.01
Total for tablet (mg)		200.0	200.0	200.0	200.0
Use of the formulation		Phase III clinical studies	Phase III clinical studies	Phase III clinical studies	Stability studies
Batch number of the drug substance used		Clinical Study A	Clinical Study B	Clinical Study C	To-be-marketed A, B, C

* 1/10 scale for commercial batch size

2.3.P.2.2.2 Overages

Not applicable

2.3.P.2.2.3 Physicochemical and Biological Properties

A dissolution test of the 20 mg tablets for the commercial product (Batch No. NDA 1) was performed in the 1st fluid in the Dissolution Test of the Japanese Pharmacopoeia (JP-1), a diluted McIlvaine buffer (pH 4.0), the 2nd fluid in the Dissolution Test of the Japanese Pharmacopoeia (JP-2), and water, with a paddle rotation speed of 50 rpm. As shown by Figure 2.3.P.2.2-1, dissolution profiles reflect the solubility, and the dissolution rate was decreased with the increase in pH.

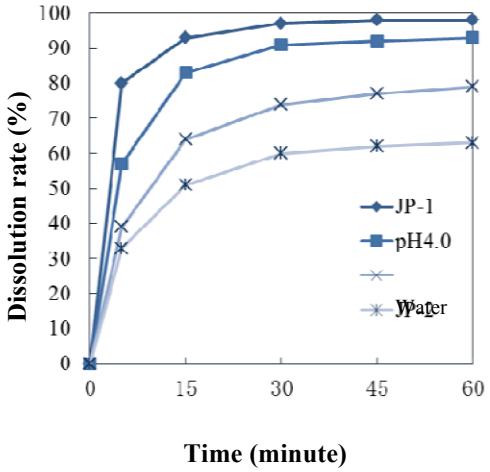


Figure 2.3.P.2.2-1 Dissolution profile of the proposed drug product

Based on the dissolution profile of the 20 mg formulation used in the phase III clinical studies, the dissolution in the diluted McIlvaine buffer (pH 4.0) with a low dissolution rate (among the dissolution media in which 85% or more was dissolved in a specified time), was used as a discriminatory dissolution method to support manufacturing process development.

2.3.P.2.3 Development of manufacturing processes

The same manufacturing process was used from the early development stage through to commercial supply. The process consists of Process 1 (granulation): granulation and drying using a fluid bed granulator along with a screening mill, Process 2 (blending): mixing the granules and lubricant, Process 3 (tableting): compressing the blend to produce tablets, Process 4 (coating), Process 5 (inspection), and Process 6 (packaging). Equipment used for each process was identical to or the same principle as the equipments to be used for commercial production. Drug substance milling was performed as part of the manufacturing process of the drug substance.

Figure 2.3.P.2.3-1 shows an overview of the QbD strategy for Sakura Bloom Tablets. To ensure the desired quality, safety, and efficacy of the product, an initial risk assessment of the CQAs (description, identification, uniformity of dosage units, assay, dissolution, impurity) was undertaken, and the CQAs (uniformity of dosage units, assay, and dissolution) that were considered high risk were identified (Figure 2.3.P.2.3-2). All the Material Attributes (MAs) that had the potential to affect the high risk CQAs were identified using techniques including brain-storming. p-CMAs were identified through risk assessment and experimental studies based on the development knowledge from this product or prior knowledge, and the final CMAs were identified by further increasing knowledge and understanding. Next, all the Process Parameters (PPs) that have the potential to affect the CMAs were thoroughly clarified. p-CPPs were identified through risk assessment and experiments, and the CPPs were identified by increase knowledge and understanding. Management of the CPPs to ensure control of the CMAs within an appropriate range (using PAT feedback system in this case) makes it possible to continue to assure the CQA throughout the product life cycle.

For the CQA of dissolution, the "appropriate ranges" of the CMAs were defined by a design space, as discussed later. In general, process parameters are equipment specific. For an example for tableting machines, the compression force required to obtain the desired tablet hardness often varies between machines, even for rotary tableting machines with the same operating principles. Considering the equipment specific parameters, in order to continually assure the CQAs to achieve the QTPP, it may be more important to appropriately control CMAs such as uncoated tablet hardness, rather than to control PPs such as compression force within an appropriate range. To meet a "target CMA value," the feedback control of CPPs, which affect CMAs with PAT, makes it possible to continuously ensure the CQA throughout the product life cycle, and supports the concept of "ongoing process verification,"* which enables continual improvement. Use of CMAs as input factors makes it possible to manufacture the product to ensure it continually satisfies the QTPP, even when we make changes in manufacturing equipment which have the same operating principle.

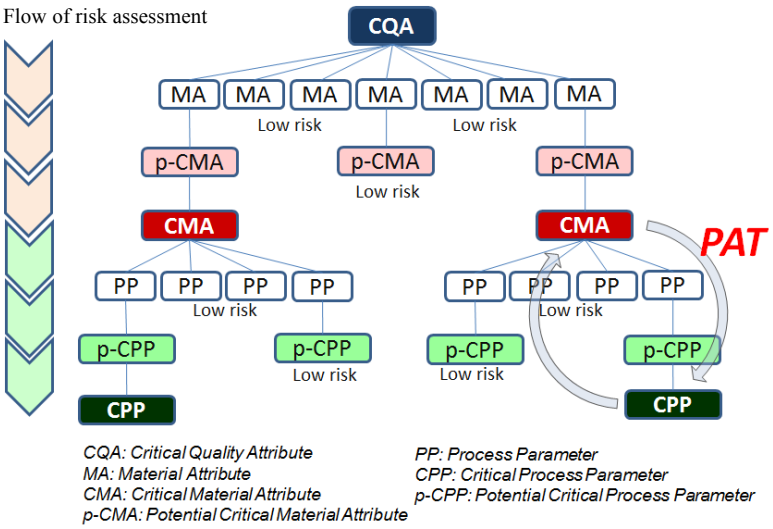


Figure 2.3.P.2.3-1 Overview of QbD strategy for Sakura Bloom Tablets

* Ongoing process verification is to confirm whether the validated process is maintained in commercial production after completion of process validation, as appropriate. Specifically, it means the actions of the underlined sentence in 3) Objectives of validation in Validation Standards based on Article 13 Validation of Ministerial Ordinance on GMP. This term is used in training material for ICH QIWG, but it is not defined in ICH Guideline.

> The objective of validation is to confirm that building and facilities in the manufacturing site as well as procedures, processes, and other manufacturing control and quality control manufacturing procedures (herein after referred to as "manufacturing procedures etc.") give the expected results, and to make it possible to continually manufacture the product that complies with the intended quality by documenting the above. To achieve this objective, knowledge and information gained through the product life cycle including drug development, ongoing process verification, and review of product qualification, should be utilized. If development of a drug or establishment of a technology were performed in places other than the present manufacturing site, a necessary technology transfer should be made.

In the FDA's Guidance for Industry Process Validation: General Principles and Practices, the term of "continued" process verification is used, but it is may be confused with "Continuous" Process Verification (ICH Q8) that means a technique of PAT tool (continuous monitoring), and the abbreviation of CPV is exactly the same between the two terms. Therefore, the term of "ongoing process verification" is used in this mock-up. To avoid confusion among related parties, the working group recommends using the term "ongoing process verification."

2.3.P.2.3.1 Initial risk assessment

2.3.S.1.3 Description, identification, uniformity of dosage units, assay, and dissolution were identified as CQAs that may need to be controlled to meet the QTPP for Sakura Bloom Tablets, based on the physicochemical properties, the knowledge and information gained through the formulation development and manufacturing experiences. An initial risk assessment assessing the quality of Sakura Bloom Tablets was performed for these CQAs using PHA. The results are shown in Figure 2.3.P.2.3-2. The details of PHA are shown in 3.2.P.2.3.

Based on the QTPP for Sakura Bloom Tablets and the results of the initial risk assessment, the uniformity of dosage units was considered high risk, because it is affected by the change in drug substance particle size, blend uniformity, uncoated tablet weight/weight variation, and segregation, and may affect the efficacy and safety in patients. Assay is considered high risk, because it is affected by the change in uncoated tablet weight, and may affect efficacy and safety. Dissolution was considered high risk, because it is affected by the change in drug substance particle size, physical property of lubricant, granule particle size, lubricity of lubricant at blending, compression force/uncoated tablet hardness, and amount of coating film, and may affect the efficacy and safety. Among the CQAs, the description is only affected by the coating process, which was confirmed to be acceptable during clinical tablet development and at the process development stages. Due to the low risk of affecting efficacy and safety in patients, description was decided to be controlled as the specifications or equivalent testing. Identification is not affected by variable factors in manufacturing, and was considered to have a low risk of affecting efficacy and safety in patients. Thus, identification was decided to be controlled as the specifications or equivalent testing. It was shown that there was no increase in related substances in formulations during the manufacturing processes, from the excipient compatibility tests and results of clinical tablet manufacturing in the formulations of each strength at the development stages. Therefore, it is considered that drug related impurity content has a low risk of affecting efficacy and safety in patients, provided that the impurities in the drug substance are controlled within the specifications. Furthermore, compatible excipients were selected and the stability test results for clinical tablets and different strength formulations at the development stage, showed no change in product quality such as assay, dissolution, and impurity content during storage. Therefore, it was considered that Sakura Bloom Tablets have a low risk of quality change on storage affecting efficacy and safety, as long as the initial quality is ensured. Justification of items (description, identification, and impurity) which were considered low risk in the initial

risk assessment is described in 2.3.P.5.4 Results of batch analysis, 2.3.P.5.6.6 Testing items not included in specifications, and 2.3.P.8 Stability.

CQA	Drug substance	Excipient	Granulation	Blending	Tableting	Coating	Rationale
Description							The coating process may affect the description but based on experiences during manufacture of clinical drug products and at the development stages there is a low risk of affecting efficacy and safety.
Identification							Identification is not affected by manufacturing variables, and has a low risk of affecting the efficacy and safety.
Uniformity of dosage units	■			■	■		The drug substance particle size, blend uniformity following the blending process, uncoated tablet weight/weight variation following tableting, and segregation have an effect on the uniformity of dosage units and may affect efficacy and safety.
Assay					■		The uncoated tablet weight following the tableting process has an effect on the content of drug substance and may affect the efficacy and safety.
Dissolution	■	■	■	■	■	■	The drug substance particle size, physical property of lubricant, granule particle size, lubricity of lubricant during blending, compression force/uncoated tablet hardness, and amount of coating film have an effect on the dissolution and may affect the efficacy and safety.
Impurity							Impurity content was not increased during manufacturing processes and has a low risk of affecting the efficacy and safety, as long as the drug substance impurities are controlled within the specifications.

*The assessment of each CQA of stability samples showed no change in product quality, and confirmed there is no change on storage if the initial quality is assured.

□ - Low risk
■ - High risk

Figure 2.3.P.2.3-2 Summary of the initial risk assessment

2.3.P.2.3.2 Determination of CMAs affecting each CQA

2.3.P.2.3.2.1 Identification of p-CMAs

MAs that can potentially affect the CQAs of Sakura Bloom Tablets are listed in Table 2.3.P.2.3-1. p-CMAs were identified for CQAs (uniformity of dosage units, assay, dissolution) which were considered high risk in the initial risk assessment utilizing knowledge gained through the formulation development up to the formulation for phase III clinical studies (refer to Section 3.2.P.2.3 for details). p-CMAs identified include drug substance particle size, blend uniformity, segregation, uncoated tablet weight, uncoated tablet weight variation, lubricant surface area, granule particle size, lubricity of lubricant, and uncoated tablet hardness. The amount of film coating listed in the initial risk assessment, was confirmed not to affect dissolution across a wide range, and thus, not included as a p-CMA.
For implementation of risk assessment, the relationship between QTPP, CQA, and p-CMA was summarized in Figure 2.3.P.2.3-3 in the form of an Ishikawa diagram. Risk assessment was performed for these p-CMA using FMEA. The details of the FMEA are shown in Section 3.2.P.2.3. The definition of risk priority number (RPN) was defined as follows: ≥40 is high risk, ≥20 and <40 is medium risk, and <20 is low risk.
Consequently, as shown in Figure 2.3.P.2.3-4 and Table 2.3.P.2.3-2, all the p-CMAs identified for each CQA were medium risk or high risk.

Table 2.3.P.2.3-1 MAs possibly affecting CQA

	Factor
Drug substance	Adherability, flowability, transition, water content, agglomeration properties, hygroscopicity, solubility, melting point, physical stability (deliquescent, efflorescent, sublimation, etc.), chemical stability, particle shape, particle size (distribution), residual solvent, wettability, specific surface area, and physical change (ex. gelation)
Excipient	Adherability, flowability, coning properties, polymorphism, transition, water content, agglomerating properties, hygroscopicity, solubility, melting point, physical stability (deliquescent, efflorescent, sublimation, etc.), manufacturer (supplier, site, etc.), grade, origin, purity of ingredient, manufacturing methods, surface condition, compatibility with drug substance (adsorption etc.), interaction between excipients, compression properties, particle size, wettability, and surface area
Granulation	Particle distribution (particle size), binder (concentration, viscosity, grade), water content of granules after drying, water content of granules during granulation, surface conditions on granules (wettability), chemical change by moisture, degradation by heating, particle shape, specific volume, drug substance content in each fraction,, flowability, granule physical strength, and material of equipment
Blending	Flowability, particle size, particle shape, blend uniformity, specific volume, lubricity of lubricant, granule physical strength, and material of equipment
Tableting	Granule particle size, dispersibility of lubricant in granules, chemical change by moisture, degradation by heating, segregation, uncoated tablet weight, weight variation, disintegration, uncoated tablets hardness/density/thickness, uncoated tablet dissolution, presence or absence of score line/imprint, and material of equipment
Coating	Chemical change by moisture, degradation by heating, tablet weight (amount of coating film), hardness, disintegration, coating agent (concentration, viscosity, grades), strength of coating film, water content in coating , water content after drying, presence or absence of score line/imprint, friability/ cracking/chipping, and material of equipment

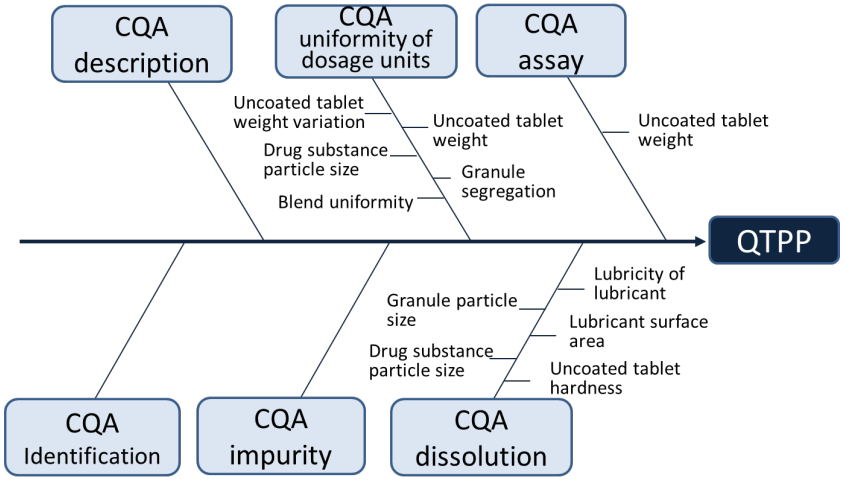


Figure 2.3.P.2.3-3 Relation among QTPP, CQA, and p-CMA

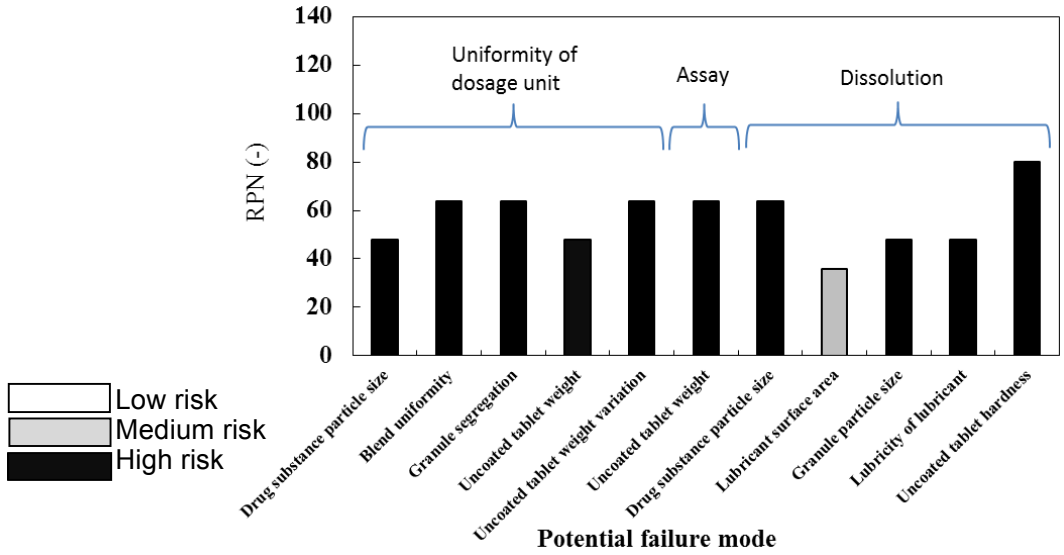


Figure 2.3.P.2.3-4 Results of FMEA risk assessment before manufacturing process development of Sakura Bloom Tablets

Table 2.3.P.2.3-2 Results of FMEA risk assessment before manufacturing process development of Sakura Bloom Tablets (refer to Section 3.2.P.2.3 for details of score)

CQA	Potential failure mode	Effect	Severity	Probability	Detectability	RPN [a]
Uniformity of dosage units	Drug substance particle size	Not uniform	3	4	4	48
	Blend uniformity	Not uniform	4	4	4	64
	Granule segregation	Not uniform	4	4	4	64
	Uncoated tablet weight	Not uniform	4	3	4	48
	Uncoated tablet weight variation	Not uniform	4	4	4	64
Content	Uncoated tablet weight	Change in content	4	4	4	64
Dissolution	Drug substance particle size	Change in dissolution	4	4	4	64
	Lubricant surface area	Change in dissolution	3	3	4	36
	Granule particle size	Change in dissolution	3	4	4	48
	Lubricity of lubricant	Change in dissolution	3	4	4	48
	Uncoated tablet hardness	Change in dissolution	4	5	4	80

a) RPN (Risk Priority Number) is severity × probability × detectability: ≥40 is high risk, ≥20 and <40 is medium risk, and <20 is low risk.

