2.3.P.3.5 Process Validation and/or Evaluation

For the items employed in the real-time release tests, calibration will be performed again if the production scale is changed. In the registration step, three batches manufactured in the pilot scale were evaluated. The first three commercial batches will be evaluated .

2.3.P.3.5.1 Blending Process (Evaluation Results Concerning Content Uniformity)

All results of homogeneity measured in the blending process with three batches manufactured in the pilot scale indicated completion of the blending process within the control range.

Content uniformity after compression was confirmed using Ultraviolet-visible Spectrophotometry. The uniformity values were 95.4% to 104.2% of the labeled amount and its RSD values were 1.5% to 2.0%. Therefore all batches met the criteria of drug product homogeneity in General Tests, Processes and Apparatus.

Table 2.3.P.3.5.1-1 Comparison of Content Uniformity Results

	Content (%)		
	Batch XX1	Batch XX2	Batch XX3
Mean	99.8	100.1	101.4
RSD	1.2	1.5	1.4
Result by ultraviolet-visible spectrophotometry			
Mean (min-max)	97.4 (96.4-102.1)	99.1 (97.4-101.0)	100.3 (96.5-102.3)
Relative standard deviation (%)	1.6	1.8	1.9
Determined value	3.9	4.0	2.6

2.3.P.3.5.2 Blending Process (Results of Dissolution Test Evaluation)

For three batches manufactured in the pilot scale, all results of the drug substance particle size, specific surface area of magnesium stearate, lubricant blending time and dissolution rate calculated from the compression pressure were within the control ranges. With three batches of Sakura tablets, it was confirmed that the dissolution of each batch in 30 minutes were 88.4% to 95.2% and met the criteria of the dissolution test.

Table 2.3.P.3.5.2-1 Comparison of Dissolution

	Batch Data		
	Batch XX1	Batch XX2	Batch XX3
Drug substance particle size	X	X	X
Specific surface area of magnesium stearate	XX	XX	XX
Lubricant blending time	XX	XX	XX
Compression pressure	XXX	XXX	XXX
Result of multivariate analysis	99.8	100.1	101.4
Dissolution test results Mean (min-max)	92.8 (88.4 to 94.2)	90.3 (89.0 to 102.5)	91.5 (90.5 to 93.5)

2.3.P.3.5.3 Compression Process (Results of Content Evaluation)

For three batches manufactured in the pilot scale, all results of blended powder content and contents calculated from tablet weight after the compression were within the control ranges. It was confirmed that the content determined using the content test (HPLC method) after compression was 98.4% to 100.2%, which met the criteria in the specifications.

Table 2.3.P.3.5.3-1 Results of Tablet Weight and Content

	Weight (mg)		
	Batch XX1	Batch XX2	Batch XX3
Mean	99.5	100.3	99.1
Relative standard deviation (%)	0.9	1.2	1.5
Results of content by HPLC	98.4%	100.2%	99.1%

2.3.P.5 Control of Drug Product

The specifications and test methods for Sakura Tablet were set based on the results of Drug Product Development, Stability results and the analytical results of the batches that were manufactured in the pilot scale.

2.3.P.5.1 Specifications and Test Methods

Real-time release is employed for the release test items of Sakura Tablet, content uniformity, dissolution test and content (assay). The summary of the method for real-time release control applied to the items in the Specifications and the test methods have been described. The summaries and criteria for the critical specifications and test methods in the control strategy have also been described.

Table 2.3.P.5.1-1 Specifications and Test Methods

Test items		Test methods	Specification
Appearance		Visual inspection	White plain tablet
Identification	Ultraviolet-visible spectrum	Ultraviolet-visible spectrophotometry (acetonitrile/water mixture (1:1))	Amokinol exhibits similar intensities of absorption at the same wavelength, compared to the reference standard.
Purity	Related substances	HPLC method (absolute calibration curve method)	Individual related substance: 0.2% and under Total related substances: 1.0% and under
Content uniformity		Omitted. Because Content Uniformity of amokinol in the blending process and compression pressure in the compression process are monitored.	
Content uniformity (*)		Ultraviolet-visible spectrophotometry (acetonitrile/water mixture (1:1))	Meet the criterion of drug product homogeneity (Content Uniformity)
Dissolution test		Omitted. Because drug substance particle size, specific surface area of magnesium stearate, lubricant blending time and compression pressure are monitored for control.	
Dissolution test (*)		Apparatus: Paddle method Test fluid: 0.1% sodium lauryl sulfate Test fluid volume: 900 mL Rotating speed: 50 rpm Assay: HPLC method (absolute calibration curve method)	Dissolution rate in 30 minutes 80% and more (Q)
Content (assay)		Omitted. Because the content of the blended powder in the blending process and weight in the compression process are determined.	
Content (assay*)		HPLC method (internal standard)	95.0% to 105.0% of labeled amount

* To be used for items described in Section 2.3.P.2.3 Manufacturing Process Development (10) Control Strategy.

