n: Total number of tested samples
s: Standard deviation of samples

System suitability
System performance
Determine the content using the blended powder, demonstrated to contain about 100% of the active ingredient, by the controlled evaluation: it is 98.0% to 102.0% of the labeled amount.

Calibration and validation
Measurement at commercial production uses pre-treatment for spectrum measurement and analytical method used in constructing a calibration curve, and also uses the same measurement parameters as those in performing calibration. The validation is performed using measurement apparatuses to be used at commercial production in a scale reflecting actual production, and the calibration curve is validated using actually manufactured batches at appropriately determined intervals. The results are as described in '2.3.P.3.4.2 Validation of Test Methods (Analytical Procedures).'

Calibration
Blended powders with the additives at the same compounding ratio were prepared at 5 levels of the content of the active ingredient in a range from 70% to 130% of the labeled amount, and a calibration curve was constructed using MSC as pre-treatment for spectrum measurement and PLS as analytical method. As test of calibration model, the blended powder samples prepared containing the active ingredient in range from 70% to 130% of the labeled amount.

Validation
The obtained calibration curve was validated using 3 batches reflecting commercial production.

Periodic revalidation
It was decided that the calibration curve would validated using actually manufactured batches at appropriately determined intervals. The controlled validation to be used in calibration and validation used the blended powder content (HPLC) as shown below:

[Blended powder content: HPLC]
Weigh accurately XX mg of the blended material, add exactly XX mL of the internal standard solution, and shake well for XX minutes. Centrifuge this solution, to XX mL of the supernatant add XX mL of the mobile phase, and use this solution as the sample solution. Separately, weigh accurately X.XXX g of Amokinol Reference Standard, dissolve in the mobile phase to make exactly XX mL. Pipet XX mL of the solution, add the mobile phase to make XX mL, and use this solution as the standard solution. Perform the test with 20 □L each of the sample solution and the standard solution according to the following conditions. Determine each peak area, Q_T and Q_S, of the solutions by the automatic integration method.

Amount (mg) of amokinol ($C_{XX}H_{XX}N_XO_X$) = $W_S \times Q_T/Q_S \times$ X.XXX
W_S: Amount (mg) of Amokinol Reference Standard

Internal standard solution: A solution of benzophenone in a mixture of acetonitrile and water (1:1) (1 in 2000)

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 210 nm).

Column: A stainless steel column about 4.6 mm in inside diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 ◘m in particle diameter).

Column temperature: A constant temperature of about 40°C.

Mobile phase: A mixture of acetonitrile and water (1:1).

Flow rate: Adjust the flow rate so that the retention time of amokinol is about X minutes.

System suitability

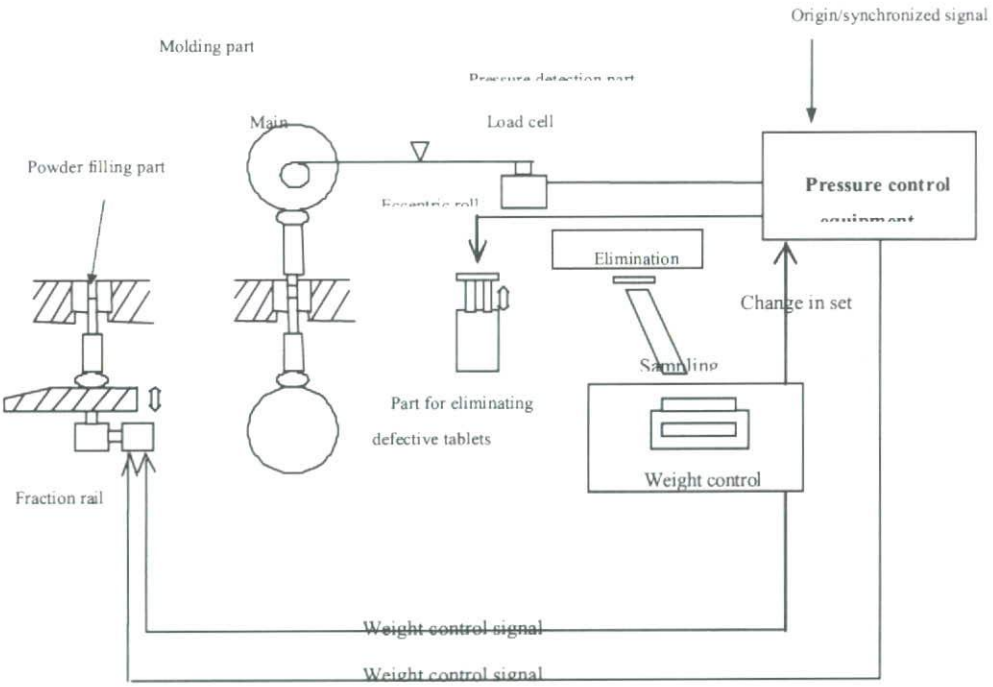
System performance: Proceed with 20 ◘L of the standard solution under the above operating conditions. Amokinol and the internal standard are eluted in this order, and a resolution between their peaks is not less than XX.