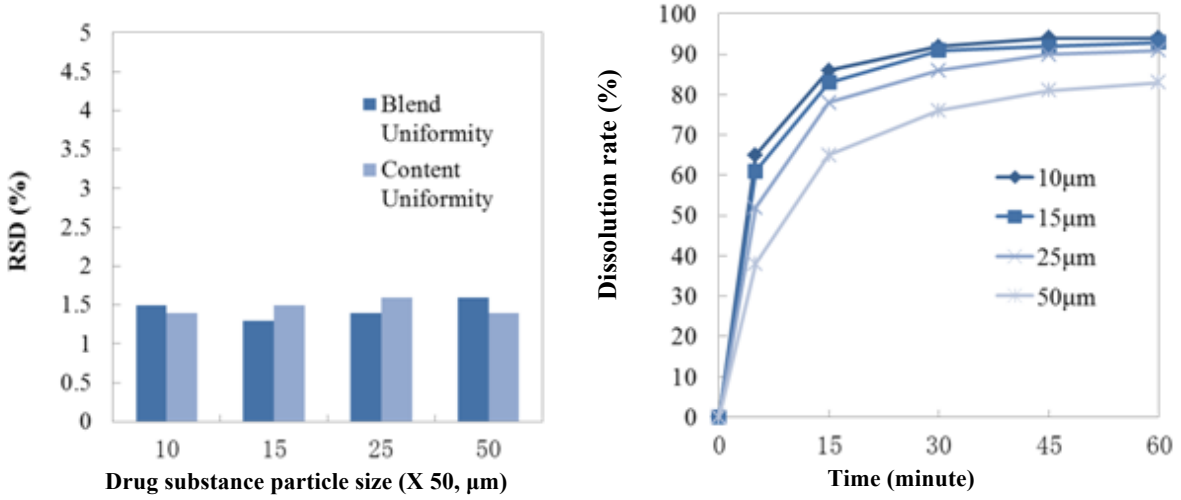
2.3.P.2.3.2.2 Identification of CMA

The effect of p-CMAs on CQAs was experimentally studied.

Effect of drug substance particle size on CQA (uniformity of dosage units and dissolution)

As shown in Figure 2.3.P.2.3-5(a), changes in drug substance particle size did not affect the blend uniformity of granules for tableting, or the uniformity of the dosage units. Therefore, it was confirmed that the drug substance particle size did not affect the uniformity of dosage units (CQA), and its severity risk score was decreased. Note)

Figure 2.3.P.2.3-5(b) shows a dissolution profile of Sakura Bloom Tablets in which the drug substance particle size was changed. The dissolution rate decreased with increasing drug substance particle size, as shown in the figure, and the drug substance particle size was confirmed to affect the dissolution (CQA). Therefore, the risk score was not decreased.



(a) Uniformity of dosage units (b) Dissolution (pH 4.0, 50 rpm)

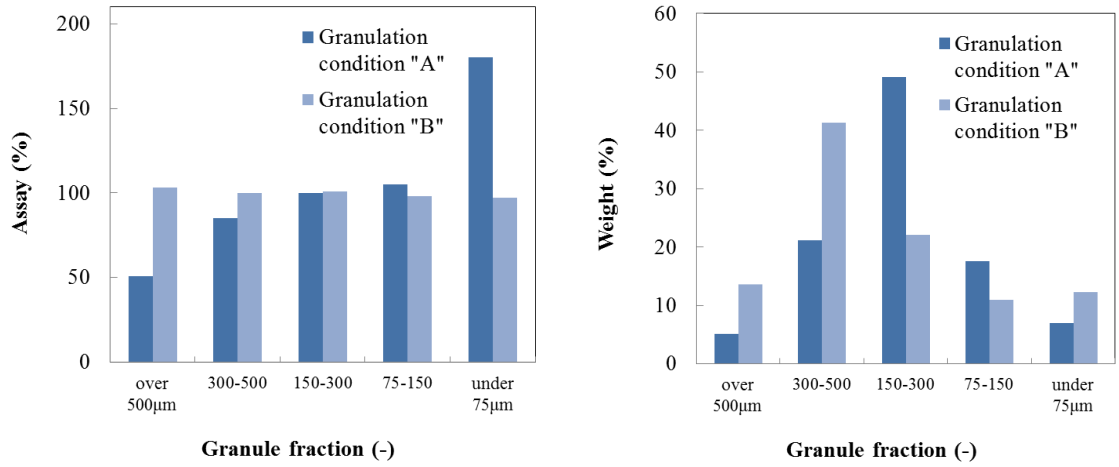
Figure 2.3.P.2.3-5 Effects of the drug substance particle size on CQA (uniformity of dosage units, and dissolution)

Note: The concept of FMEA "severity" in this mock up is shown below.

The items for which the significance of the risk is unknown are assumed to have a high score of significance in the early development stage with poor accumulation of knowledge. As new knowledge is accumulated in the course of development, the significance of the risk is better understood. During the course of development, the significance of the risk assumed to be "high" at an early stage can turn out to be "low" in reality. The level of significance is unchanged until new knowledge is accumulated.

Effects of blend uniformity /granule segregation / uncoated tablet weight/ uncoated tablet weight variation on uniformity of dosage units (CQA)

In the fluid-bed granulation process for Sakura Bloom Tablet, changes in granulation parameters (such as spray rate) lead to a high drug substance concentration in the small granules using operating condition A, where granulation did not proceed completely, i.e., different drug substance concentrations in different granulation sizes (see Figure 2.3.P.2.3-6[a]). As shown in Figure 2.3.P.2.3-6(b) "the granule particle size distribution", high or low drug substance concentrations were found in about 10% of the granules for condition A. Thus, granule segregation due to differences in granule particle size could be a potential risk causing drug substance content segregation in tablets. When granules for tableting were prepared using these granules, rapid blend uniformity was obtained for both granulation conditions, as shown in Figure 2.3.P.2.3-7. Therefore, although the risk score of severity that blend uniformity has on uniformity of dosage units remained unchanged, the risk score of probability of blend non-uniformity decreased in FMEA.



(a) Drug substance content in each fraction (b) Granule particle size distribution

Figure 2.3.P.2.3-6 Effects of granulation conditions on granules

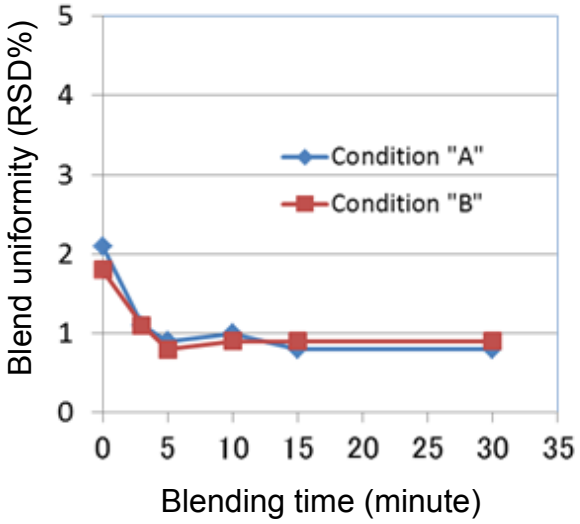
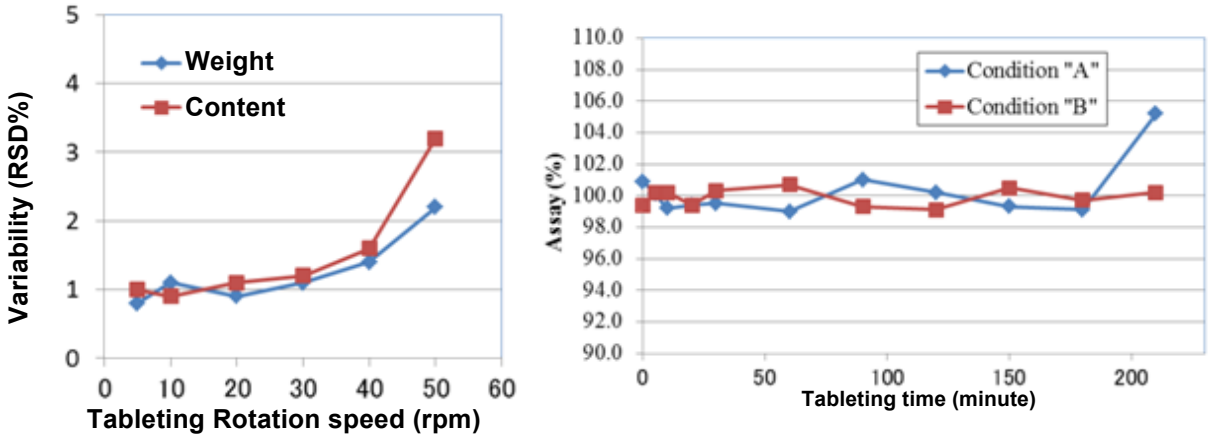


Figure 2.3.P.2.3-7 Blend uniformity profile

Because the uncoated tablet weight and granule segregation clearly affect the uniformity of dosage units, the severity risk score did not decrease. Also, as shown in Figure 2.3.P.2.3-8, weight variation increased with

increasing press speed, thus, the probability risk score did not significantly decrease. Similarly, as shown in Figure 2.3.P.2.3-8(a), when the granules prepared under the condition A were tableted, there was a difference between tablet weight variation and granule segregation with increasing tablet rotation speed, and it was confirmed that there is a risk that granule segregation can occur during tableting. Based on these findings, continuous tableting was performed using two grades of granules shown in Figure 2.3.P.2.3-6, at a tableting rotation speed of 50 rpm when there was a difference between tablet weight and drug substance content. As a result, the drug substance content in tablet was the highest under the condition A at the last tableting. Although the probability risk score decreased as the granule segregation did not occur across a wide range of tableting rotation speeds, it was considered that there was a risk that granule segregation could lead uniformity of dosage units.



(a) Relationship between the tableting rotation speed and the variation (condition A)

(b) Continuous tableting at 50 rpm (mean of 3 tablets)

Figure 2.3.P.2.3-8 Effects of tableting rotation speed

Effects of the mass of uncoated tablet weight on content (CQA)

It is obvious that the uncoated tablets weight during tableting affects the content (CQA). Therefore, risk score of severity did not decrease as the risk assessment proceeded. On the other hand, as shown in Figure 2.3.P.2.3-9, in a total of 6 batches, 3 clinical batches and 3 primary stability batches, the drug substance content in uncoated tablets during tableting over time was almost constant at a mean of 3 tablets, when the target value of the uncoated tablets weight was specified and the tableting was performed under appropriate conditions. Therefore, the risk score of probability that the uncoated tablet weight affects the content was considered to be low.

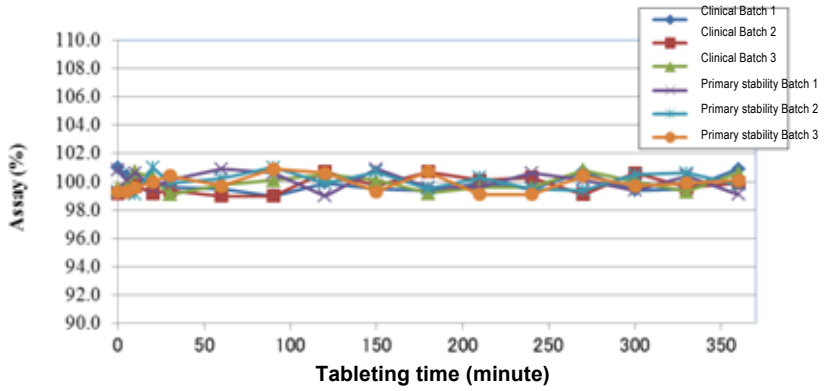
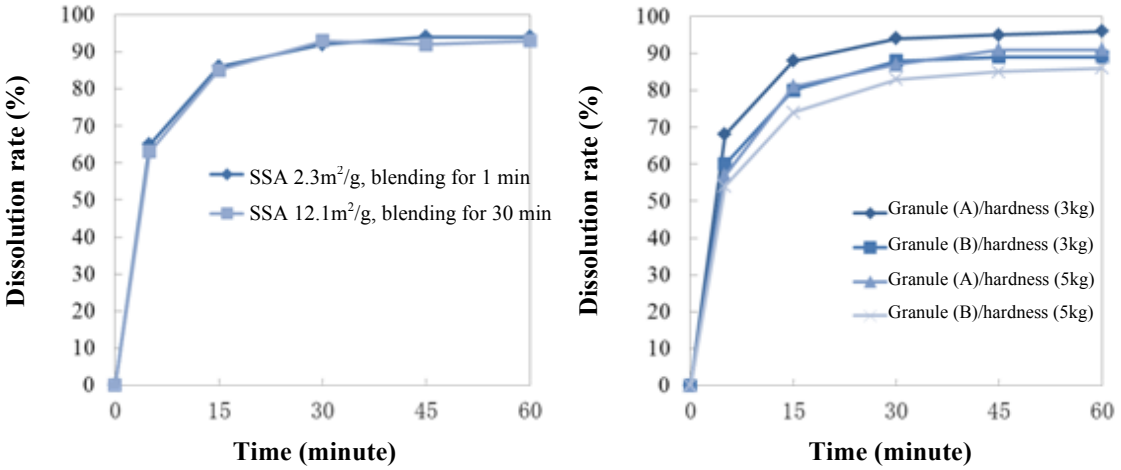


Figure 2.3.P.2.3-9 Drug substance content at tableting over time (mean of 3 tablets)

Effect of lubricity of lubricant/granule particle size of uncoated tablets on dissolution (CQA)

The effects of lubricity of lubricant on dissolution were assessed at a range of blending times with 3 grades of lubricant (magnesium stearate) with different specific surface areas (SSA). As shown in Figure 2.3.P.2.3-10(a), there were no differences in the dissolution profiles between tablet with "small specific surface area and short blending time (small lubricity of lubricant) and table with "large specific surface area and long blending time (large lubricity of lubricant)." Therefore, the significance of the risk was low. On the other hand, in uncoated tablets with large granules size (granules shown in Figure 2.3.P.2.3-6 are used) or hard uncoated tablets, the dissolution rate was significantly slower as shown in Figure 2.3.P.2.3-10(b). Because the granule particle size and uncoated tablets hardness affect dissolution, the severity risk score was not decreased. Regarding the probability risk score of changing granule particle size and uncoated tablet hardness, the risk was not significantly reduced, based on the manufacturing history of the clinical tablets.



(a) Lubricant/lubricity of lubricant (b) Granule particle size/uncoated tablet hardness

Figure 2.3.P.2.3-10 Effect of lubricant/granule particle size/lubricity of lubricant/ uncoated tablets hardness on dissolution

Based on the above results, the RPNs from the FMEA for the p-CMA are shown in Figure 2.3.P.2.3-11 and Table 2.3.P.2.3-3, where the MAs with a high risk or medium risk were defined as CMA. Therefore, CMAs for each CQA were as follows:

Assay:	Uncoated tablet weight
Uniformity of dosage units:	Granule segregation, uncoated tablet weight, and tablet weight variation
Dissolution:	Drug substance particle size, granule particle size, and uncoated tablet hardness.

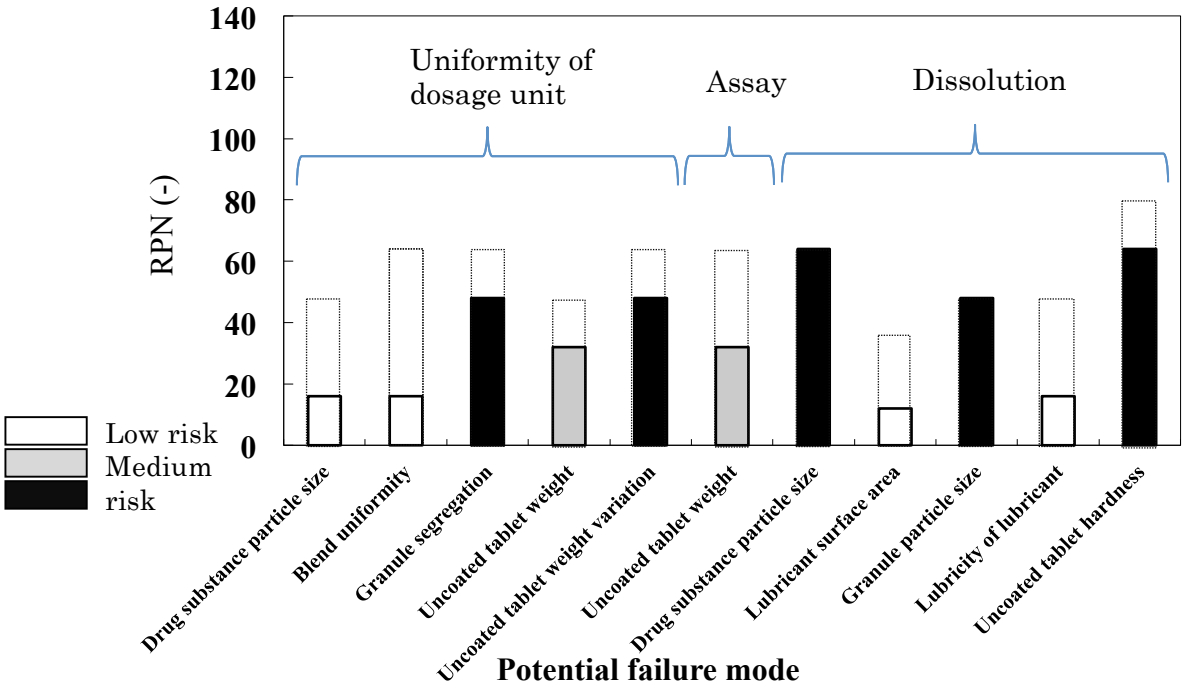


Figure 2.3.P.2.3-11 Results of FMEA risk assessment after manufacturing process development of Sakura Bloom Tablets

Note: A dot-lined rectangle represents the results of FMEA risk assessment.