2.3.P.5.2 Test Methods (Analytical Procedures)

Real time release was employed for content uniformity, the dissolution test and content (assay). For validation of the test methods and analytical procedures, those used in the real-time release are described in Section 2.3.P.3.4 Management of Critical Processes and Critical Intermediates. For test items in the real-time release, the test methods for qualities will be described in cases of use in control strategies, such as changes to the manufacturing facilities and use in stability tests.

2.3.P.5.2.1 Dissolution Test
2.3.P.5.2.2 Content Uniformity
2.3.P.5.2.3 Content (Assay)

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

2.3.P.5.4 Justification of Specification and Test Methods

2.3.P.5.4.1 Dissolution Test

Setting of dissolution test using the paddle method, in accordance with JP general tests, processes and apparatus was investigated. The dissolution rate was assayed by HPLC method.

With tablets manufactured in processes with varied parameters (refer to P.2.3. Manufacturing Process Development), dissolution tests were performed using each of the test fluids, Solution 1 and Solution 2, under the following conditions: solvent volume = 900 mL, 50 rpm. Not all the tablets were fully dissolved under these conditions.

Then, 0.1% polysorbate 80 was added to the test fluids. Although the compounded tablets were nearly 100% dissolved after 15 minutes, it was not possible to discriminate each tablet batch as shown in Figure 2.3.P.5.3-1.

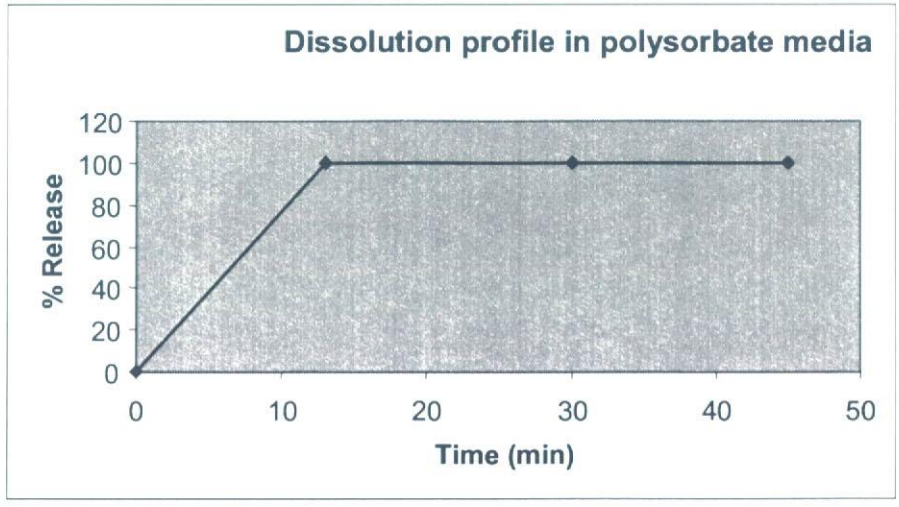

Figure 2.3.P.5.3-1 Dissolution Profiles in the Polysorbate 80 Added Test Fluids

In addition, the dissolution test method was evaluated in a test fluid with 0.1% sodium lauryl sulphate. The results indicated that sufficient discrimination capability and dissolution were obtained using this test fluid as shown in Figure 2.3.P.5.3-2.

