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2.3.P.5.2.4	Dissolution
2.3.P.5.2.4.1	Test Methods of RTRT

2.3.P.5.2.4.2	Test methods of conventional tests
2.3.P.5.2.5	Assay
2.3.P.5.2.5.1	Test Methods of RTRT
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2.3.P.5.3.1	Validation of Test Methods for RTRT (Analytical Procedures)
2.3.P.5.3.1.1	Drug substance concentrations of uncoated tablets <on-line NIR method>
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2.3.P.5.6.3	Uniformity of dosage units
2.3.P.5.6.3.1	Uniformity of dosage units（RTRT）
2.3.P.5.6.4	Dissolution
2.3.P.5.6.4.1	Dissolution (conventional test)
2.3.P.5.6.4.1	Dissolution（RTRT）
2.3.P.5.6.5	Assay

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).

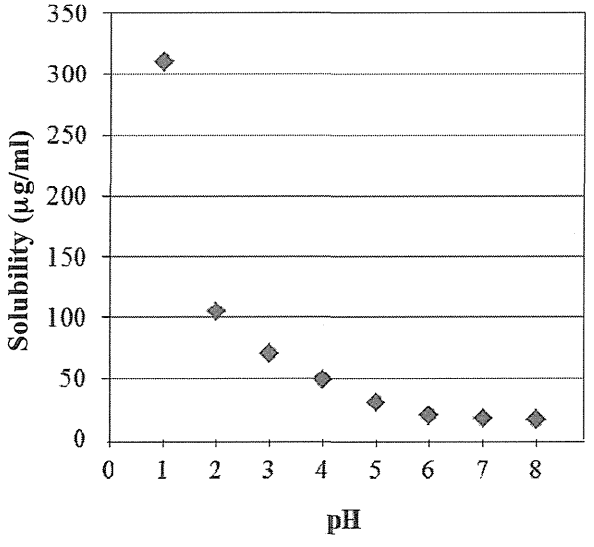

Figure 2.3.P.2.1-1 Solubility of prunus in buffers at various pH

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.

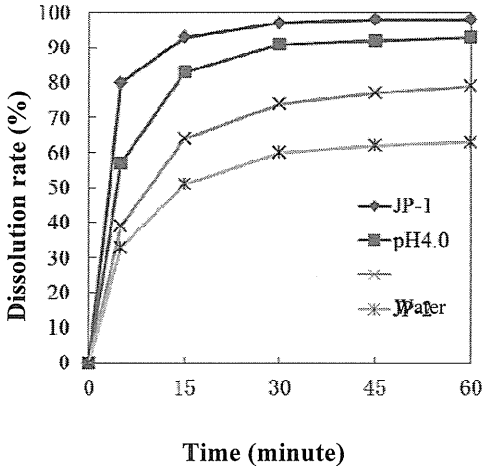


Figure 2.3.P.2.2-1 Dissolution profile of the proposed drug product

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.