Table 2.3.P.2.3-3 Results of FMEA risk assessment after manufacturing process development of Sakura Bloom Tablets (refer to Section 3.2.P.2.3 for details of score)

CQA	Potential failure mode	Effect	Severity	Probability	Detectability	RPN [a)]
Uniformity of dosage units	Drug substance particle size	Not uniform	1	4	4	16
	Blend uniformity	Not uniform	4	1	4	16
	Granule segregation	Not uniform	4	3	4	48
	Uncoated tablet weight	Not uniform	4	2	4	32
	Uncoated tablet weight variation	Not uniform	4	3	4	48
Assay	Uncoated tablet weight	Change in content	4	2	4	32
Dissolution	Drug substance particle size	Change in dissolution	4	4	4	64
	Lubricant surface area	Change in dissolution	1	3	4	12
	Granule particle size	Change in dissolution	3	4	4	48
	Lubricity of lubricant	Change in dissolution	1	4	4	16
	Uncoated tablet hardness	Change in dissolution	4	4	4	64

a) RPN of ≥40 is high risk, ≥20 and <40 is medium risk, and <20 is low risk.

Note: the values which were changed following the manufacturing process development are highlighted in gray.

2.3.P.2.3.3 Determination of CPPs affecting each CMA

2.3.P.2.3.3.1 Extraction of potential CPPs (p-CPPs)

Table 2.3.P.2.3-4 lists the Process Parameter (PP) that could potentially affect each identified CMA of Sakura Bloom Tablets in 2.3.P.2.3.2. Particle size of drug substance is a CMA for dissolution CQA, but the control of particle size of drug substance is performed during the drug substance process, thus it is not described in this section. The uncoated tablet weight is a common CMA for assay and uniformity of dosage units, thus the risk assessment was performed as a CMA for assay.

From the listed process parameters, p-CPPs were identified utilizing the knowledge gained through pharmaceutical development up to the phase III clinical studies (refer to Section 3.2.P.2.3 for details). Identified p-CPPs included inlet air volume, inlet air temperature, spray rate, tableting rotation speed, and compression force. Risk assessment was performed for these p-CPP using FMEA. The details of FMEA are shown in Section 3.2.P.2.3. As for the definition of risk priority number (RPN), ≥ 40 was high risk, ≥ 20 to < 40 was medium risk, and < 20 was low risk. As a result, as shown in Figure 2.3.P.2.3-12 and Table 2.3.P.2.3-5, every p-CPP extracted for each CMA was medium risk or high risk. The relation among QTPP, CQA, CMA and p-CPP was summarized in Figure 2.3.P.2.3-13 in the form of an Ishikawa diagram.

Table 2.3.P.2.3-4 Process parameters that can affect CMA

	Factor
Granulation	Spray rate, spray air volume, nozzle size, cap opening, inlet air temperature, exhaust air temperature, inlet air volume, mesh size (bug filter, bottom screen), charged amount, spray gun position, bug filter cleaning(shaking, pulse)
Blending	Blending time, rotation speed, charge-in quantity
Tableting	Compression force (main and pre-compression), tableting rotation speed, rotation speed of power assisted feeder, feeder type

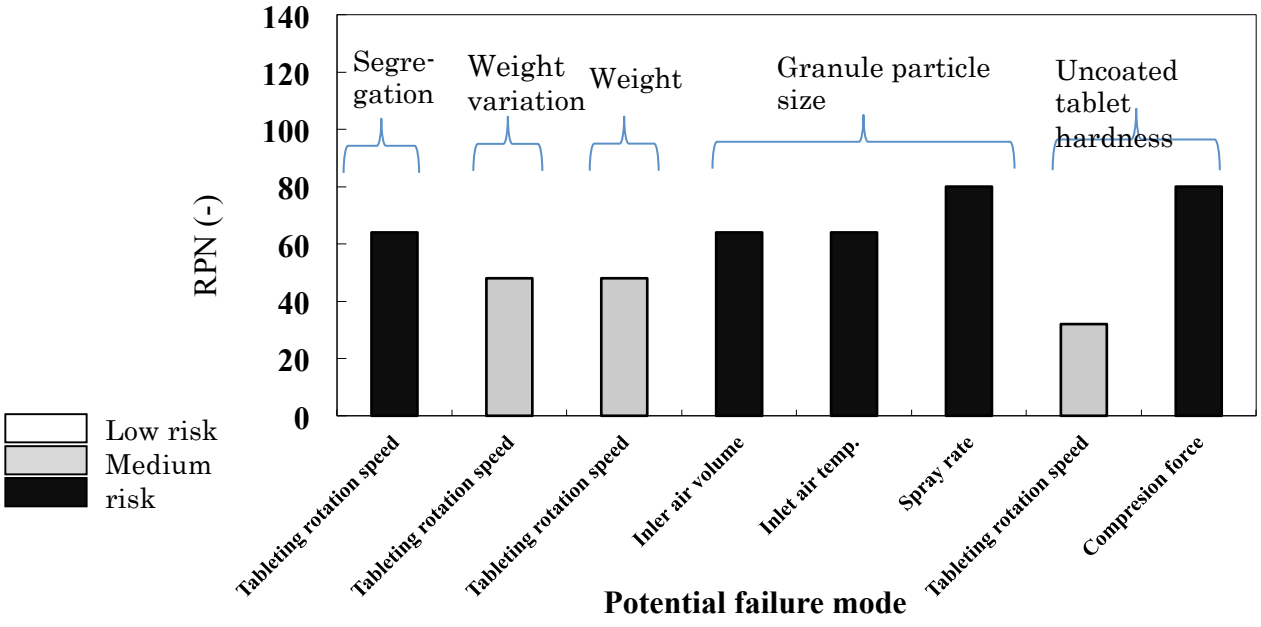


Figure 2.3.P.2.3-12 Results of FMEA risk assessment before manufacturing process development of Sakura Bloom Tablets

Table 2.3.P.2.3-5 Results of FMEA risk assessment before manufacturing process development for Sakura Bloom Tablets
(refer to Section 3.2.P.2.3 for details of score)

CQA	CMA	p-CPP	Severity	Probability	Detectability	RPN [a)]
Uniformity of dosage units	Granule segregation	Tableting rotation speed	4	4	4	64
	Uncoated tablet weight variation	Tableting rotation speed	4	3	4	48
Assay	Uncoated tablet weight	Tableting rotation speed	4	3	4	48
Dissolution	Particle size of drug substance	Refer to the drug substance process				
	Granule particle size	Inlet air volume	4	4	4	64
		Inlet air temperature	4	4	4	64
		Spray rate	5	4	4	80
	Uncoated tablet hardness	Tableting rotation speed	4	2	4	32
		Compression force	5	4	4	80

a) RPN of ≥ 40 is high risk, ≥ 20 and < 40 is medium risk, and < 20 is low risk.

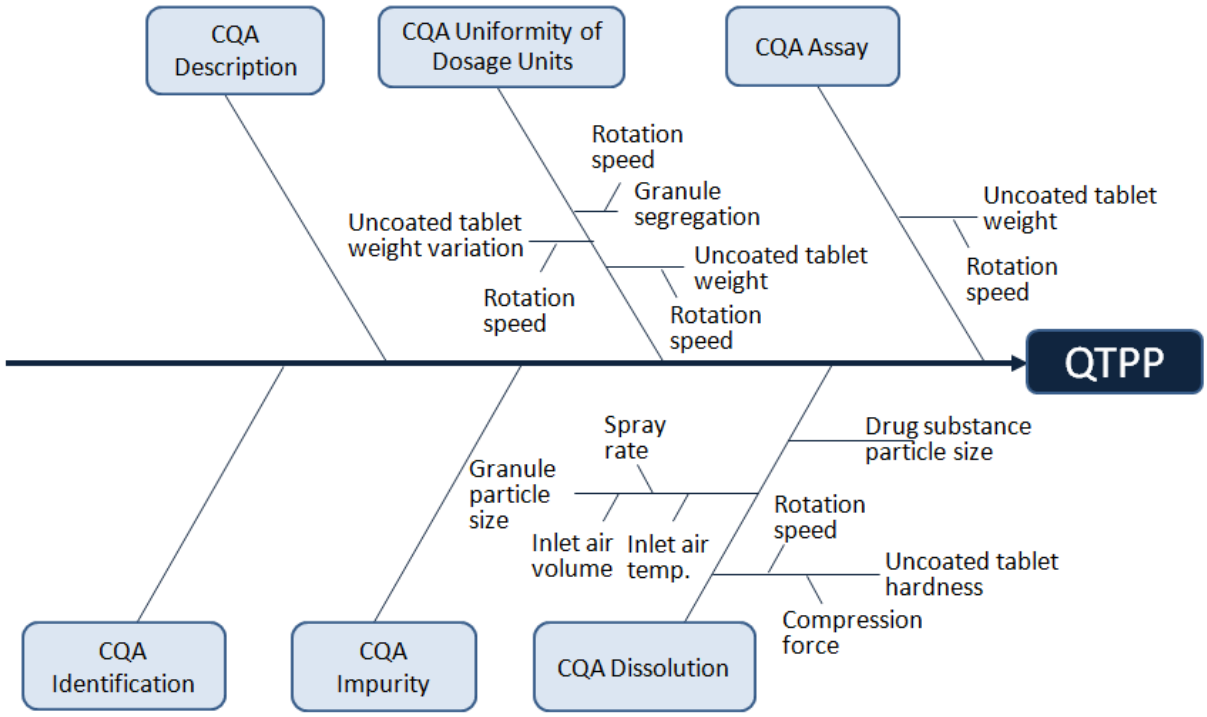


Figure 2.3.P.2.3-13 Relationship between QTPP, CQA, CMA, and p-CPP

2.3.P.2.3.3.2 Identification of CPP

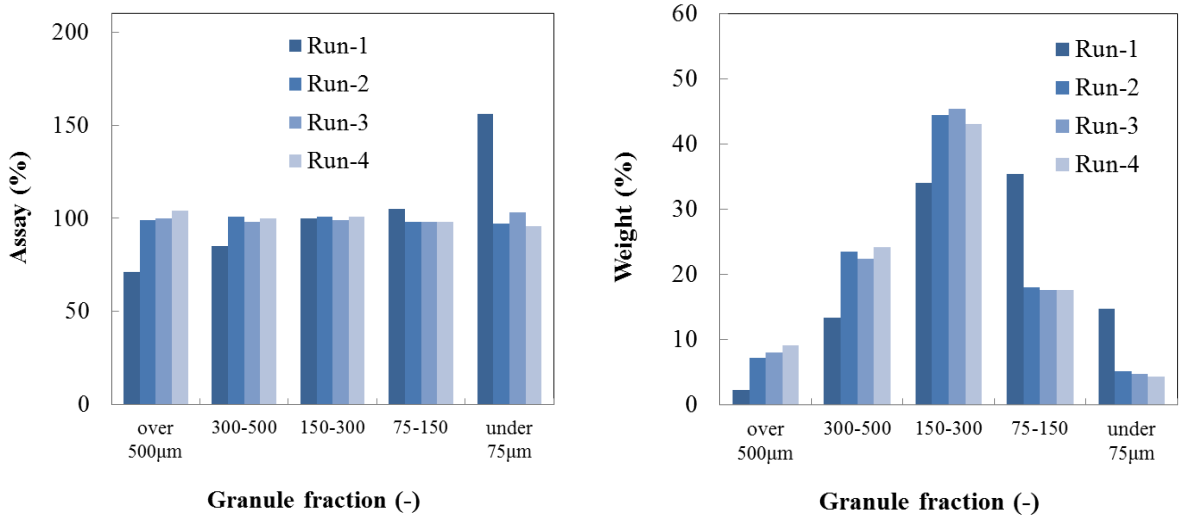
The effect of p-CPPs on CMAs was studied using mainly commercial production equipment.

Effects of tableting rotation speed on granule segregation (CMA)

Upon assessing the affect of tableting rotation speed on granule segregation (CMA), the affects of inlet air volume/inlet air temperature/spray rate on drug substance content of granules by particle size were assessed. Before investigation on a commercial scale, the effects of these variable factors on drug substance content in each fraction were assessed by laboratory scale experiments. As a result, the lower the water content in the granules as a result of the manufacturing conditions (high inlet air volume/high inlet air temperature/low spray rate), the smaller the granule particle size was, and the drug substance content in each fraction tended to be non-uniform. Then, fluid bed granulation was performed using a commercial scale fluid bed granulating machine, according to the design of experiments with L4 (2^3) orthogonal system shown in Table 2.3.P.2.3-6. As shown in Figure 2.3.P.2.3-14, under the manufacturing condition of Run-1, where low water content of granules was expected, the particle size was small and the drug substance content in each fraction was non-uniform, and the risk of segregation may be high as is the case in the laboratory scale experiments. Under the other conditions (Run-2 to Run-4), it was confirmed that granules with a uniform content were obtained regardless of the granule particle size.

Table 2.3.P.2.3-6 Design of experiments with L4 (2^3) orthogonal system

Run	Inlet air volume(m^3/min)	Inlet air temperature(°C)	Spray rate(g/min)
1	50	90	800
2	35	90	1200
3	50	70	1200
4	35	70	800



(a) Content of drug substance by granule particle size (b) Distribution of granulation granules

Figure 2.3.P.2.3-14 Drug substance content in each fraction of granules manufactured at commercial scale

The effects of tableting rotation speed on granule segregation (CMA) were studied on a tableting machine to be used for commercial production, using granules prepared by blending the granules produced above with lubricant. To remove the effects of weight variation, the content of the tablets was adjusted to the weight of a target tablet. As shown in Figure 2.3.P.2.3-15, uniformity was poorer for tablets produced from granules with a high risk of segregation (Run-1) at a rotation speed of 50 rpm of the tableting machine. Therefore, the severity risk score was not decreased, although the probability risk score, for affect of tableting rotation speed on granule segregation (CMA), was decreased.

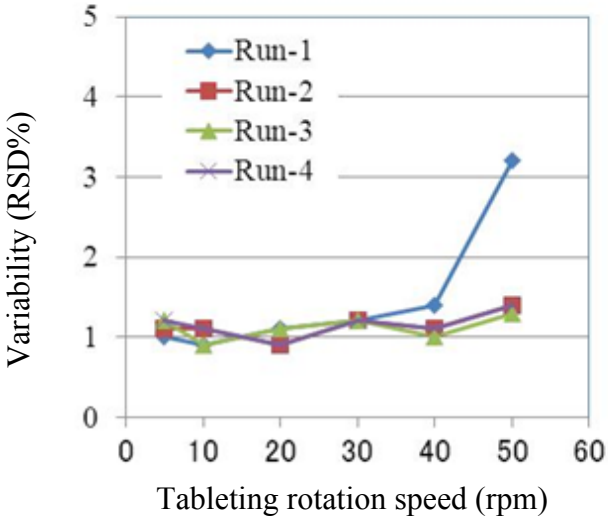


Figure 2.3.P.2.3-15 Relationship between tableting rotation speed and content variation

The affect of tableting rotation speed on the CMA of uncoated tablet weight variation was assessed using granules for tableting shown in Figure 2.3.P.2.3-14. As a result, as shown in 2.3.P.2.3-16, the tableting rotation speed did not affect weight variation in any granules for tableting. Also, the uncoated tablet weight was not affected by the rotation speed. Therefore, it was found that the severity risk score of the effects of a rotation speed on CMA uncoated tablet weight/uncoated tablet weight variation was low.

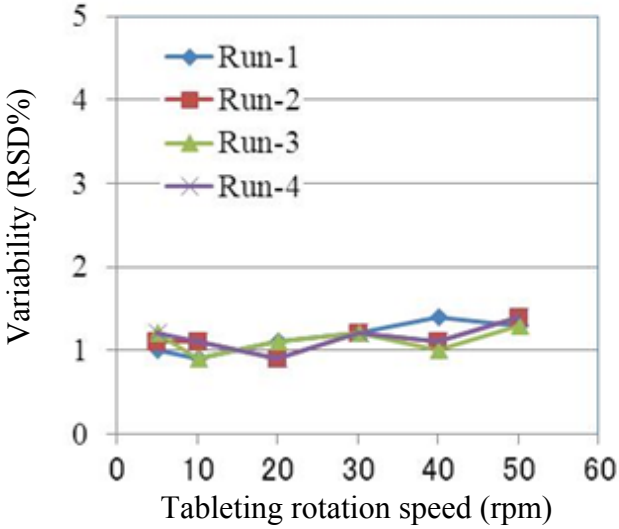


Figure 2.3.P.2.3-16 Relationship between tableting rotation speed and weight variation

Effects of inlet air volume/inlet air temperature/spray rate on CMA granule particle size

The affect of inlet air volume/inlet air temperature/spray rate in fluid bed granulation on granule particle size was assessed. Fluid bed granulation was performed at a production scale, based on the DoE with L4 (2^3) orthogonal system shown in Table 2.3.P.2.3-6. The particle size of the granules produced was analyzed with multiple linear regressions, and the affect of each parameter on the granule particle size were examined. As shown in Figure 2.3.P.2.3-17 and 2.3.P.2.3-18, all 3 factors affected the granule particle size, and spray rate had the greatest effect. Therefore, only the probability risk score in which inlet air volume/inlet air temperature affects the granule particle size was decreased, and the risk score of spray rate was not reduced.