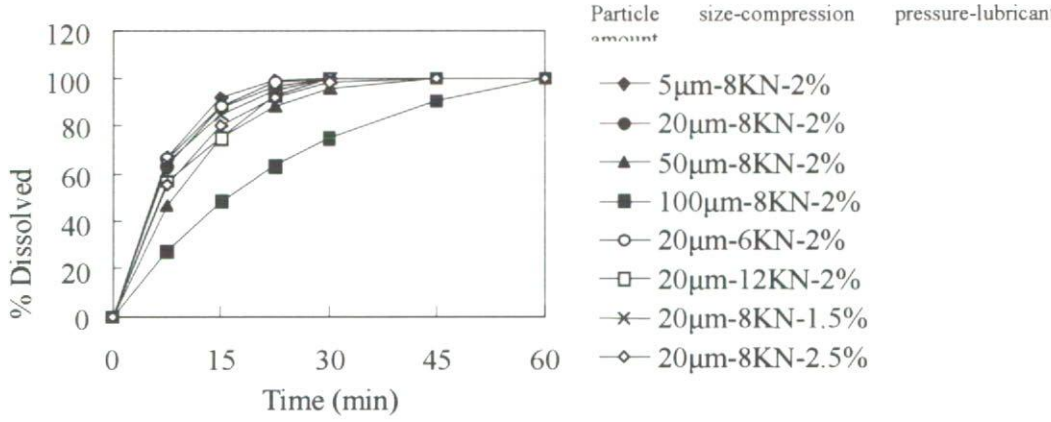

Figure 2.3.P.5.3-2 Dissolution Profiles in 0.1% Sodium Lauryl Sulphate Test Fluid

Based on the above results, the test fluid of 0.1% sodium lauryl sulphate was chosen in which a difference in the dissolution of the inter-products was observed. A sampling point at 30 minutes after start of dissolution was selected, where the dissolution profiles become steady.

As the linearity, accuracy and precision were all satisfactory, as shown in Table 2.3.P.5.3-1 Summary of Validation of Analytical Procedure, the analytical procedures have been justified.

Table 2.3.P.5.3-1 Summary of Validation of Analytical Procedure

Items		Results
Linearity	Correlation coefficient	r = 0.99994
	Regression formula	y = 0.00191x + 0.00090
	Residual sum of squares	6.8694×10^{-6}
Range (%)		0 to 150
Accuracy	Recovery rate (%)	100.6
	95% confidence interval of accuracy	-1.94 to 2.94
Repeatability	Standard deviation	0.84
	Relative standard deviation (%)	0.84
	95% confidence interval of standard deviation	0.60 to 1.44
Intermediate precision	Standard deviation	0.8
	Relative standard deviation (%)	0.8
	95% confidence interval of standard deviation	0.7 to 1.0

2.3.P.5.4.2 Content Uniformity

2.3.P.5.4.3 Content (Assay)

3.2.P.2 Pharmaceutical Development (Sakura Tablet, Film-coated Tablet)
3.2.P.2.2 Drug Product

3) Initial Risk Assessment (Design Risk Assessment)

Preliminary Hazard Analysis (PHA)[1] was used for the initial risk assessment.

First, the following quality properties were listed as below from the target profile of Sakura Tablet.

- *In vivo* performance
- Dissolution
- Assay
- Degradation
- Content uniformity
- Appearance
- Friability
- Chemical stability
- Physical stability

Material properties and processes that are likely to affect tablet quality properties were selected as hazards from process inputs, and listed as below.

- Drug substance particle size
- Filler selection
- Moisture control in manufacturing process
- Blending
- Lubrication
- Compression
- Coating
- Packaging

The severity and probability of risks on which each hazard has an effect are rated during risk assessment using PHA.

Definitions of severity and probability are shown in Figure 3.2.P.2.2-1.

Severity	Score
Minor	1
Major	2
Critical	3
Catastrophic	4

Probability	Score
Very unlikely	1
Remote	2
Occasional	3
Probable	4
Frequent	5

Figure 3.2.P.2.2-1 Definition of Severity and Probability in Preliminary Hazard Analysis

The risk assessment in this development stage were qualitatively evaluated by team member and company experts who are responsible for developing the drug product, based on experience in the development of drug products, namely oral solid dosage and research data of Sakura Tablet. The results of the evaluation were discussed and confirmed by the team member and company experts. When the rating given by the team members differed, the higher risk rating was employed.

Criteria for severity and probability are qualitatively shown in Figure 3.2.P.2.2-2. The degree of each definition is shown below.