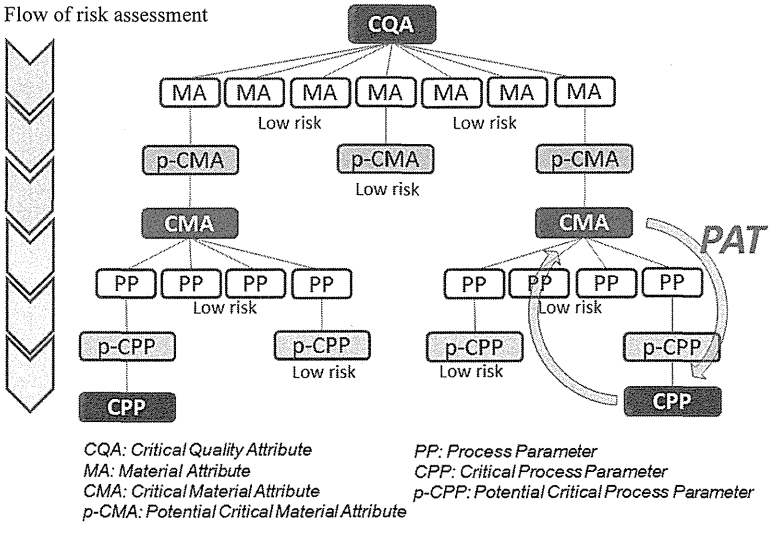


Figure 2.3.P.2.3-1 Overview of QbD strategy for Sakura Bloom Tablets

* 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

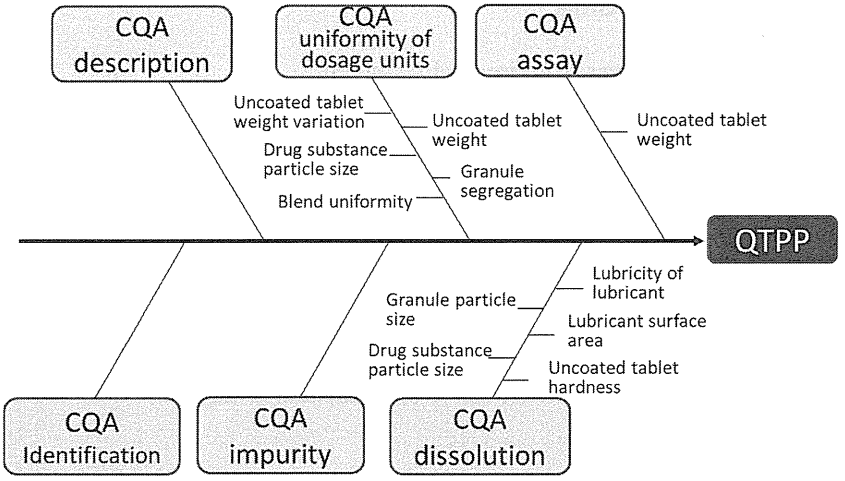


Figure 2.3.P.2.3-3 Relation among QTPP, CQA, and p-CMA

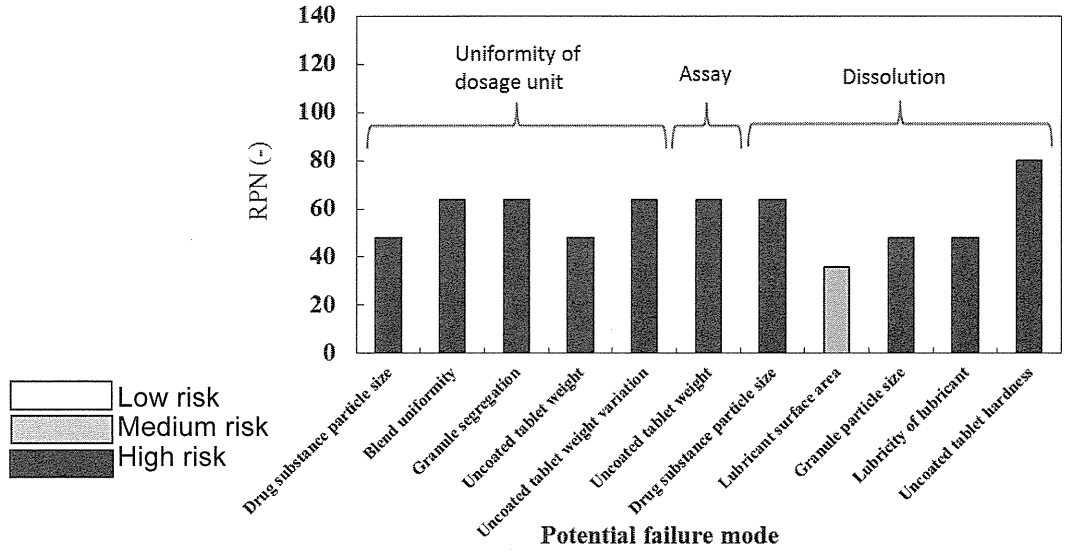


Figure 2.3.P.2.3-4 Results of FMEA risk assessment before manufacturing process development of Sakura Bloom Tablets

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.