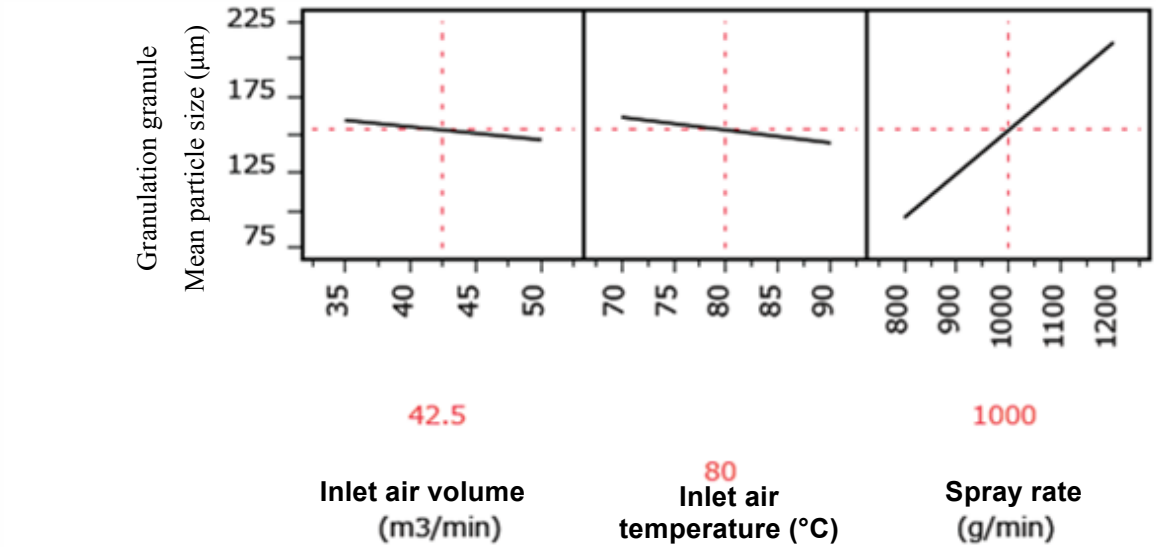


Figure 2.3.P.2.3-17 Effects of each process parameter on granule particle size

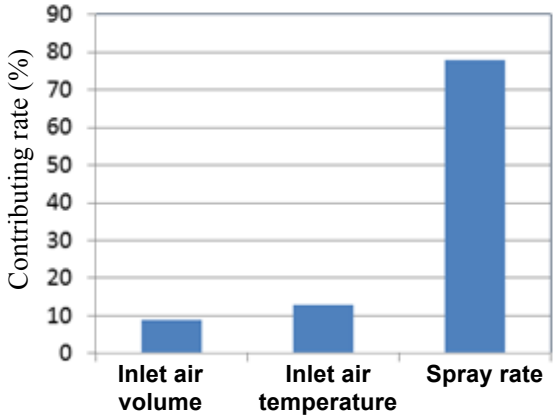


Figure 2.3.P.2.3-18 Contributing rate of each parameter on granule particle size

Effects of tableting rotation speed/Compression force on CMA uncoated tablet hardness

The affect of tableting rotation speed/compression force on the CMA uncoated tablet hardness was assessed using Run-2 granules shown in Figure 2.3.P.2.3-14. As a result, as shown in Figure 2.3.P.2.3-19, the tableting rotation speed did not affect the uncoated tablet hardness, but the compression force did. Even in the case of tableting at different rotation speeds, the rotation speeds used did not affect the compression force on hardness of the tablets, and no interaction was found between them, thus, only the compression force should be considered for the uncoated tablet hardness. Therefore, the risk score of the significance of the effects on uncoated tablet hardness was found to be low in terms of rotation speed, but not decreased in terms of compression force.

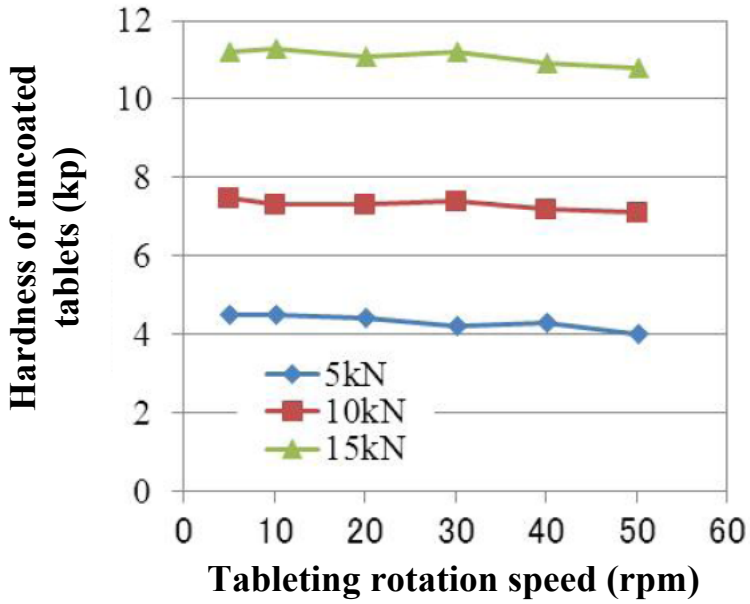


Figure 2.3.P.2.3-19 Effects of tableting rotation speed/compression force on uncoated tablet hardness

Based on the above results, the risk assessment after process development and the RPNs from the FMEA for p-CPP is shown in Figure 2.3.P.2.3-20 and Table 2.3.P.2.3-7. Here, the PPs with medium risk or high risk were defined as CPP. Therefore, the CPPs for each CMA were as follows.

Granule segregation:	Tableting rotation speed
(Uncoated tablet weight variation)	
(Uncoated tablet weight)	
Granule particle size:	Inlet air volume, inlet air temperature, spray rate
Uncoated tablet hardness:	Compression force

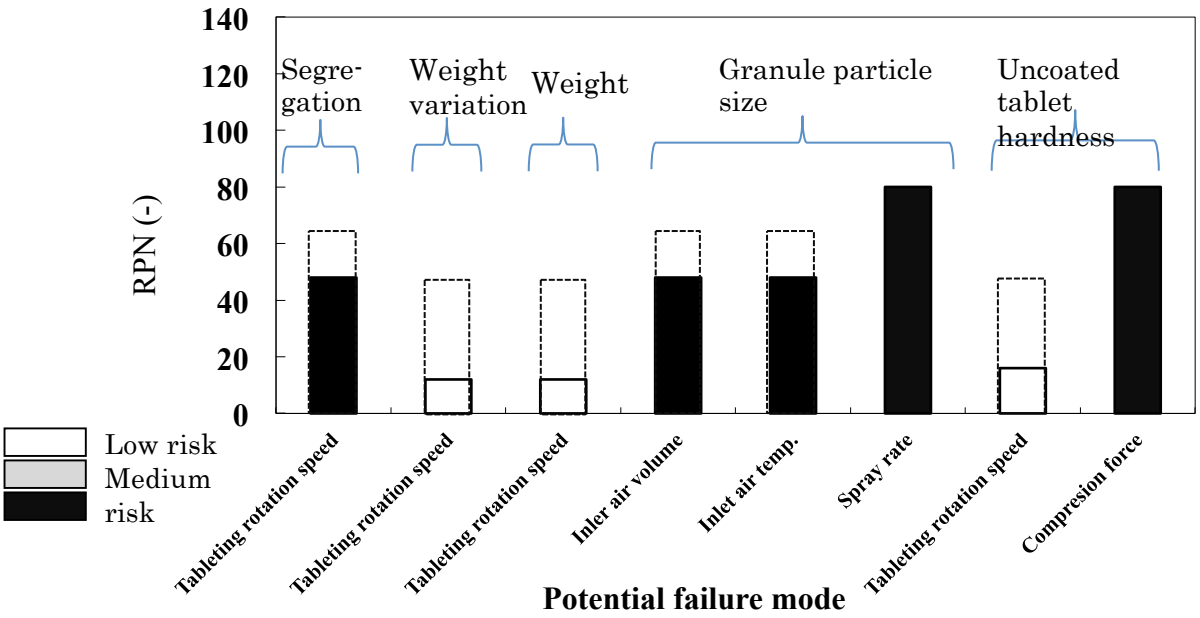


Figure 2.3.P.2.3-20 Results of FMEA risk assessment after manufacturing process development for Sakura Bloom Tablets

Note: A dot-lined rectangle represents the results of FMEA risk assessment..

Table 2.3.P.2.3-7 Results of FMEA risk assessment after manufacturing process development for Sakura Bloom Tablets (refer to Section 3.2.P.2.3 for details of score)

CQA	CMA	p-CPP	Severity	Probability	Detectability	RPN [a)]
Uniformity of dosage units	Granule segregation	Tableting rotation speed	4	3	4	48
	Uncoated tablet weight variation	Tableting rotation speed	1	3	4	12
Assay	Uncoated tablet weight	Tableting rotation speed	1	3	4	12
Dissolution	Particle size of drug substance	Refer to the drug substance process				
	Granule particle size	Inlet air volume	4	3	4	48
		Inlet air temperature	4	3	4	48
		Spray rate	5	4	4	80
	Uncoated tablet hardness	Tableting rotation speed	2	2	4	16
		Compression force	5	4	4	80

a) RPN of ≥40 is high risk, ≥20 and <40 is medium risk, and < 20 is low risk.

Note: where a value was changed following manufacturing process development ishighlighted in gray

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2.3.P.2.3.4 Construction of the control strategy

The relationship between each CMA/CPP, QTPP, and CQA of Sakura Bloom Tablets, which was defined in 2.3.P.2.3.2 and 2.3.P.2.3.3, is summarized in Figure 2.3.P.2.3-21 in the form of an Ishikawa diagram.

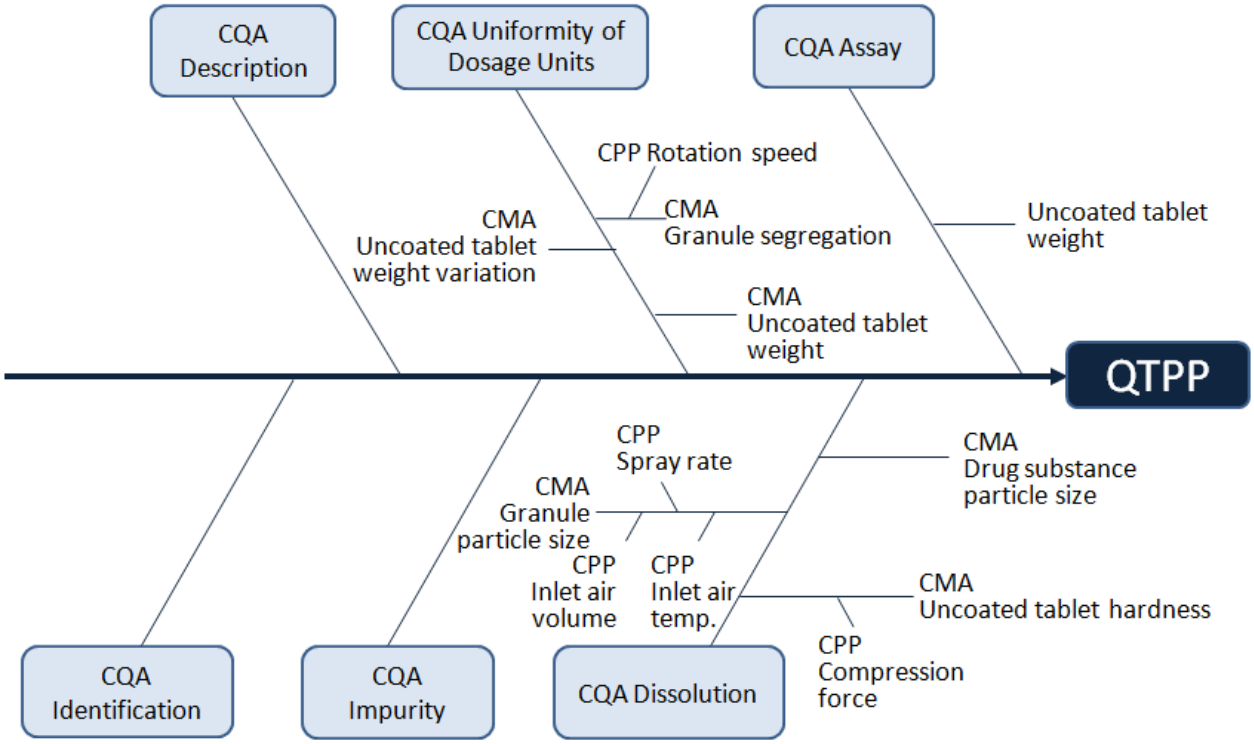


Figure 2.3.P.2.3-21 Relationship between QTPP, CQA, CMA, and CPP

The control strategy to assure each CQA is shown below.

2.3.P.2.3.4.1 uniformity of dosage units (CQA)

For the 3 CMAs affecting uniformity of dosage units (CQA), uncoated tablet weight and uncoated tablet weight variation are determined by in-process control, and granule segregation is monitored by determining drug substance concentrations of the uncoated tablet by an NIR method. If the results exceeded the threshold, PAT feedback control, which controls the rotation speed (CPP) is to be employed. As the drug substance concentration of uncoated tablets is determined in 200 or more tablets per batch, RTRT is to be performed in principle.

2.3.P.2.3.4.2 assay (CQA)

The CMA of uncoated tablet weight which affects assay (CQA) is to be controlled by in-process control. Because Sakura Bloom Tablets specific CPPs are not present, online monitoring control was employed for the compression force of every tablet through the tableting process, as generally performed. A compression force controller allows correction of the amounts of filled blended powder (filling depth) and removal of tablets out of the acceptable range from the system based on the information of compression force measured. In addition, a correcting system that adjusts the amounts of filled blended powder (filling depth) and compression force control equipment by means of the average weight information periodically measured by automatic sampling, and fed back to the tableting machine by weight control equipment is also used. As is the case in uniformity of dosage units, the drug substance concentration of uncoated tablets is determined in 200 or more tablets; thus, RTRT is to be performed using the mean data in principle.

2.3.P.2.3.4.3 Dissolution (CQA)

The granule particle size is controlled within a certain range in the following ways: 1) Particle size (CMA) of drug substance affecting dissolution (CQA) is a specification item for drug substance, 2) Uncoated tablet hardness (CMA) is controlled by feedback of CPP compression force, 3) Granule particle size (CMA) is monitored using Focused Beam Reflectance Measurement (FBRM), and 4) CPP of spray rate that mostly affects the granule particle size is controlled by PAT feedback.

Regarding uniformity of dosage units and content of drug substance, RTRT is to be performed by determining the drug substance content in uncoated tablets after tableting in principle. On the other hand for dissolution, because a factor controlling CMA covers 2 or more unit processes, feedforward control can be employed from the upstream to the downstream in the manufacturing process. Thus, dissolution prediction formula can be constructed using 3 CMA values, and the dissolution is controlled by establishing design space consisting of these 3 CMA to make feedforward control easy.

Figure 2.3.P.2.3-22 shows the design of experiments performed on a laboratory scale, when preparing the response aspect of dissolution. For experiments, a central composite design was employed.

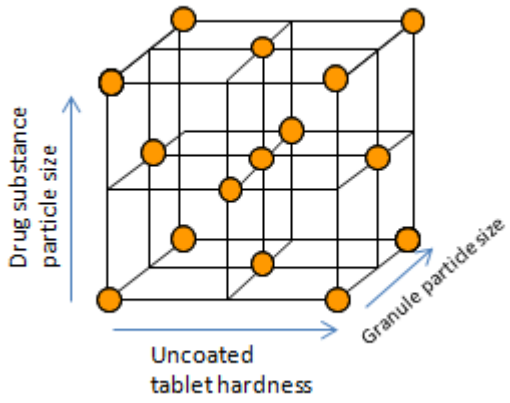


Figure 2.3.P.2.3-22 Dissolution DoE, central composite design

Dissolution test was performed for the drug product manufactured under the conditions allocated by DoE, and the affect of each factor on the dissolution rate were investigated. The test results were subjected to multidimensional analysis. For the formula for the sum of each factor which is multiplied by a coefficient, the coefficients that make the residual sum of squares minimum were calculated (the formula is shown below).

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

To verify the validity of the formula, each CMA (particle size of drug substance, granule particle size, uncoated tablet hardness; refer to Table 2.3.P.2.3-8) of the formulation produced at pilot scale (20 kg) and at commercial scale (200 kg) was input into the formula, and the predicted values and the actual values were compared. As a result, as shown in Figure 2.3.P.2.3-23, error in prediction, i.e., Root Mean Square Error of Prediction (RMSEP) was 1.6%, showing good agreement. Based on the above results, the formula for dissolution prediction, which was established by DoE at a laboratory scale, was found to be applicable at pilot scale or commercial scale.

Table 2.3.P.2.3-8 Sample for verification of dissolution model

Scale	Particle size of drug substance × 50 (μm)	Granule particle size (μm)	Uncoated tablet hardness (kN)
Pilot (20 kg)	9.8	102	3.9
			7.1
			11.2
	20.2	147	3.8
			7.2
			11.1
	38.9	202	4.0
			7.2
			11.3
Production (200 kg)	10.1	99	3.7
			7.1
			11.1
	19.3	151	3.6
			7.0
			11.0
	19.3	148	3.9
			7.2
			11.4
	40.2	197	3.8
			7.1
			11.2

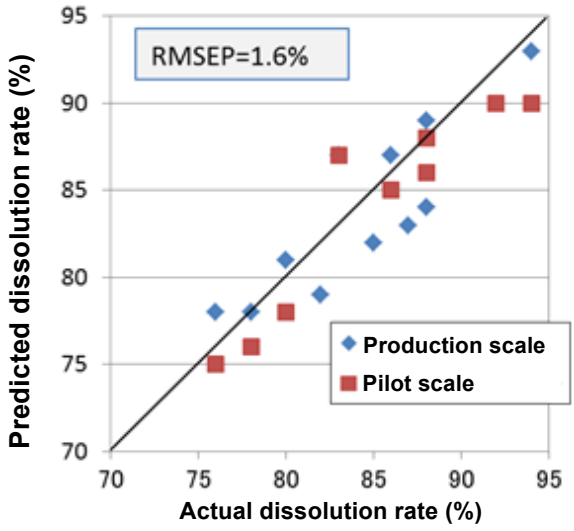


Figure 2.3.P.2.3-23 Fitting verification for the formula of dissolution model

Based on this formula, the response surface is shown in Figure 2.3.P.2.3-24. The cuboid, defines an area that satisfies 80% or more of the dissolution rate (predicted value), specification, was employed to define a design space to assure the dissolution of Sakura Bloom Tablets.
A feedforward control will be used in commercial production to ensure that the dissolution rate is about 90%. In other words, a control to keep the predicted dissolution value constant is established made by appropriately determining the target value for "granule particle size (CMA)" and "uncoated tablet hardness (CMA)" within

this design space, according to the particle size of drug substance obtained in the drug substance process. The overview is shown in Figure 2.3.P.2.3-25.