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[1] *Preliminary Hazard Analysis*, Marvin Rausand, Norwegian University of Science and Technology, May 2005

Severity

- Catastrophic: Products will be recalled by the degree of effects of the hazard.
- Critical: The manufacturing line will be stopped (product shortage will occurred) by the degree of effects of the hazard.
- Major: Products will be deviated by the degree of effects of the hazard.
- Minor: No effects on the product quality properties.

Probability

- Frequent: Outbreak frequency not less than about once per month, assuming the manufacture of about 100 lots per year
- Probable: Outbreak frequency about once per month
- Occasional: Outbreak frequency about once per year
- Remote: Outbreak frequency about once every 10 years
- Very unlikely: Outbreak frequency about once every 100 years or less

Each hazard was rated by their severity and outbreak probability, then classified into high risk (H), medium risk (M) or low risk (L) according to the risk rating table shown in Table 3.2.P.2.2-2.

Hazards with high risk or medium risk must be controlled as low risk by the control strategy from the drug product design.

Severity / Probability	1	2	3	4	5
Catastrophic: 4	M	H	H	H	H
Critical: 3	L	M	M	H	H
Major: 2	L	L	M	M	H
Minor: 1	L	L	L	M	M

H High risk
M Medium risk
L Low risk

Table 3.2.P.2.2-2 Risk Ranking of Preliminary Hazard Analysis

The results of the actual score rating and risk ranking using the Preliminary Hazard Analysis described above are shown in Table 3.2.P.2.2-1 and summarized in Figure 3.2.P.2.2-3.

Table 3.2.P.2.2-1 Results of Preliminary Hazard Analysis

Hazard	Event	Severity	Probability	Risk score
Drug substance particle size	*In vivo* performance	3	5	H
Drug substance particle size	Dissolution	3	5	H
Drug substance particle size	Assay	3	1	L
Drug substance particle size	Degradation	2	1	L
Drug substance particle size	Content uniformity	3	3	M
Drug substance particle size	Appearance	1	1	L
Drug substance particle size	Friability	1	2	L
Drug substance particle size	Stability – chemical	1	2	L
Drug substance particle size	Stability – physical	1	2	L
Filler selection	*In vivo* performance	3	3	M
Filler selection	Dissolution	3	4	H
Filler selection	Assay	1	2	L
Filler selection	Degradation	1	3	L
Filler selection	Content uniformity	2	2	L
Filler selection	Appearance	3	3	M
Filler selection	Friability	4	4	H
Filler selection	Stability – chemical	3	3	M
Filler selection	Stability – physical	3	3	M
Moisture control in manufacturing	*In vivo* performance	1	2	L
Moisture control in manufacturing	Dissolution	1	3	L
Moisture control in manufacturing	Assay	2	4	M
Moisture control in manufacturing	Degradation	4	4	H
Moisture control in manufacturing	Content uniformity	1	1	L
Moisture control in manufacturing	Appearance	1	2	L
Moisture control in manufacturing	Friability	2	2	L
Moisture control in manufacturing	Stability – chemical	3	3	M
Moisture control in manufacturing	Stability – physical	2	2	L

Table 3.2.P.2.2-1 Results of Preliminary Hazard Analysis (continued)

Hazard	Event	Severity	Probability	Risk score
Blending	*In vivo* performance	2	2	L
Blending	Dissolution	1	2	L
Blending	Assay	3	3	M
Blending	Degradation	1	2	L
Blending	Content uniformity	3	3	M
Blending	Appearance	2	2	L
Blending	Friability	1	2	L
Blending	Stability – chemical	1	2	L
Blending	Stability – physical	1	2	L
Lubrication	*In vivo* performance	3	3	M
Lubrication	Dissolution	3	4	H
Lubrication	Assay	1	2	L
Lubrication	Degradation	1	2	L
Lubrication	Content uniformity	3	3	M
Lubrication	Appearance	2	3	M
Lubrication	Friability	3	3	M
Lubrication	Stability – chemical	1	2	L
Lubrication	Stability – physical	2	2	L
Compression	*In vivo* performance	3	3	M
Compression	Dissolution	3	3	M
Compression	Assay	2	2	L
Compression	Degradation	2	2	L
Compression	Content uniformity	1	2	L
Compression	Appearance	2	4	M
Compression	Friability	2	4	M
Compression	Stability – chemical	1	2	L
Compression	Stability – physical	2	3	M

Table 3.2.P.2.2-1 Results of Preliminary Hazard Analysis (continued)