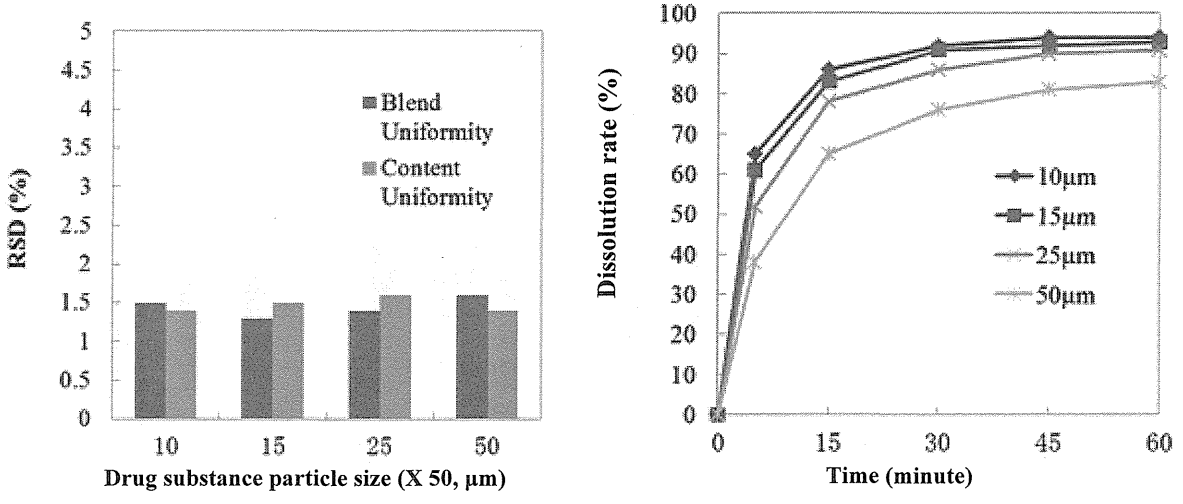
2.3.P.2.3.2.2 Identification of CMA

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)

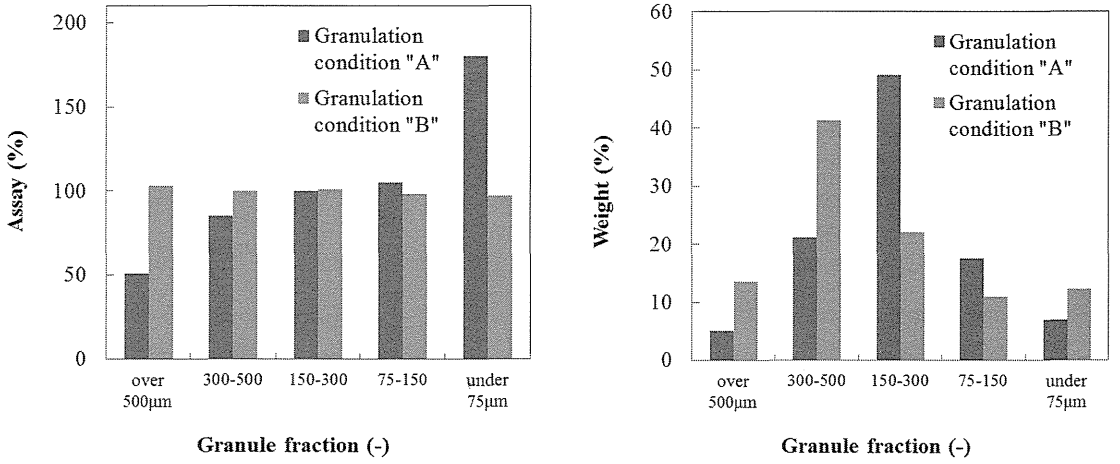
Figure 2.3.P.2.3-5 Effects of the drug substance particle size on CQA (uniformity of dosage units, and dissolution)

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

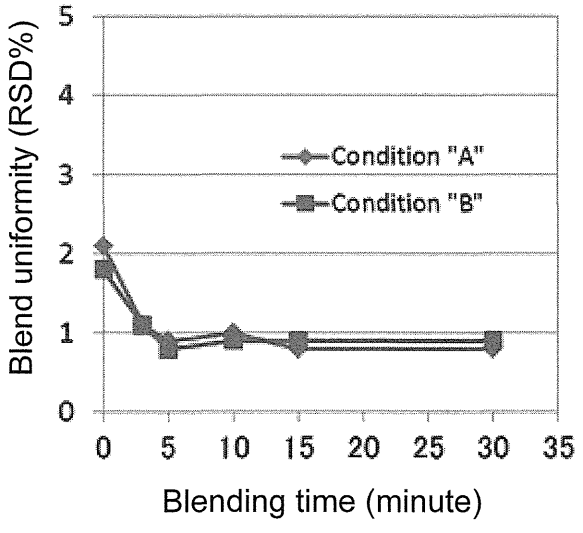
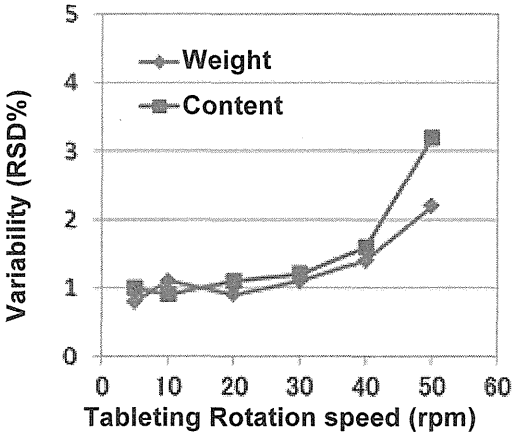