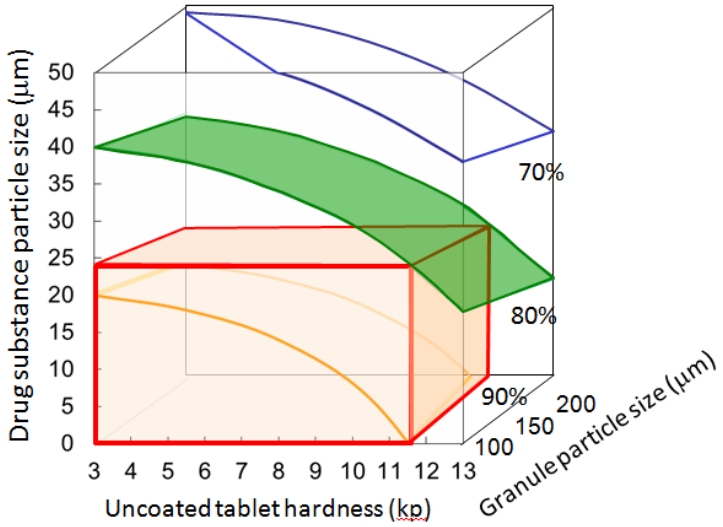


Figure 2.3.P.2.3-24 Design space to assure dissolution CQA (red cuboid)

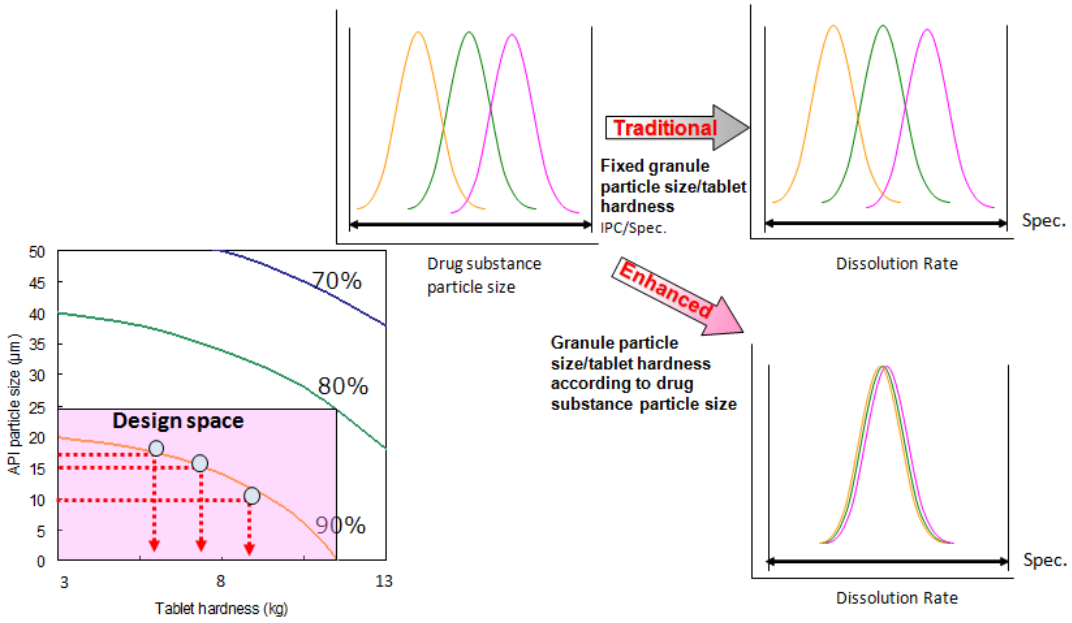


Figure 2.3.P.2.3-25 Overview of feedforward control of dissolution

2.3.P.2.3.4.4 Specifications except for CQA

For identification, it is considered possible to apply an alternative test, by applying an NIR method as an in-process control in the inspection process, and by using a discriminating model constructed by a spectrum in the wavenumber domain indicating the specific peaks of the drug substance. Furthermore, for the description (appearance) it is also considered possible to apply an alternative test as an in-process control in the inspection process.

2.3.P.2.3.5 Review of the risk assessment after implementation of the control strategy

By applying the above control strategy, the risk of each CMA (Figure 2.3.P.2.3-26, Table 2.3.P-2.3-9) and CPP (Figure 2.3.P.2.3-27, Table 2.3.P-2.3-10) was as follows, and all CMA/CPPs were found to be low risk.

2.3.P.2.3.5.1 Risk assessment of CMA

Granule segregation

The risk score of probability was decreased and the detectability was improved as well, by establishing an appropriate acceptable range for the tableting rotation speed (CPP), by measuring the content of uncoated tablets with an NIR method during tableting in real time, with a feedback loop to the CPP tableting rotation speed.

Uncoated tablet weight/weight variation

The detectability was improved by establishing in-process control. Although the tableting rotation speed affected the uncoated tablet weight/weight variation during the laboratory scale test, rotation speed did not affect uncoated tablet weight/weight variation using a commercial production machine, resulting the risk score of probability decreasing.

Particle size of drug substance

As shown in Section 2.3.S.2, the risk score of probability was decreased and the detectability was improved as well, by establishing an appropriate acceptable range for rotation speed of milling and setting a specification for particle size of the drug substance.

Granule particle size

The risk score of probability was decreased and the detectability was improved as well, by establishing an appropriate acceptable range for spray rate (CPP), by measuring the granule particle size at granulation in real time, with the feedback loop to CPP spray rate, and by defining a design space including granule particle size.

Uncoated tablet hardness

The risk score of probability was decreased and the detectability was improved as well, by establishing an appropriate acceptable range for compression force (CPP), with the feedback loop to CPP compression force during tableting in real time, and by defining a design space including uncoated tablet hardness.

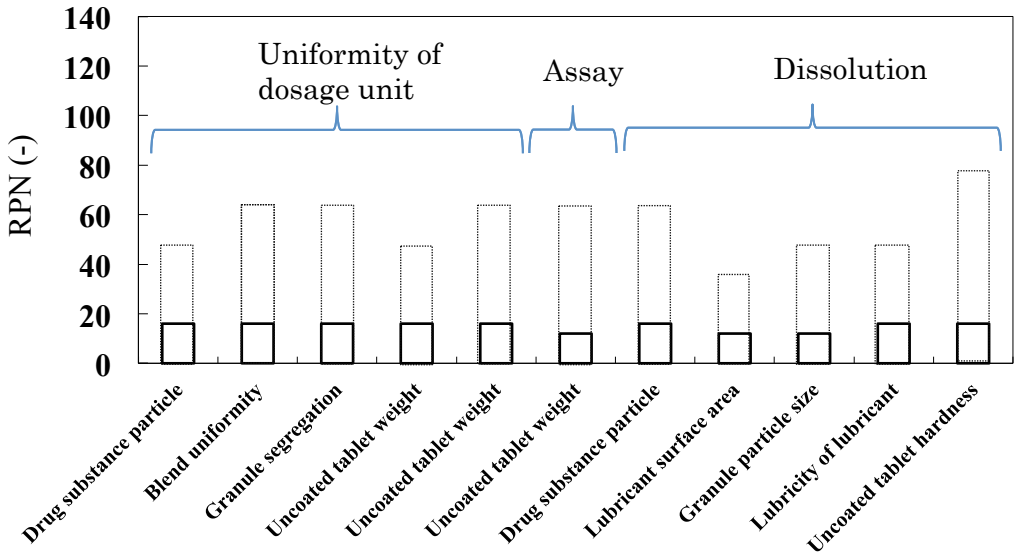


Figure 2.3.P.2.3-26 Results of FMEA risk assessment after applying CMA control strategy for Sakura Bloom Tablets

Note: A dotted line rectangle represents the results of FMEA risk assessment before manufacturing process development.

Table 2.3.P.2.3-9 Results of FMEA risk assessment after applying CMA control strategy for Sakura Bloom Tablets (refer to Section 3.2.P.2.3 for details of score)

CQA	Potential failure mode	Effect	Severity	Probability	Detectability	RPN [a)]
Uniformity of dosage units	Particle size of drug substance	Not uniform	1	4	4	16
	Blend uniformity	Not uniform	4	1	4	16
	Granule segregation	Not uniform	4	2	2	16
	Uncoated tablet weight	Not uniform	4	1	3	12
	Uncoated tablet weight variation	Not uniform	4	2	2	16
Assay	Uncoated tablet weight	Change in content	4	1	3	12
Dissolution	Particle size of drug substance	Change in dissolution	4	2	2	16
	Lubricant surface area	Change in dissolution	1	3	4	12
	Granule particle size	Change in dissolution	3	2	2	12
	Lubricity of lubricant	Change in dissolution	1	4	4	16
	Uncoated tablet hardness	Change in dissolution	4	2	2	16

a) RPN of ≥ 40 is high risk, ≥ 20 and < 40 is medium risk, and < 20 is low risk.
Note: the places where a value was changed after applying control strategy were highlighted with a gray color.

2.3.P.2.3.5.2 Risk assessment of CPP

Tableting rotation speed

The risk score of probability was decreased and the detectability was improved as well, by establishing an appropriate acceptable range and measuring the content of uncoated tablets with an NIR method, and using the feedback loop to CPP tableting rotation speed.

Inlet air volume

The risk score of probability was decreased and the detectability was improved as well, by establishing an appropriate acceptable range and measuring the granule particle size at granulation, and using the feedback loop to CPP spray rate.

Inlet air temperature

The risk score of probability was decreased and the detectability was improved as well, by establishing an appropriate acceptable range and measuring the granule particle size at granulation, and using the feedback loop to CPP spray rate.

Spray rate

The risk score of probability was decreased and the detectability was improved as well, by establishing an appropriate acceptable range and measuring the granule particle size at granulation, and using the feedback loop to CPP spray rate.

Compression force

The risk score of robability was decreased and the detectability was improved as well, by establishing an appropriate acceptable range and using the feedback loop to the CPP compression force during tableting.

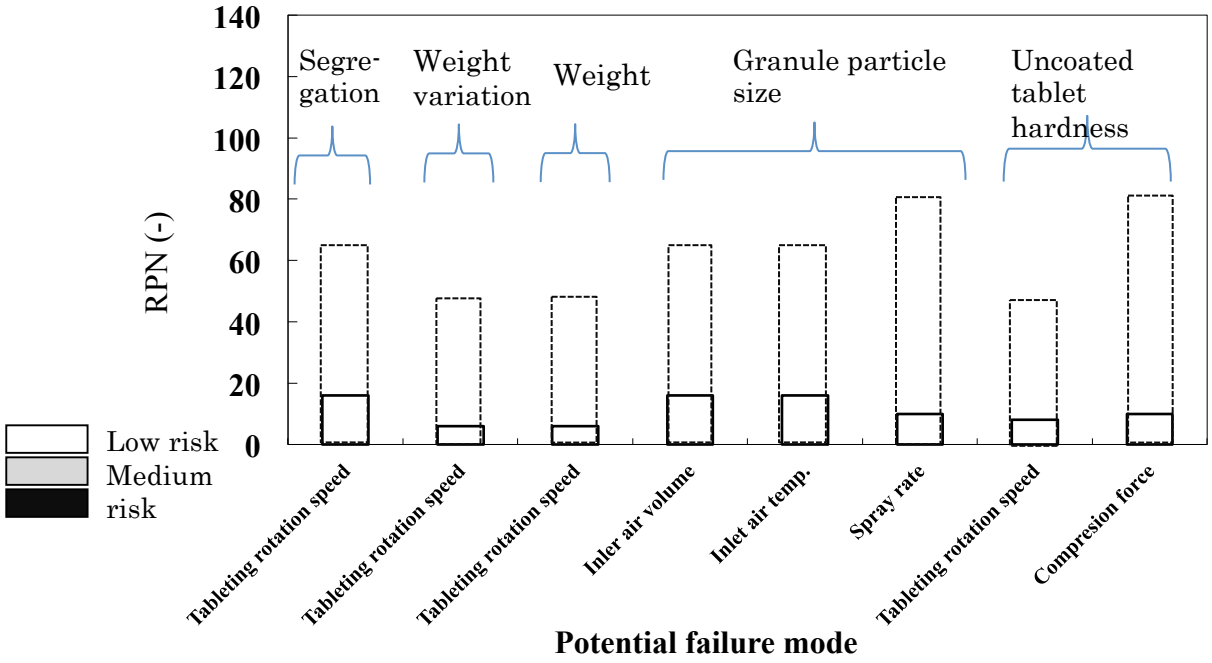


Figure 2.3.P.2.3-27 Results of FMEA risk assessment after applying CPP control strategy for Sakura Bloom Tablets

Note: A dot-lined rectangle represents the results of FMEA risk assessment.

Table 2.3.P.2.3-10 Results of FMEA risk assessment after applying CPP control strategy for Sakura Bloom Tablets (refer to Section 3.2.P.2.3 for details of score)

CQA	CMA	p-CPP	Severity	Probability	Detectability	RPN [a)]
Uniformity of dosage units	Granule segregation	Tableting rotation speed	4	2	2	16
	Uncoated tablet weight variation	Tableting rotation speed	1	2	2	4
Assay	Uncoated tablet weight	Tableting rotation speed	1	2	2	4
Dissolution	Particle size of drug substance	Refer to the drug substance process				
	Granule particle size	Inlet air volume	4	2	2	16
		Inlet air temperature	4	2	2	16
		Spray rate	5	2	1	10
	Uncoated tablet hardness	Tableting rotation speed	2	1	2	4
		Compression force	5	2	1	10

a) RPN of ≥ 40 is high risk, ≥ 20 and < 40 is medium risk, and < 20 is low risk.

Note: the columns where a value was changed after applying control strategy are highlighted in gray

2.3.P.2.3.5.3 Overall evaluation of risk assessment

As part of the risk assessment after applying the control strategy, we verified the items that were considered to be low risk at initial risk assessment (Figure 2.3.P.2.3-2), and for which no more examination was made.

Description and identification

As shown in sections of "2.3.P.5 Control of Drug Product" and "2.3.P.8 Stability," differences in production scale, batch of drug substance, batch of excipients, or manufacturing conditions did not affect the description (appearance) and identification, from the stability test results of clinical tablets and formulations for the NDA (pilot scale) and the results of manufacture in commercial scale production. It was thus concluded that the affect of manufacturing processes on these attributes was minimal and they have a low risk.

Impurity

For impurity, as shown in sections "2.3.P.5 Control of Drug Product" and "2.3.P.8 Stability", related impurities in the drug product were not produced/increased during formulation and storage (including stress testing). It was thus found that the affect of the manufacturing processes on impurity was minimal and they have a low risk.

Uniformity of dosage units and assay

We verified the items that were considered to be low risk at initial risk assessment shown in Figure 2.3.P.2.3-2.

- ✓ To assess the affect of drug substance on content, we examined the content of the drug product having drug substance with different particle sizes, as shown in Figure 2.3.P.2.3-5. As a result, the particle size of drug substance was confirmed not to affect the content.
- ✓ To assess the affect of excipients on uniformity of dosage units and assay, the uniformity of dosage units and assay were examined in the drug products manufactured by DoE at each experimental point. As a result, it was confirmed that there were no differences in uniformity of dosage units and assay at all experimental points. Since the formulations for the NDA, which were prepared with even different batches of excipients, and the manufacturing experience on a commercial scale did not matter, it was confirmed that excipients do not affect the uniformity of dosage units and assay.
- ✓ The affect of the granulation process on uniformity of dosage units and assay was examined. As shown in "2.3.P.2.3.2.2 Identification of CMA" and "2.3.P.2.3.3.2 Identification of CPP," it was found that only inappropriate tableting affects the uniformity of dosage units and assay, under the granulation conditions where the drug substance content in each fraction is non-uniform. Since it is obvious that these risks can be controlled by applying the control strategy shown in Section 2.3.P.2.3.4, they were confirmed to be low risk.
- ✓ With respect to the affect of the blending process on content, the blending process was confirmed to have a low risk, because there was no content reduction such as loss of drug substance in the blending process, in any of the drug products shown in "2.3.P.2.3 Manufacturing Process Development."
- ✓ As for the risk that the coating process affects the uniformity of dosage units and assay, a case was considered where damage or degradation of tablets affects the content in the coating process. However, none of the two cases was observed through the manufacturing experiences, and the coating process was confirmed to have a low risk.

Based on the above results, it was verified that the items that were considered to be low risk in the initial risk assessment, following an overall evaluation of the risk assessment, had a low risk.

2.3.P.2.4 Container Closure System

In a stability test, tablets adsorbed water at a maximum of 3% under the high humidity condition of ≥ 75%RH. Afterwards, packaging/vapour permeation test confirmed that PTP/Al (polypropylene on one side and aluminum foil on the other side) and bottle (polyethylene bottle + plastic cap) packagings could control water adsorption to ≤ 3%. From the results of the stability study and evaluation of the design space, it was estimated that Sakura Bloom Tablets manufactured in the range of the design space and packed in the PTP/Al and bottle was stable for not less than 36 months.

2.3.P.2.5 Microbiological Attributes

Microbial limit testing was set. However, the testing by each release test is not considered necessary because of the following reasons.

- Prunus has no propensity to promote microbial growth.
- Water and excipients used in drug product manufacturing meet JP.
- Microbial Limit Test JP is performed in every 10 batches.

2.3.P.2.6 Compatibility

Not applicable because the final product is a tablet.