Hazard	Event	Severity	Probability	Risk score
Coating	*In vivo* performance	2	2	L
Coating	Dissolution	2	2	L
Coating	Assay	2	2	L
Coating	Degradation	2	2	L
Coating	Content uniformity	1	1	L
Coating	Appearance	3	3	M
Coating	Friability	2	2	L
Coating	Stability – chemical	1	1	L
Coating	Stability – physical	1	2	L
Packaging	*In vivo* performance	1	1	L
Packaging	Dissolution	1	1	L
Packaging	Assay	1	1	L
Packaging	Degradation	1	1	L
Packaging	Content uniformity	1	1	L
Packaging	Appearance	1	1	L
Packaging	Friability	1	1	L
Packaging	Stability – chemical	3	3	M
Packaging	Stability – physical	3	3	M

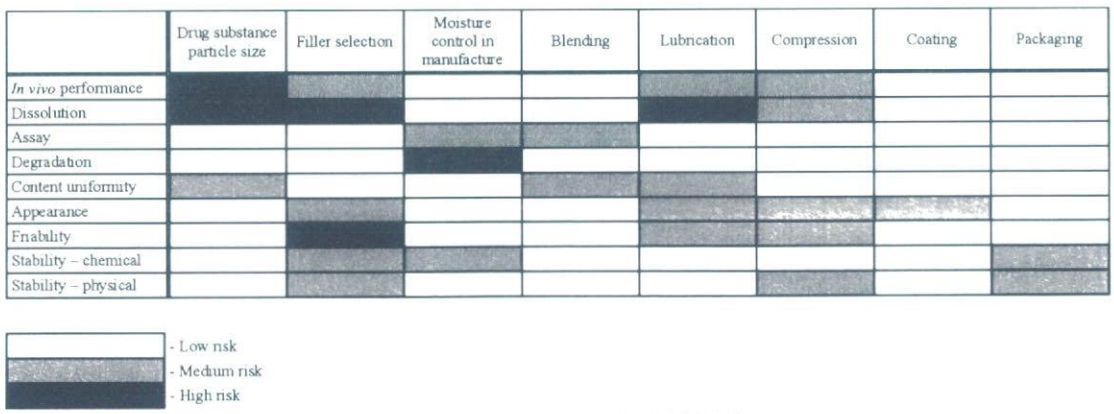

Figure 3.2.P.2.2-3 Summary of Initial Risk Assessment

Drug substance particle size, excipients and water content were assessed as properties that could affect tablet quality, based on the initial risk assessment before development of the drug product described above. Details of the assessment are shown in Table 3.2.P.2.2-2.

Table 3.2.P.2.2-2 Initial Risk Assessment of Sakura Tablet

Factor	Risk assessment
Drug substance	Particle size could affect *in vivo* drug behaviors due to the low dissolution rate and high permeability.
Excipients	The addition of poorly soluble (inorganic) excipients may reduce dissolution rate.
	The addition of soluble (organic) excipients could affects compressibility in compression.
	The addition of hydrophobic excipients (lubricant) may reduce dissolution rate.
Manufacturing process	Due to hydrolysis of the drug substance, the wet-granulation method cannot be used.
	The blending process must homogeneous distribution of the drug substance to achieve the desired content uniformity. Overblending should be avoided.
	Overblending of the lubricant increases surface hydrophobicity, and may decreases dissolution rate.
	Homogeneity must be controlled in the blending process.
	The disintegration time increases and the dissolution rate becomes slow when excess compression pressure is used.

3.2.P.2.3 Manufacturing Process Development

1) Risk Assessment on Drug Product Composition and Manufacturing Process

Risk assessment using Failure Mode Effects Analysis (hereafter FMEA) was performed to establish the drug product composition and its manufacturing process on a commercial scale.

The risk assessment will be performed on factors that are selected based on initial risk assessment results. The product composition and manufacturing process will then be designed.

Among the process inputs identified in the initial risk assessment that affect critical quality properties, the effects of excipients selection (poorly soluble, soluble) and water content in the granulation process on drug substance quality properties were deleted from the FMEA risk assessment criteria because the direct compression method was employed.

The initial risk assessment to establish the manufacturing process is likely to indicate that the blending time in the blending process could be a critical process. In addition, selection of direct compression was likely to require compression pressure in the tableting process as a critical process. In the FMEA assessment, the effects of batch size on the blending process and the effects of compression speed on the compression process were included as assessment criteria.