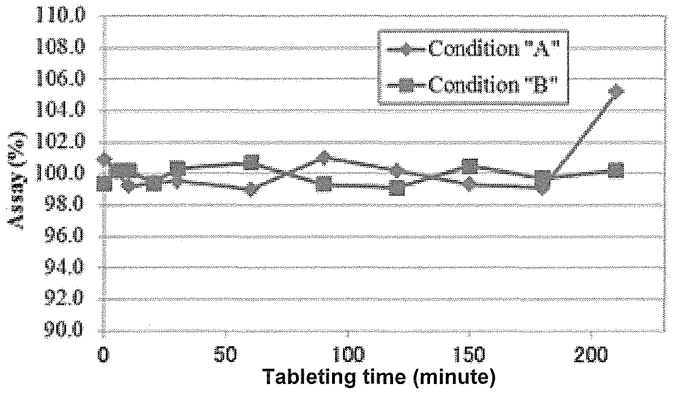
Figure 2.3.P.2.3-7 Blend uniformity profile

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.

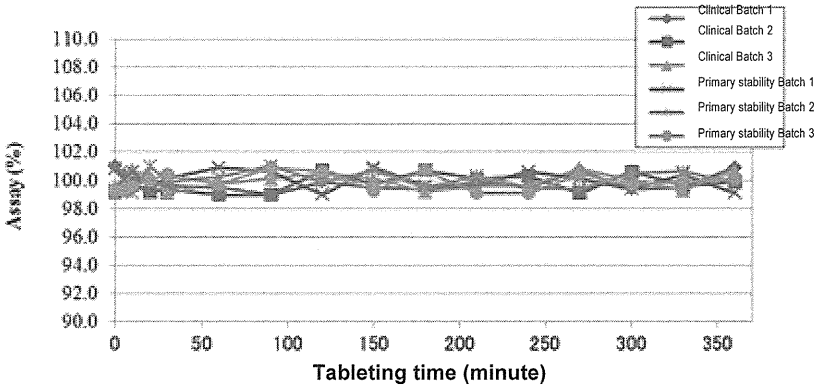
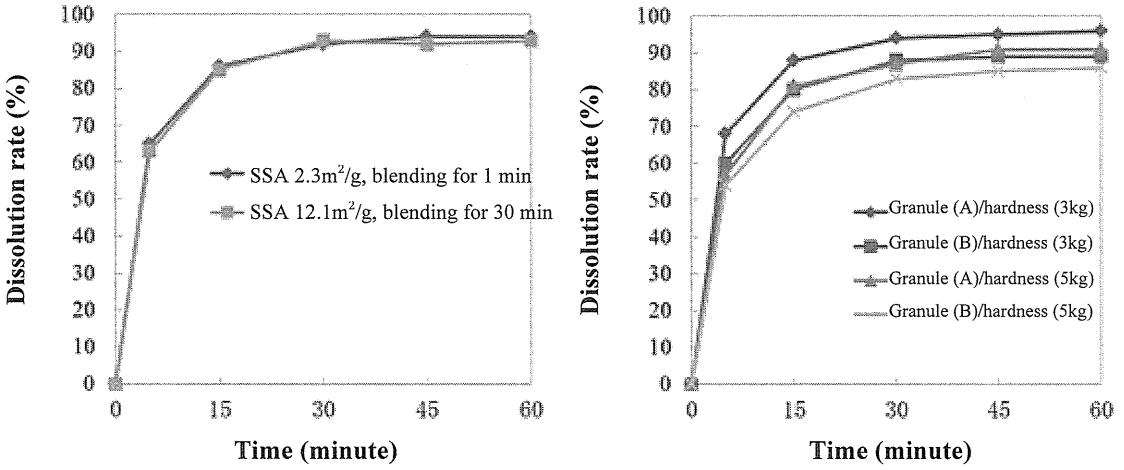


Figure 2.3.P.2.3-9 Drug substance content at tableting over time (mean of 3 tablets)

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