2.3.P.3 Manufacture

2.3.P.3.3 Manufacturing Process and Process Control

Figure 2.3.P.3.3-1 shows the process flow of the drug product manufacturing process in commercial production of Sakura Bloom Tablets. Equipment used for the manufacturing process in commercial production will be identical to or have the same principle as the equipment used at the development stage. The manufacturing processes having CMA and CPP that should be controlled to assure the CQAs shown in "2.3.P.2.3.4 Construction of control strategy," i.e., Process 1 (granulation process) and Process 3 (tableting process) were considered as critical steps.

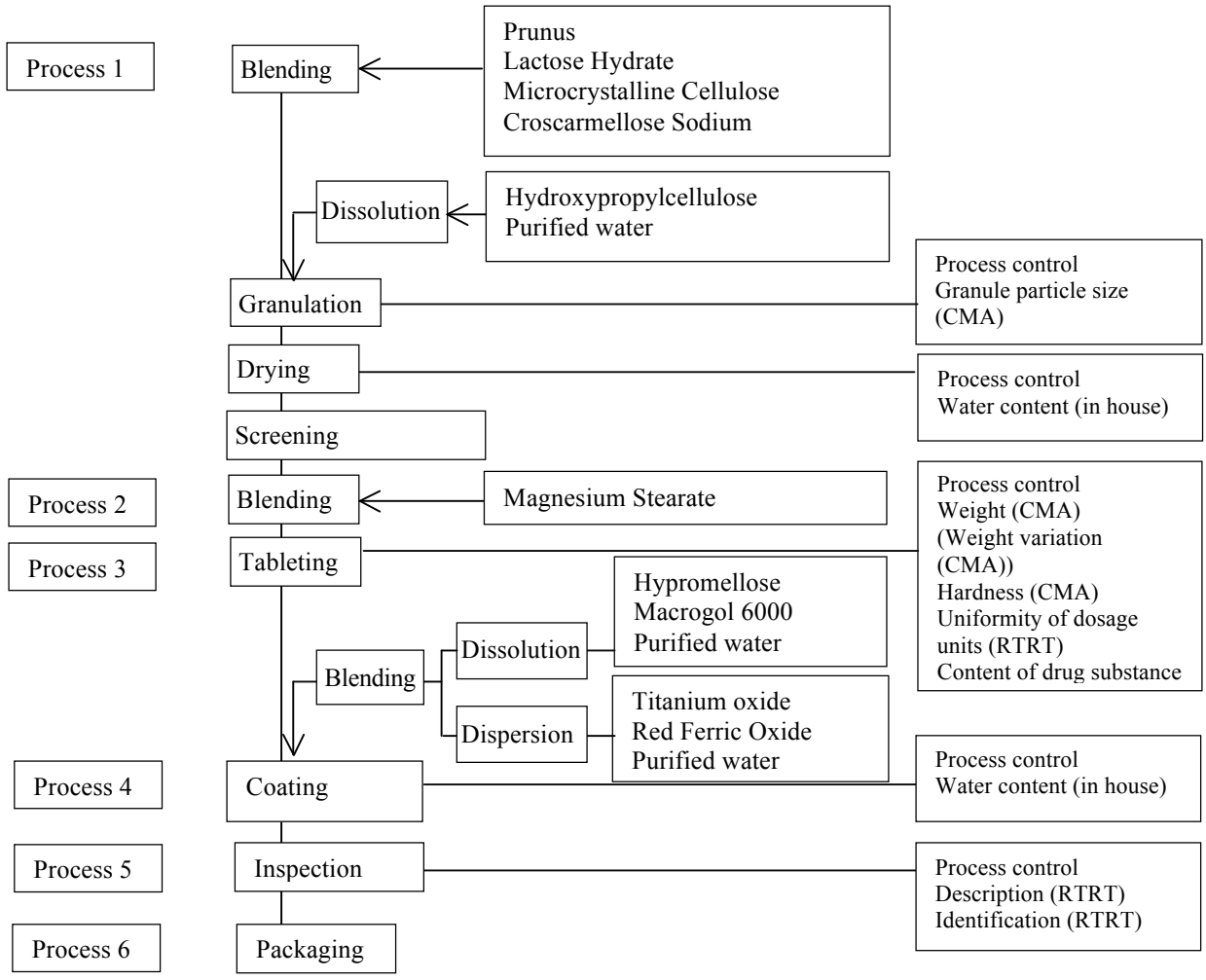


Figure 2.3.P.3.3-1 Overview of manufacturing processes for Sakura Bloom Tablets

<Detail manufacturing process description is omitted in this mock-up>

2.3.P.3.3.1 Manufacturing Parameters and Criteria

Target values/set values in commercial production are shown in Table 2.3.P.3.3-1. These values were set based on the performance assessment conducted by manufacturing of the proposed drug product at pilot scale and commercial scale, and experiences of production in performance qualification. These values will be verified in commercial scale validation and reviewed, as appropriate.

Table 2.3.P.3.3-1 Process parameters of each manufacturing process for Sakura Bloom Tablets and justification
(The reasons in the case of no setting or notification matter) (1/2)

Process	Items	Application Form (Notification matter)	Product master formula etc. (Control range)	Proven Acceptable Range (PAR) and its study scale	Reason/rationale for including in the Application Form or the reason why these are not described in the Application Form.
<Process 1> Granulation process Critical step	Inlet air volume	-	40-45 m^3/min	35-50 m^3/min (Commercial scale)	Inlet air volume is a CPP, but has small effects on CMA granule particle size, and the PAR is assured within a wide range, and the particle size of granules is determined in real time during granulation and the CMA can be appropriately controlled by the feedback control to CPP spray rate. Thus, these manufacturing process parameters were not included in the Application Form.
	Inlet air temperature	-	75-85°C	70-90°C (Commercial scale)	Inlet air temperature is a CPP, but has small effects on the CMA granule particle size, and the PAR is assured within a wide range, and the particle size of granules is determined in real time during granulation and the CMA can be appropriately controlled by the feedback control to CPP spray rate. Thus, these manufacturing process parameters were not included in the Application Form.
	Spray rate	"900-1100 g/min"	900-1100 g/min	800 to 1200 g/min (Commercial scale)	Spray rate is a CPP and has large effects on the CMA, but the PAR is assured within a wide range, and the particle size of granules is determined in real time during granulation and the CMA can be appropriately controlled by the feedback control to the CPP spray rate. Thus, these minor change notification items were included in the Application Form.
<Process 2> Blending Process	Blending time	-	10 minutes	5 to 20 minutes (Commercial scale) 5 to 30 minutes (Pilot scale)	Blending time did not affect the CQA/CMA with a wide range. Therefore, this manufacturing process parameter was not included in the Application Form.
	Rotation speed	-	20 rpm	20 rpm (Commercial scale)	Blending time did not affect the CQA/CMA with a wide range. Therefore, this manufacturing process parameter was not included in the Application Form because it is considered that rotation speed does not affect the CQA/CMA.

- : Not described in the Application Form

Table 2.3.P.3.3-1 Process parameters of each manufacturing process for Sakura Bloom Tablets and justification
(The reasons in the case of no setting or notification matter) (2/2)

Process	Items	Application Form (Notification matter)	Product master formula etc. (Control range)	PAR and its study scale	Reason/rationale for including in the Application Form or the reason why these are not described in the Application Form.
<Process 3> Tableting Process Critical step	Tableting Rotation Speed	-	20-30 rpm	5-50 rpm (Commercial scale)	Rotation speed of tableting is a CPP, but has small effects on the CMA uniformity of dosage units and the PAR is assured within a wide range, and the granule segregation (CMA) can be appropriately controlled by feedback control of changing rotation speed in the case of abnormal values of the content of tablets examined by an on-line NIR method during tableting. Thus, these manufacturing process parameters were not included in the Application Form.
	Compression force	"6-14 kN"	6-14 kN	5-15 kN (Commercial scale)	Compression force is a CPP and has large effects on the CMA, but the PAR is assured within a wide range, and Uncoated tablet hardness (CMA) can be appropriately controlled by feedback control to compression force in real time during tableting. Thus, these minor change notification items were included in the Application Form.
<Process 4> Coating process	Inlet air temperature	-	70-80°C	70-80°C (Commercial scale)	Because the coating process does not affect the CQA/CMA, these manufacturing process parameters were not included in the Application Form.
	Inlet air volume	-	40-45 m^3/min	40-45 m^3/min (Commercial scale)	Because the coating process does not affect the CQA/CMA, these manufacturing process parameters were not included in the Application Form.
	Spray rate	-	280-420 g/min	280-420 g/min (Commercial scale)	Because the coating process does not affect the CQA/CMA, these manufacturing process parameters were not included in the Application Form.
	Pan rotation speed	-	2.0-6.0 rpm	2.0-6.0 rpm (Commercial scale)	Because the coating process does not affect the CQA/CMA, these manufacturing process parameters were not included in the Application Form.
<Process 5> Inspection process	Omission of description				
<Process 6> Packaging process					

- : Not described in the Application Form

2.3.P.3.3.2 Control Method

Based on the control strategy described in Section 2.3.P.2.3.3, each CQA of assay, uniformity of dosage units, and dissolution, and other specification item CQAs were controlled as shown in Table 2.3.P.3.3-2.

Table 2.3.P.3.3-2 Relationship among CQA and monitoring process and material attributes

CQA	Process	CMA (control item)	Control Method	Control range
Assay	Tableting	Uncoated tablet weight	In-process control	Mean value is within a range of 194 mg ± 3%.
Uniformity of dosage units	Tableting	Uncoated tablet weight variation Granule segregation	In-process control and feedback control of rotation speed of tableting by concentrations of drug substance in uncoated tablets (NIR methods)	Each value is within a range of 90.0% to 110.0%. If the value is out of the range, a feedback control is made.
Dissolution*	(Drug Substance)	(Particle size)	It is controlled in three-dimensional design space so that the dissolution is about 90% (feedback control of spray rate by FBRM, compression force control by compression force controller).	25 μm or less*
	Granulation	Granule particle size		90-210 μm *
	Tableting	Hardness		3-11.5 kp *
Description	Inspection	(Appearance)	Visual observation	-
Identification	Inspection	(Identification)	Identification using an NIR method	-

Process control range of the uncoated tablet weight was set to "the mean mass is within a range of 194 mg ± 3%." To ensure the specification for Assay is met, the range of process control of mass was set to be narrower than that of the specification for Assay, because the specification for Assay is "95.0% to 105.0%."

The range of process control of uniformity of dosage units was set to "each value is within 90% to 110%." Because the specification of uniformity of dosage units is "the number of tablets exceeding the range of 85.0% to 115.0% is 6 or less," the control range of each value was set to be 90% to 110.0%, narrower than 85% to 115.0%. Establishment of the know-how of feedback control in the case of being out of range would make it possible to ensure a good test of uniformity of dosage units. The CMA of uncoated tablet weight variation has been judjed no need to be controlled since the individual tablet assay value calculated by API content in uncoated tablets and the tablet weight is controlled during tableting process.

* With respect to dissolution, as shown in "2.3.P.2.3.4.3 Dissolution (CQA)," RTRT will be performed based on the dissolution prediction formula (shown below) using the parameters of particle size of drug substance, granule particle size, and uncoated tablet hardness.

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

Figure 2.3.P.3.3-2 shows the response surfaces prepared based on this formula. The cuboid consisting of straight lines within an area that satisfies 80% or more of dissolution rate (specification, see 2.3.P.5) was employed as a design space to assure the dissolution of Sakura Bloom Tablets. A feedforward control will be performed as an operation in commercial production so that the dissolution rate is about 90%. In other words, a control to keep the predicted dissolution value being always constant will be made by appropriately determining the target value for a granule particle size and uncoated tablet hardness within this design space according to the particle size of drug substance.
<The design space may be shrinked when the prediction error in the dissolution prediction formula is taken into account.>

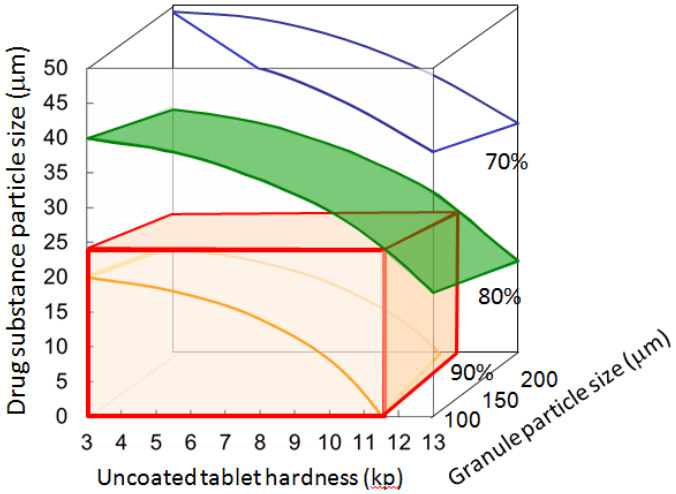


Figure 2.3.P.3.3-2 Response surfaces based on the dissolution prediction formula

2.3.P.3.3.3 Monitoring of Quality Attribute

Based on the control method of Section 2.3.P.3.3.2, quality attributes were to be monitored by the Large-N method, in which content of tablets at tableting is determined with an NIR method, as RTRT of Assay and uniformity of dosage units. For dissolution, RTRT was to be performed based on the dissolution prediction formula, which consists of particle size of drug substance, granule particle size, and uncoated tablet hardness.

2.3.P.3.3.3.1 Granulation process

FBRM was employed as a method to monitor the granule particle size, which is a CMA for dissolution. The measurement conditions of FBRM were assessed by evaluating the position of the sensor and measurement conditions, and the conditions were set as below: Figure 2.3.P.3.3-3 shows the overview.

Equipment: FBRM: C35
Position of the sensor: Side panel of the container of the fluid bed granulator.
Diameter of the measurement probe: φ35 mm
Measurement interval: 5 s

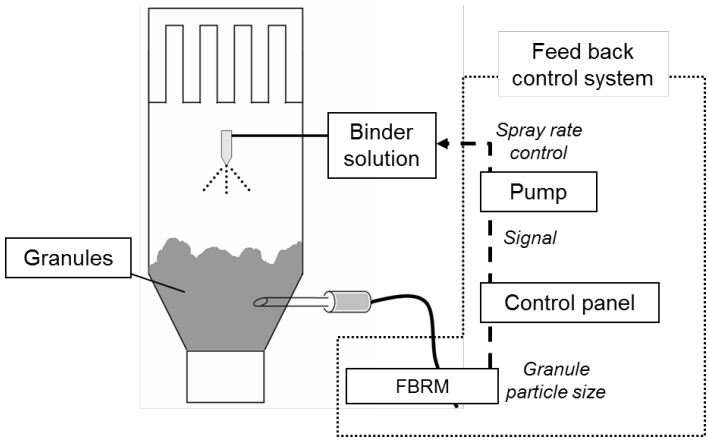


Figure 2.3.P.3.3-3 Overview of the feedback control of fluid bed.

The change in particle size over time during granulation is measured in real time with FBRM, and the spray rate is feedback-controlled to obtain the target particle size of granules after granulation. The target particle size after granulation is established from the obtained particle size of drug substance so that the dissolution rate is about 90%. This target particle size profile is considered ideal. A feedback control is made in real time so that if the particle size is larger than the profile, the spray rate is decreased, and if the particle size is smaller, then the speed is increased.

2.3.P.3.3.3.2 Tableting Process

Online monitoring control was employed for the compression force of each tablet in the tableting process, as control of uncoated tablet weight and weight variation that are CMA for the assay and uniformity of dosage units. A compression force controller allows correction of the amounts of filled blended powder (filling depth) and removal of tablets out of the acceptable range from the system based on the information of compression force measured. In addition, a correcting system that adjusts the amounts of filled blended powder (filling depth) and compression force control equipment by means of the average weight information periodically measured by automatic sampling, and fed back to the tableting machine by weight control equipment, was also employed. The overview of feedback is shown in Figure 2.3.P.3.3-4.

For the uncoated tablet weight, which is a CMA for the content, a system is established so that a control is performed if the mean value is out of the range of 194 mg ± 3%.

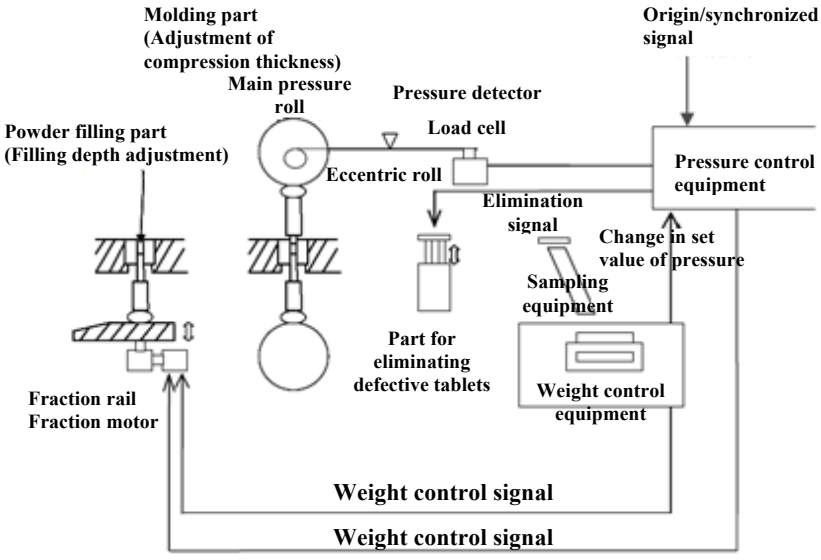


Figure 2.3.P.3.3-4 Overview of the feedback control for tableting weight

For the granule segregation, which is a CMA for uniformity of dosage units, the drug substance concentrations in uncoated tablets were to be monitored with an NIR method, and if the value is over the threshold, PAT feedback control was to be made, which controls the rotation speed (CPP). The drug substance concentrations in uncoated tablets were determined with an on-line NIR method at tableting over time. If each value of drug substance content calculated from the drug substance concentration and tablet weight is out of the range of 90% to 110%, the rotation speed was to be adjusted.