The results of the above assessment are shown in Table 3.2.P.2.3-1.

Table 3.2.P.2.3-1 Results of Item Evaluation

Factor	Critical quality properties identified in the initial risk assessment	Items for the FMEA assessment (critical quality properties)
Drug substance particle size	*In vivo* performance (solubility)	Dissolution (because amokisinol was confirmed as a BCS class 2 compound)
Excipient selection	Dissolution	Omitted from test items because direct compression was employed.
	Compressibility in compression	
Lubricant amount	Dissolution	Dissolution
Granulation	Water content	Omitted from test items because direct compression was employed.
Blending (blending time)	Content uniformity	Content uniformity
Blending (batch size)	Content uniformity	Content uniformity
Blending (lubricant)	Dissolution	Dissolution
Compression (compression pressure)	Disintegration and dissolution	Dissolution
Compression (compression speed)	Disintegration and dissolution	Dissolution

FMEA assessment, which treats factors listed in the initial risk assessment as failure mode, was performed. For evaluation, scores for severity, probability, and detectability are defined as below. When the value obtained by multiplying the severity, probability and detection timings by the risk priority number is <20, the rank is defined as low. When the value is from 20 or more to less than 40, the rank is defined as medium, and when the value is 40 or more, the rank is high.

The risk assessment was evaluated by team members who are responsible for drug product development. The results of the evaluation were discussed and confirmed by the team members. When the ratings among the team members differed, the higher rates were employed.

Table 3.2.P.2.3-2 Definition of Severity

Severity rank	Score	Remarks
Deviation	1	In case which affects the quality significantly, rank is 3 or 4.
Passed the re-test	2	———
Sub-batch or rejected batch	3	———
Stop the flow of manufacture	4	Affecting stable product supply
Recall	5	———

Table 3.2.P.2.3-3 Definition of Outbreak Probability

Probability rank	Score	Remarks
≤1/10000	1	Not more than once per 10,000 lots.
1/1000	2	Not more than once per 1,000 lots and not less than once per 10,000 lots
1/100	3	Not more than once per 100 lots and not less than once per 1,000 lots
1/10	4	Not more than once per 10 lots and not less than once per 100 lots
>1/10	5	Not less than once per 10 lots

Table 3.2.P.2.3-4 Definition of detectability

Detectability rank	Score	Remarks
Before each unit operation	1	———
During a unit operation	2	———
During series of unit operations	3	———
Test of the final product	4	———
Found by customers	5	———

The results of the risk analysis on each failure mode based on definitions of FMEA assessment are shown in Figure 3.2.P.2.3-1 and Table 3.2.P.2.3-5.

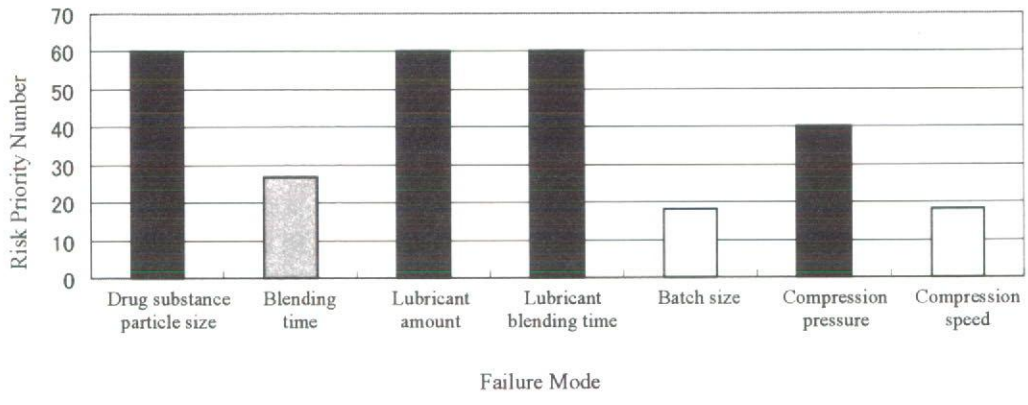

Figure 3.2.P.2.3-1 Results of FMEA Risk Assessment

Table 3.2.P.2.3-5 Results of FMEA Risk Assessment

Target product profile quality property	Potential failure mode	Effect	Severity	Outbreak probability	Detectability	Risk priority number
Dissolution	Drug substance particle size	Decreased dissolution	3	5	4	60
Content uniformity	Blending time	Not uniform	3	3	3	27
Dissolution	Lubricant amount	Decreased dissolution	3	5	4	60
Dissolution	Lubricant blending time	Decreased dissolution	3	5	4	60
Content uniformity	Batch size	Not uniform	3	2	3	18
Dissolution	Compression pressure	Decreased dissolution	4	5	2	40
Content uniformity	Compression speed	Not uniform	3	2	3	18

Severity	Score
Deviation	1
Passed the re-test	2
Rejection of sub-batch or batch	3
Stop the flow of manufacture	4
Recall	5

Outbreak probability	Score
≤1/10000	1
1/1000	2
1/100	3
1/10	4
>1/10	5

Detectability	Score
Before each unit operation	1
During a unit operation	2
During series of unit operations	3
Test of the final product	4
Found by customers	5

Risk priority number	Rank
≥40	
20≤ <40	
<20	

Based on the above results of risk analysis, the manufacturing process was designed mainly according to the nature of the drug substance particles, lubricant blending condition (lubricant amount, lubricant blending time) and compression pressure, which are process inputs that possibly affect critical quality properties.

4) Effects on Manufacturing Process Quality

PHA was used to assess the effects of the process inputs, which were identified during the manufacturing process evaluation, on the tablet quality properties.

Following hazards were listed for the risk analysis.

Material property

- Material particle size
- Excipient amount on tablet surface area

Process parameter

- Blending (blending speed and blending time)
- Lubricant blending (blending speed and blending time)
- Compression pressure
- Compression speed
- Batch size

The following items were listed for the event (effect) analysis.

Quality properties influencing clinical performance

- Dissolution
- Assay
- Content uniformity

Physical quality properties

- Appearance
- Hardness

For risk assessment using PHA, the severity and probability of risks were rated in a similar manner to the initial risk assessment.

The definition of severity and probability were the same as in the initial risk assessment.

Details of summary of effects and conclusions are shown in Table 3.2.P.2.2-6 and Figure 3.2.P.2.2-2 respectively.

Table 3.2.P.2.2-6 Results of Preliminary Hazard Analysis

Hazard	Event (Effect)	Severity	Probability	Risk score
Drug substance particle size	Dissolution	3	5	H
Drug substance particle size	Assay	3	1	L
Drug substance particle size	Content uniformity	3	4	M
Drug substance particle size	Appearance	1	1	L
Drug substance particle size	Hardness	1	2	L
Lubricant amount on tablet surface	Dissolution	3	3	M
Lubricant amount on tablet surface	Assay	1	1	L
Lubricant amount on tablet surface	Content uniformity	2	2	L
Lubricant amount on tablet surface	Appearance	3	3	M
Lubricant amount on tablet surface	Hardness	3	3	H
Blending (speed and time)	Dissolution	1	2	L
Blending (speed and time)	Assay	2	2	L
Blending (speed and time)	Content uniformity	3	3	M
Blending (speed and time)	Appearance	1	2	L
Blending (speed and time)	Hardness	2	2	L
Lubricant blending (speed and time)	Dissolution	3	3	M
Lubricant blending (speed and time)	Assay	2	2	L
Lubricant blending (speed and time)	Content uniformity	1	1	L
Lubricant blending (speed and time)	Appearance	2	2	L
Lubricant blending (speed and time)	Hardness	2	2	L
Compression pressure	Dissolution	3	3	M
Compression pressure	Assay	2	2	L
Compression pressure	Content uniformity	2	2	L
Compression pressure	Appearance	2	4	M
Compression pressure	Hardness	3	4	H
Compression speed	Dissolution	2	2	L
Compression speed	Assay	2	2	L
Compression speed	Content uniformity	1	1	L
Compression speed	Appearance	2	2	L
Compression speed	Hardness	2	2	L
Batch size	Dissolution	1	1	L
Batch size	Assay	1	1	L
Batch size	Content uniformity	2	2	L
Batch size	Appearance	1	1	L
Batch size	Hardness	1	1	L

	Quality properties influencing clinical performance			Physical quality properties	
	Dissolution	Assay	Content uniformity	Appearance	Hardness
Material characteristics					
Drug substance particle size					
Lubricant amount on tablet surface					
Process parameters					
Blending (speed and time)					
Lubricant (blending speed and time)					
Compression pressure					
Compression speed					
Batch size					

- Low risk
- Medium risk
- High risk

Figure 3.2.P.2.2-2 Summary of Effects of Each Parameter on Quality Properties

Based on the above summary, it was concluded that it was highly likely that the drug substance particle size affects dissolution, and that compression pressure affects tablet hardness. However it is considered that appropriate tablet quality properties can be maintained by controlling the compression pressure in the manufacturing because the results of an *in vivo* study showed a low effect of the compression pressure on the tablet quality.