Measuring method: Diffuse transmittance method
Light source: NIR
Detector: InGaAs
Scan: A range of 12,500 to 3,600 cm^{-1}
Number of scans: 64 times
Resolution power: 8 cm^{-1}
Analysis method: Partial Least Squares (PLS) regression analysis

The uncoated tablet hardness, which is a CMA for dissolution, was to be controlled by on-line measurement of the tablets automatically sampled with time in the tableting process. For the uncoated tablet hardness, a target value of a dissolution rate of about 90% was established from the previously obtained particle size of drug substance and the granule particle size, and a system is employed, which feeds back to a tableting machine through a compression force controller.

2.3.P.3.3.3.3 Inspection process

Ten representative samples of film coated tablets after inspection were to be measured for the description (appearance), according to the method described in Table 2.3.P.3.3-3. In a similar way, 3 of the representative samples of film coated tablets after inspection were to be subject to identity testing with an at-line NIR method shown below.

Table 2.3.P.3.3-3 Measurement of description (appearance) by a visual observation method

Measuring method	Sakura Bloom Tablet is taken on a piece of white paper, and the color and shape are observed.
Number of samples	10 tablets

Identification by an at-line NIR method

Measuring method: Diffuse transmittance method
Light source:NIR
Detector: InGaAs
Scan range: 12,500-3,600 cm^{-1}
Number of scans: 64 times
Resolution power: 8 cm^{-1}
Analysis method: Principal Component Analysis (PCA)
Number of samples: 3 tablets

2.3.P.3.4 Control of Critical Process and Critical Intermediates

Among the specifications, RTRT was employed for the description (appearance), identification, uniformity of dosage units, dissolution and content. The process control methods that serve as each test method are as shown below.

2.3.P.3.4.1 Test items for RTRT

Based on the control strategy described in Section 2.3.P.2.3 Manufacturing Process, description (appearance), identification, uniformity of dosage units, dissolution and assay were considered as possible items for RTRT.

2.3.P.3.4.1.1 Description (appearance) (RTRT)

As RTRT of description (appearance) in the specifications, 10 film-coated tablets after the inspection process were to be tested for description by a visual observation method shown in Table 2.3.P.3.3-3.

2.3.P.3.4.1.2 Identification (RTRT)

As RTRT of identification in the specifications, 3 film-coated tablets after the inspection process were tested for the existence of drug substance, according to (1) at-line NIR method described in Identification (alternative test) <Specifications and Test Methods> in 2.3.P.5.2 Test Methods (Analytical Procedure).

2.3.P.3.4.1.3 Uniformity of dosage units

As RTRT of uniformity of dosage units in the specifications, the drug substance concentrations in uncoated tablets are determined with an on-line NIR method at tableting over time, and the content of drug substance in uncoated tablets is calculated from the drug substance concentration and weight of each tablet. Assessment is

conducted for 200 tablets (10 tablets x 20 time points). Refer to "2.3.P.3.3.3.2 Tableting Process" and "2.3.P.5.6.3.1 Uniformity of Dosage Units (RTRT).

2.3.P.3.4.1.4 Dissolution

The particle size of drug substance is measured as a specification testing in the process of drug substance, by a laser diffraction-scattering type particle size distribution measuring device. Without preparing samples for measurement, the powder of drug substance is measured for particle distribution by the dry method (specification testing of drug substance). Regarding the particle size of the granulation, the particle size at the end of granulation, which is obtained by a FBRM method is used. The uncoated tablet hardness is measured in 200 tablets (10 tablets × 20 time points) sampled over time as described in "2.3.P.3.4.1.3 Uniformity of Dosage Units."
As shown in "2.3.P.2.3.4.3 Dissolution (CQA)," RTRT will be performed based on the dissolution prediction formula using the parameters of particle size of drug substance, granule particle size, and uncoated tablet hardness (formula shown below).

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

By controlling each process using this system, dissolution of the drug product is considered to be assured. Therefore, a conventional dissolution test could be omitted.

2.3.P.3.4.1.5 Assay

As RTRT of assay in the specifications, the content of drug substance in uncoated tablets is determined by an on-line NIR method described in "2.3.P.3.4.1.3 Uniformity of Dosage Units," and assessment is made by calculating the mean of 200 tablets.

2.3.P.3.5 Process Validation/Evaluation

For adopted RTRT items, if an unacceptable change in production scale occurred, a RTRT model is re-constructed and re-calibration is carried out. At the stage of NDA filing, assessment was made in a total of 21 batches (refer to Table 2.3.P.2.3-7) manufactured at pilot scale and commercial scale, but process validation using the first 3 batches for commercial production will be performed again.

Quality (CQA) of Sakura Bloom Tablets is ensured by CMAs (composing quality) that are maintained by routine production. The control strategy in production of Sakura Bloom Tablets operates the following maintenance program to verify the model.

Daily check
• Trend analyses of CQA and CMA are performed for every batch produced, and the changes are confirmed to be within an acceptable range.
• If the trend is out of the acceptable level, a comparison is made between the model and conventional testing methods. If the model has some problems, it should be revised. If the model has no problems, the relationship between CPP and CMA is considered to be broken. Thus, control of CPP is reviewed so that CMA has an appropriate value.

Periodical check
• A comparison is made between the values calculated by the model and those obtained by the conventional testing methods at a certain production interval. If the difference between the two is out of the acceptable level, the model should be revised.

Event check
• If raw material or manufacturing equipment is changed, a comparison is made between the values calculated by the model and those obtained by the conventional testing methods under the Pharmaceutical Quality System (PQS). If the difference between the two is out of the acceptable level, the model should be revised.

2.3.P.5 Control of Drug Product

The specifications and test methods for Sakura Bloom Tablets were set based on the results of drug product development, of stability test, and the analytical results of the batches manufactured at pilot scale.

2.3.P.5.1 Specifications and Test Methods

RTRT is employed for description, identification, uniformity of dosage units, dissolution, and assay of the release test items for Sakura Bloom Tablets. Usually, these items for RTRT are used for release tests, and the summary of specifications and test methods is described. In addition, the specifications and test methods of conventional tests by using final drug product are also summarized because of the necessity for the control strategy or stability.

Table 2.3.P.5.1-1 Specifications and test methods for Sakura Bloom Tablets 20 mg

Test items			Test methods	Specification
Description	RTRT	Appearance	The Japanese Pharmacopoeia General Notice	Pale red film-coated tablets
	Conventional tests			
Identification	RTRT		Near infrared absorption spectrometry (NIR method)	Identified as Sakura Bloom Tablet
	Conventional tests	HPLC Retention time	HPLC method	The retention time of the main peak from the sample solution coincides with that of the standard solution.
		Ultraviolet absorption spectrum	Ultraviolet-visible spectrophotometry	The shape of the ultraviolet absorption spectrum from the sample solution coincides with that of the standard solution.
Uniformity of dosage units	RTRT		Near infrared absorption spectrometry (NIR method)	When 200 uncoated tablets, which were sampled to represent the whole batch during the tableting process, are tested for Assay, the number of tablets exceeding the range of 85.0% to 115.0% is 6 or less and that of 75.0% to 125% is 1 or less.
	Conventional tests		Content Uniformity HPLC method	It meets the criteria of the Content Uniformity Test of the Japanese Pharmacopoeia.
Dissolution	RTRT		Calculation by the dissolution model Input parameter • Particle size of drug substance: Laser diffraction particle size distribution analyzer • Granule particle size: FBRM • Uncoated tablet hardness: Tablet hardness tester	The dissolution rate calculated by the dissolution model at the time point of 30 minutes is 80% or higher.
	Conventional tests		Dissolution test (paddle method) Ultraviolet-visible spectrophotometry	Q value in 30 minutes is 80%.
Assay	RTRT		Near infrared absorption spectrometry (NIR method)	The results of the uniformity of dosage units test (RTRT) show a mean of 95.0% to 105.0% of the labeled amount.
	Conventional tests		HPLC method	95.0% to 105.0% of the labeled amount

* According to the Decision Tree, RTRT is usually performed. If RTRT is not available, conventional tests will be performed.

2.3.P.5.2 Test Methods (Analytical Procedures)

Unless otherwise specified, the specifications and test methods for Sakura Bloom Tablets shall apply General Notices, General Rules for Preparations, and General Tests, Processes and Apparatus of the Japanese Pharmacopoeia.

Specifications and test methods for Sakura Bloom Tablets

Describe the information of the Application Form (RTRT & Conventional)

2.3.P.5.2.1 Description

2.3.P.5.2.1.1 Test methods of RTRT

Refer to Section 2.3.P.3.4.1.1

2.3.P.5.2.1.2 Test methods of conventional tests

<Omitted>

2.3.P.5.2.2 Identification

2.3.P.5.2.2.1 Test methods of RTRT

A discriminating model was used to test the presence of drug substance in film-coated tablets by an at-line NIR method. As shown in Figure 2.3.P.5.2-1, a discriminating model is an approach to make a decision using a library reference prepared by each NIR spectrum of active and placebo tablets. The film-coated tablet tested is judged to be an active tablet if the results are within the threshold of an active tablet. If the test with an at-line NIR method cannot be properly performed, HPLC method is applied. The meaning of "the test cannot be properly performed" is limited to the case where measurement results cannot be obtained due to measuring instruments or a NIR discriminating model.

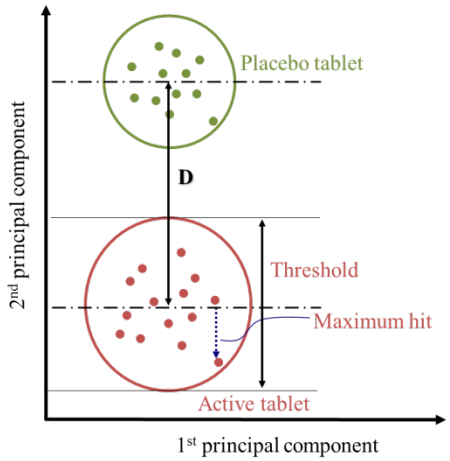


Figure 2.3.P.5.2-1 Overview of a discriminating model

2.3.P.5.2.2.2 Test methods of conventional tests

<Omitted>

2.3.P.5.2.3 Uniformity of dosage units

2.3.P.5.2.3.1 Test methods of RTRT

Refer to Sections 2.3.P.3.3.3.2 and 2.3.P.3.4.1.3.

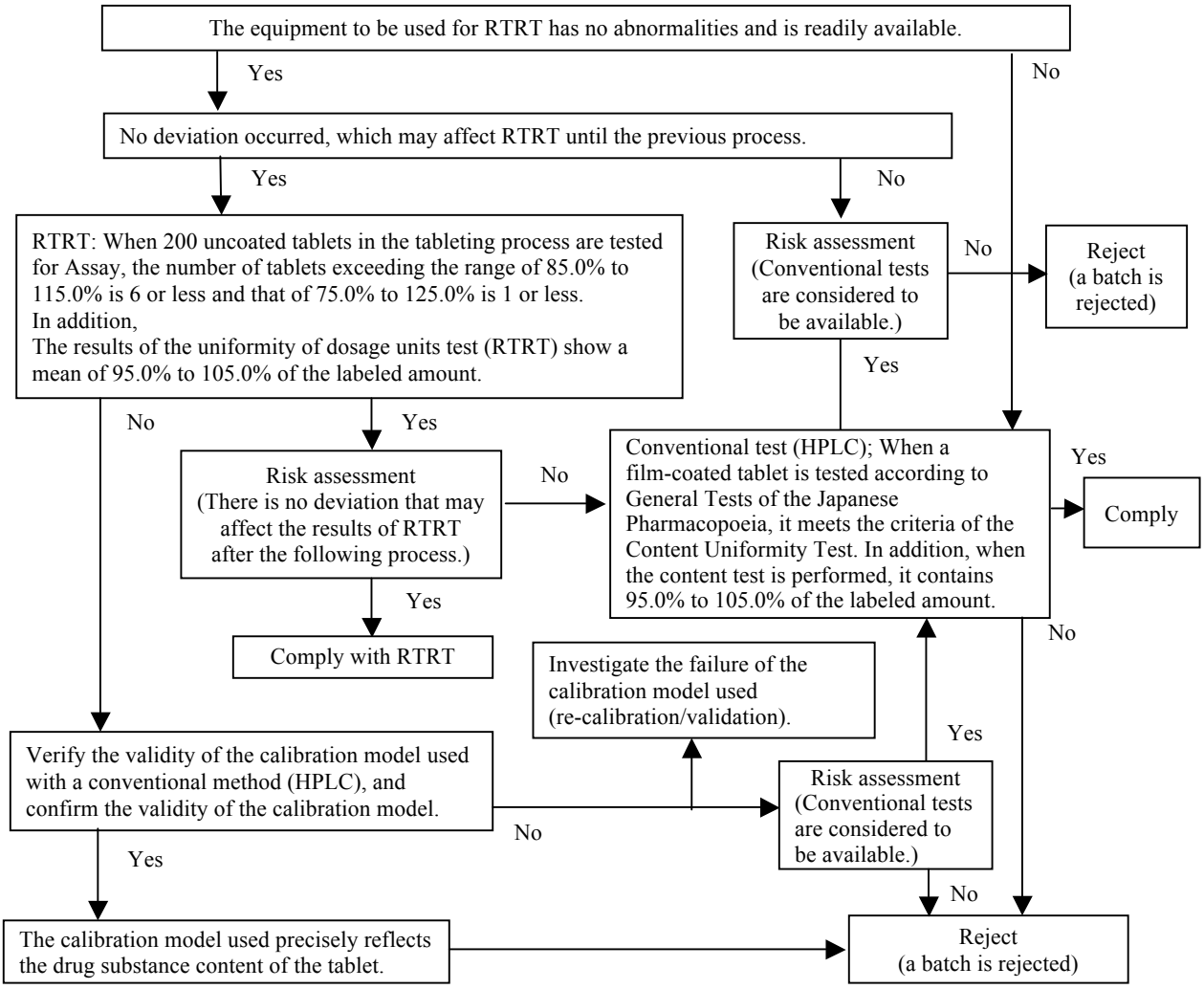
The content of each drug product shall be calculated according to the following formula, using drug substance concentrations of uncoated tablets and the uncoated tablet weight determined by the methods described in 2.3.P.3.3.3.2 Tableting process.

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

2.3.P.5.2.3.2 Test methods of conventional tests

<Omitted>

The test shall be performed according to the following decision tree. This decision tree is the same as that of the Assay.



2.3.P.5.2.4 Dissolution

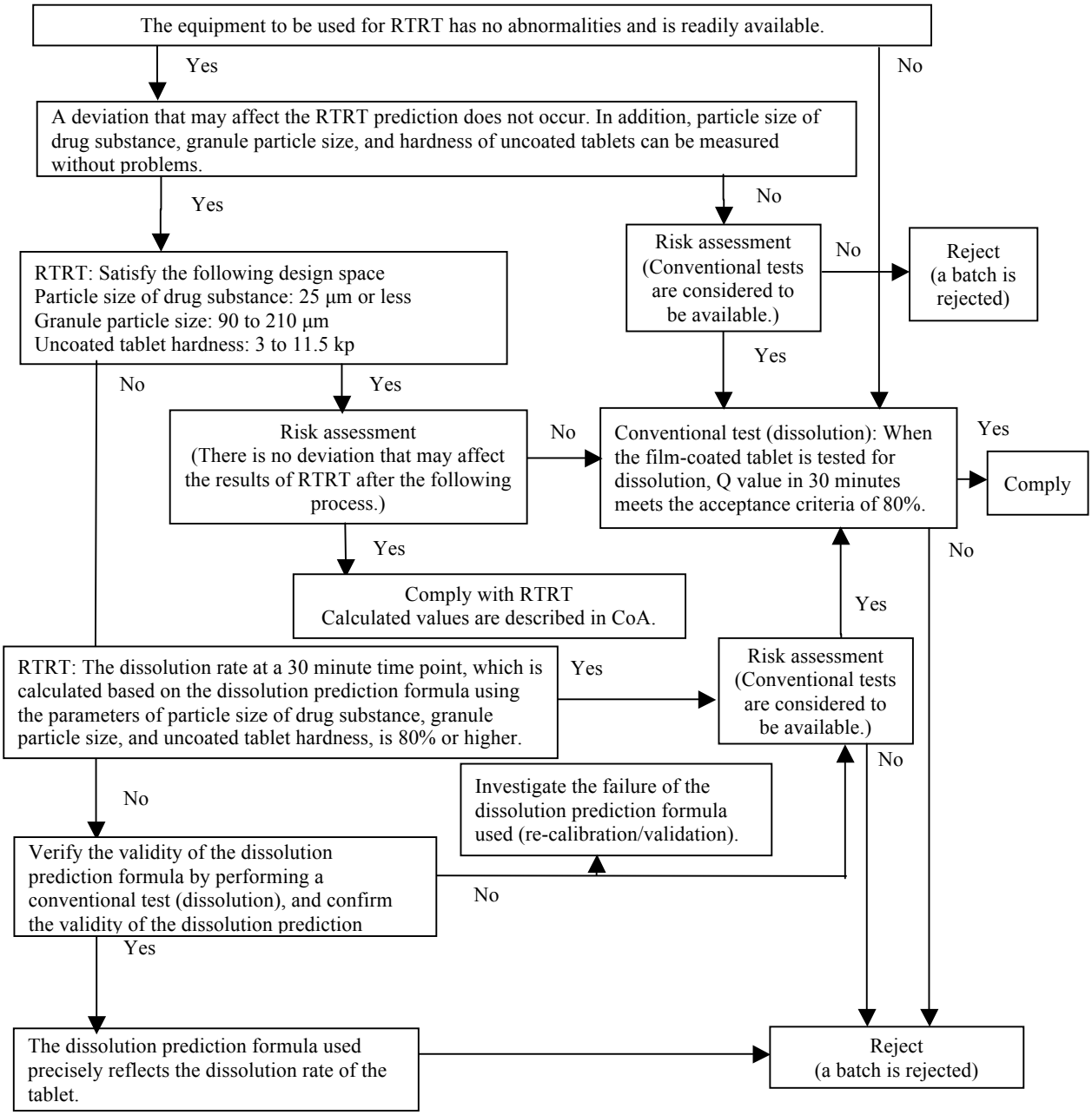
2.3.P.5.2.4.1 Test methods of RTRT

Refer to Section 2.3.P.3.4.1.4

2.3.P.5.2.4.2 Test methods of conventional tests

<Omitted>

The test shall be performed according to the following decision tree.