5) Risk Assessment after Development of the Manufacturing Process

The results of the risk assessment using FMEA on the manufacturing process in the planned commercial scale after development of the manufacturing process are shown in Figure 3.2.P.2.3-3 and Table 3.2.P.2.3-7. The definitions of severity, probability and detectability follow section 1) described above.

The lubricant amount and lubricant blending time at the risks of the failure mode were judged as low based on the results of design evaluation of the lubricant blending process. In addition, for the compression pressure, the control range was determined and its risk could be decreased. Regarding the blending time, however, its risk was judged as medium both of before and after development of the manufacturing process, because it was found that the blending process needed to be monitored in the control strategy according to the results of design evaluation of the blending process.

The blending process and compression process, which were judged to contain failure mode of medium risk in the risk assessment after assessment of the manufacturing process, were judged as critical. In this direction, the risk concerning drug substance particle size remains high also after the manufacturing process development, because control is required at the acceptance step.

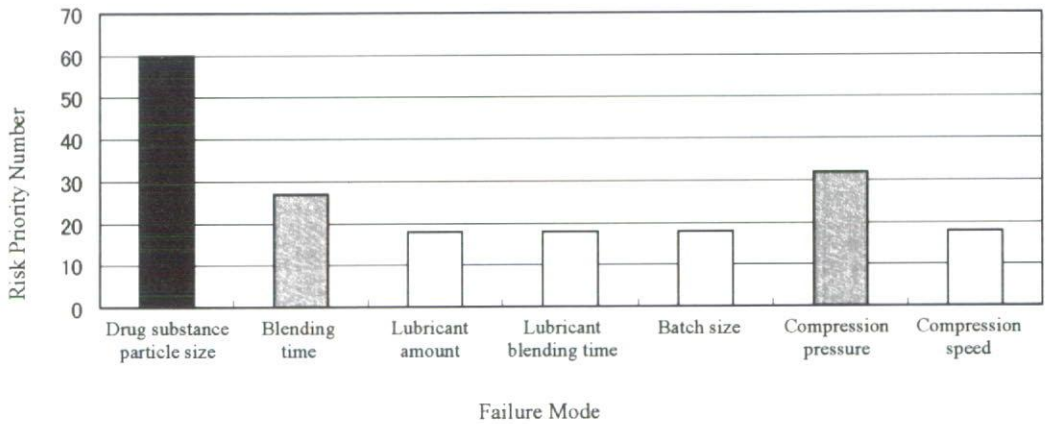

Figure 3.2.P.2.3-3 Results of FMEA Risk Analysis

Table 3.2.P.2.3-7 Results of FMEA Risk Analysis

Target product profile quality property	Potential failure mode	Effect	Severity	Outbreak probability	Detectability	Risk priority number
Dissolution	Drug substance particle size	Decreased dissolution	3	5	4	60
Content uniformity	Blending time	Not uniform	3	3	3	27
Dissolution	Lubricant amount	Decreased dissolution	3	3	2	18
Dissolution	Lubricant blending time	Decreased dissolution	3	3	2	18
Content uniformity	Batch size	Not uniform	3	2	3	18
Dissolution	Compression pressure	Decreased dissolution	4	4	2	32
Content uniformity	Compression speed	Not uniform	3	2	3	18

Severity	Score
Deviation	1
Passed the re-test	2
Rejection of sub-batch or batch	3
Stop the flow of manufacture	4
Recall	5

Outbreak probability	Score
≤1/10000	1
1/1000	2
1/100	3
1/10	4
>1/10	5

Detectability	Score
Before each unit operation	1
During a unit operation	2
During series of unit operations	3
Test of the final product	4
Found by customers	5

Risk priority number	Rank
≥40	
20≤ <40	
<20	