2.3.P.5.2.5 Assay

2.3.P.5.2.5.1 Test methods of RTRT

Refer to Section 2.3.P.3.4.1.5

The content is calculated by averaging each content of 200 tablets, determined with an NIR method in Section 2.3.P.5.2.3.1.

2.3.P.5.2.5.2 Test methods of conventional tests

<Omitted>

The test shall be performed according to the decision tree described in 2.3.P.5.2.3 Uniformity of Dosage Units.

2.3.P.5.3 Validation of Test Methods (Analytical Procedures)

2.3.P.5.3.1 Validation of Test Methods for RTRT(Analytical Procedures)

The validation was performed for the on-line NIR method to determine drug substance concentrations of uncoated tablets in the tableting process and the at-line NIR method for identification in the inspection process.

2.3.P.5.3.1.1 Drug substance concentrations of uncoated tablets <on-line NIR method>

(1) Preparation of Calibration Model (Calibration)

Tablets containing 5 levels of drug substance (60, 80, 100, 120, and 140% of the labeled amount) were prepared. The drug substance content was determined with spectra from NIR method and a conventional method (HPLC) using 5 tablets at each level, and was incorporated into the calibration model. Instrument B from Company A and Software Y from Company X were used for NIR measurement and the analysis, respectively.

The results of optimization of analytical parameters for the calibration model were as follows. It was confirmed that the loading spectra used in the calibration model were similar to the NIR spectra of the drug substance.

Items	Results
Range of wavelength for the analysis	6100 – 5500 cm^{-1}
Spectrum pre-treatment conditions	First derivative + Vector normalization
PLS component number	3
Multiple correlation coefficient	0.985
Prediction error	0.67%

(2) Test of the Calibration Model (Validation)

The drug substance content was determined with spectra from NIR method and a conventional method (HPLC) using tablets (5 levels × 3 tablets) different from those used for calibration. The obtained NIR spectra were applied to the calibration model, which was prepared by the results of calibration of the above (1), and the drug substance content was calculated. The results were as follows, and satisfied the requirements of the validation.

Items	Methods and acceptance criteria	Results
Linearity	The multiple correlation coefficient is 0.97 or higher as a result of test using 5 levels × 3 tablets.	Multiple correlation coefficient: 0.981
Accuracy	Differences in the content of tablets at 70, 100, and 130% levels between HPLC method and NIR method are within ±5% for individual values and within ±2% for the average.	70% level Individual values = 5%, 4%, -3%; average = 2% 100% level Individual values = 3%, -4%, -1%; average = -1% 130% level Individual values = 1%, 2%, -3%; average = 0%
Precision	RMSEP (standard error) is 1.5% or less.	RMSEP: 0.75%
Range	A decision is made based on the results of linearity/accuracy/precision.	70% to 130%
Robustness	Assessment is made using samples containing various variable factors (xx, yy, zz, etc.).	Good linearity, accuracy, and precision were obtained.

(3) Test of commercial production facilities

The prepared calibration model was incorporated into the NIR equipment in a commercial production facility, and the content of tablets was determined with an NIR method in a system reflecting commercial production, and then, the content was determined with a HPLC method.

The standard error between the content determined with an NIR method and the content with a HPLC method was 1.0%, showing a good correlation.

2.3.P.5.3.1.2 Identification <at-line NIR method>

(1) Preparation of a discriminating model (calibration)

A discriminating model was prepared by incorporating 5 tablets from each of the 3 batches of the active and placebo tablets of Sakura Bloom Tablets into a library. Instrument B from Company A and Software Y from Company X were used for NIR measurement and the analysis, respectively.

The results of optimization of analytical parameters for the discriminating model were as follows. It was confirmed that the loading spectra used in the calibration model were similar to the NIR spectra of the drug substance.

Items	Results
Range of wavelength for the analysis	10000 – 7500 cm^{-1}, 6500 – 5500 cm^{-1}
Spectrum pre-treatment conditions	Second derivative
PCA component number	2

(2) Test of the Discriminating model (Validation)

NIR spectra were obtained using, active tablets and placebo tablets different from those used for calibration, and 3 other drug products, and then incorporated into the discriminating model. As the result, only the active tablets complied with the requirement, while other tablets did not have conformity.

2.3.P.5.3.2 Validation of test methods necessary for stability studies (analytical procedures)

The validation of the test methods for Sakura Bloom Tablets was assessed based on "Text on Validation of Analytical Procedures" (Notification No. 755 of the Evaluation and Licensing Division, PAB dated July 20, 1995) and "Text on Validation of Analytical Procedures" (Notification No. 338 of the Evaluation and Licensing Division, PAB dated October 28, 1997).

<Omitted>

2.3.P.5.6 Justification of Specification and Test Methods

2.3.P.5.6.3 Uniformity of dosage units

2.3.P.5.6.3.1 Uniformity of dosage units (RTRT)

Specifications: When 200 uncoated tablets, which were sampled to represent the whole batch during the tableting process, are tested for assay, the number of tablets exceeding the range of 85.0% to 115.0% is 6 or less and that of 75.0% to 125.0% is 1 or less.

<Description of justification was omitted>

2.3.P.5.6.4 Dissolution

2.3.P.5.6.4.1 Dissolution (conventional test)

Specification: Q value in 30 minutes is 80%.

<Description of justification was omitted>

2.3.P.5.6.4.2 Dissolution (RTRT)

Specifications: The dissolution rate calculated by the dissolution model at the time point of 30 minutes is 80% or higher.

When RTRT is employed for dissolution, justification of the specification is described below.

When a predicted dissolution rate is calculated by the dissolution model, basically due to assessment of the mean dissolution rate, a specification of "dissolution rate at the time point of 30 minutes is 80% or higher" is established as the similar specification of "Q value in 30 minutes is 80%" tested by a conventional method. For the variation of dissolution rate, experiments according to a central composite design were performed using parameters of particle size of drug substance, granule particle size, and uncoated tablet hardness, to calculate the dissolution prediction formula. As the result, the variability was within xx% at any experimental time point, thus, it was considered to comply well with the criteria of S2 on a conventional test. Based on the clinical drugs manufactured to date and the stability data of proposed drug product (manufactured at pilot scale), and the investigational results of commercial scale manufacturing, the solubility can be well assured.

2.3.P.5.6.5 Assay

<Omitted>

Attachment to Sakura Bloom Tablet Mock

Justification of Specifications when the Real Time Release Testing is Employed for Uniformity of Dosage Units

By the Health and Labour Sciences Research Group

The uniformity of dosage units (UDU) test harmonized by ICH in the Japanese Pharmacopoeia (JP), United States Pharmacopoeia (USP), and European Pharmacopoeia (Ph. Eur.), employs a two-step sampling system, 10 dosage units at the first step, and 30 dosage units at the second step, which is listed in "6.02 Uniformity of Dosage Units" of the 16th Japanese Pharmacopoeia (JP16) General Test Process and Apparatus. The acceptance value ($AV = |M - \overline{X}| + ks$) is calculated from the mean of individual contents and the standard deviation. The acceptance criteria are based on a combination of a parametric test (the requirements are met if the AV is less than the limit) and a non-parametric test (the requirements are met if no individual content of the dosage unit is outside of the limit). This test method, however, has the drawback that the content of the active ingredient cannot be followed with time due to sampling from the final drug products.

When many samples are treated with PAT (Process Analytical Technology), which is different from a small size of 10 or 30 tablets, it is most reasonable to compare the consumer's risk with the producer's risk to ensure the acceptable quality specified in the pharmacopoeia. These relations are shown as an Operating Characteristic (OC) curve in Figure 1. When establishing the specifications, it is necessary to consider that large sample sizes increase the probability of detecting samples falling outside the range compared with the conventional method. To ultimately ensure the quality of the products released after passing tests, the acceptance rate is less than 5 to 10% that corresponding to the consumer's risk. In other words, it is unlikely that a product will be released with a quality worse than this level. Whereas, in the case of PAT, too much producer's risk will increase the risk of not continuing production.

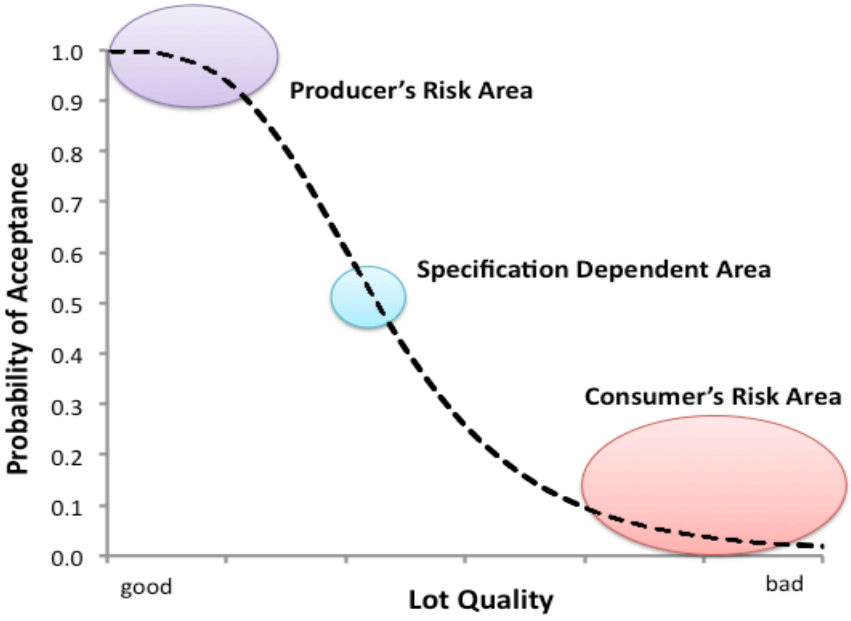


Figure 1. The relationship between consumer's risk and producer's risk in the OC curve.

The research group has established the specifications of Sakura Bloom Tablets, referring to the Large-N method [1][2] and the modified Large-N method (nonparametric test), which were proposed by the PhRMA for the first time. The OC curves based on the Large-N and modified Large-N methods are shown in Figure 2. Compared with the current OC curve of JP16 (dotted line), the curve of the Large-N method coincides with that of JP16 at the consumer's risk level, but the curve of the modified Large-N method appears more fitted to that of JP16 at the producer's risk level. Although it may be interpreted that the test has simply become stricter, it must be important for the level of the producer's risk to coincide with that of JP16, considering the control of

the product after release, which may lead to reduce the risk of non-conformance after marketing.

Table 1 shows the acceptance criteria for UDU (Ph.Eur.2.9.47 [3]) proposed by the Ph. Eur., which is suitable for PAT. The ALTERNATIVE 1 described in the Ph. Eur. is the same as UDU test described in JP16, the combination of a parametric test (use of acceptability constant k) and a non-parametric test (C1 criteria) while ALTERNATIVE 2 is the combination of 2 non-parametric tests with different limits (C1 criteria and C2 criteria). The comparison of OC curves of these two options (Figure 3) did not show much difference in the producer's risk level between ALTERNATIVE 1 (option 1 in Figure 3), ALTERNATIVE 2 (option 2 in Figure 3), and JP16 (ICH UDU in Figure 3). Therefore, after implementation of RTRT, non-compliance to the specifications is unlikely to be observed at the producer's risk level.

The research group had a discussion about Large-N specifications, on the assumption that it is necessary to pay attention to both consumer's risk and producer's risk. In particular, regarding the specifications for RTRT, the producer's risk is important, and an inconvenience could occur in which the risk of non-compliance to specifications increases in terms of release control, unless the conventional specifications and those for RTRT coincide to some extent. Based on these backgrounds, the specifications of "Modified Large-N" of PhRMA or those of the EU are appropriate as the acceptance criteria of Large-N, and the method of Ph. Eur. seems to be better because it can be used for non-normal distribution risk. The comparison between ALTERNATIVE 1 and 2 of the Ph. Eur. resulted in a recommendation of ALTERNATIVE 2, because it can be easily implemented by companies, and a non-parametric test can have high precision with a large sample size. Therefore, ALTERNATIVE 2 of the Ph. Eur. will be employed for the release criteria for the uniformity of dosage units of Sakura Bloom Tablets.

Sakura Bloom Tablet Mock also uses Real Time Release Testing for the content test, and the mean of individual sample contents used for the uniformity of dosage units is adopted for the content of Sakura Bloom Tablets.

Left figure: Large-N method
Right figure: Modified Large-N method

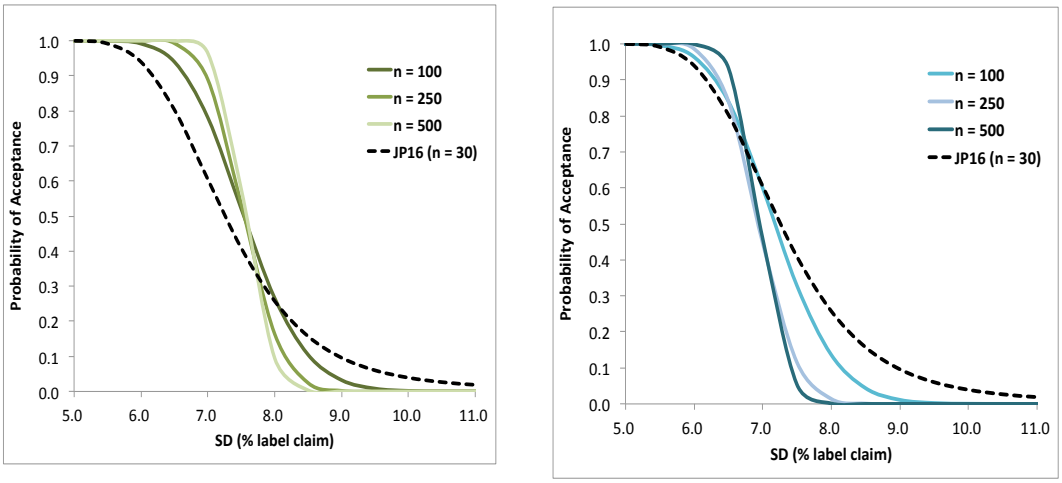


Figure 2. The OC curves of Large-N and Modified Large-N methods.

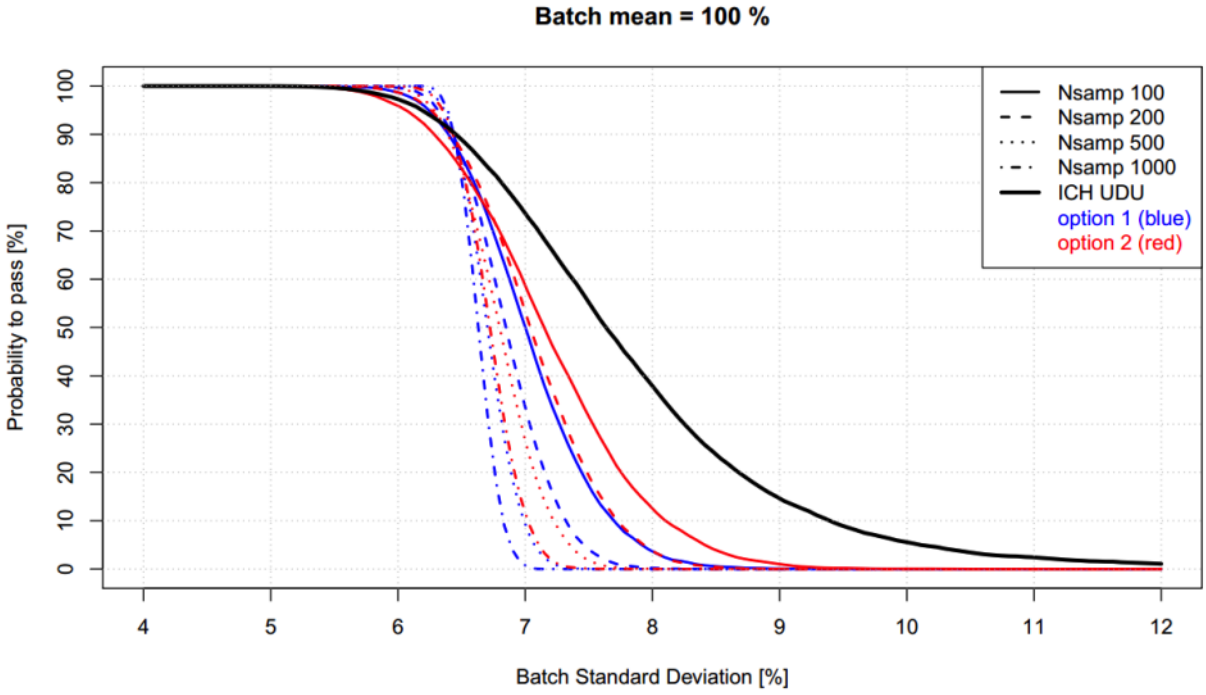


Figure 3. OC curves of selected sample sizes for the adopted 2.9.47 (Alternative 1 and 2, respectively).

Table 1. UDU criteria suitable for PAT, proposed by Ph. Eur..

Sample size (n)	Alternative 1		Alternative 2	
	Acceptance constant (k)	C2 (±25.0%)	C1 (±15.0%)	C2 (±25.0%)
50	-	-	-	-
75	-	-	-	-
100	2.15	0	3	0
150	2.19	0	4	0
200	2.21	1	6	1
300	2.23	2	8	2
500	2.25	4	13	4
1000	2.27	8	25	8
2000	2.29	18	47	18
5000	2.30	47	112	47
10000	2.31	94	217	94

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[3] Ø. Holte, M. Horvat, "Uniformity of Dosage Units Using Large Sample Sizes", Pharm. Sci.Technol 36 (10), pp.118-122, 2012