System reproducibility: Repeat the test six times with 20 ◘L of the standard solution under the above operating conditions. The relative standard deviation of the peak area of amokinol is not more than 1.0%.

2.3.P.3.3.2.3. Compression Process

Online monitoring control was employed for the compression pressure of each tablet in the compression process. A compression pressure 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 on measured compression pressure. In addition, the mean weight information periodically measured by automatic sampling is fed back to the compression pressure control equipment, a correcting system that adjusts the amounts of filled blended powder (filling depth) and compression pressure control equipment was also selected.

Balance: XXXXX
Equipment for measuring the compression pressure: XXXXX
Equipment for conducting automatic sample measurements/equipment for controlling weight: XXXX



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

Among the specification test items, real-time release was employed for the content uniformity test, dissolution test and content (assay). The process control methods that serve as each test method are as shown below.

2.3.P.3.4.1 Test Items in Real-time Release

Based on the control strategy described in Section 2.3.P.2.3 Manufacturing Process, the dissolution test, content uniformity test and content were judged as candidates for real-time release.

2.3.P.3.4.1.1 Content Uniformity Test

To ensure content uniformity in the final product, the homogeneity of the blended powder in the blending process and compression pressure in the compression process were monitored for control.

The authors employed a control method whereby homogeneity was monitored in the blending process by the in-line NIR that finished the blending process when the values of six continuous samples were within the acceptable range shown in Table 2.3.P.3.4.1-1.

Based on evaluation of blended powder using HPLC method at pilot plant scale, and result obtained from assay homogeneity following compression, it was confirmed that assay homogeneity for tablet can always be managed to fall within acceptance criteria when blending homogeneity is monitored within inline NIR during blending process.

Taking into consideration the case where blending homogeneity evaluation other than monitoring by NIR is needed, the content of blended powder (HPLC) has been set in 2.3.P.3.3.3. The test will be performed on blended powder from 6 sampling points. The same control range as the acceptable range by NIR has been employed.

Table 2.3.P.3.4.1.1-1 Acceptable Range of the Homogeneity of Blended Powder

Number of points sampled	n = 10
Acceptable range	Mean = within 2% of the labeled value
	RSD: less than 3.0%

Compression pressure in the compression process was controlled using Auto Weight Control (AWC). AWC is a control method that utilizes the linear relationship between the compression pressure and the weight of the drug product. The weight of the tablet is calculated from the determined compression pressure. Tablets not meeting the specified criteria are rejected. The application of this system makes it possible to control the compression pressure of all tablets. The combination of this method with control of the homogeneity of the blended powder is believed to control content uniformity of the drug product. Therefore, it was decided that the content uniformity test could be omitted from the specifications.

Table 2.3.P.3.4.1.1-2 Control of Compression Pressure

Control range (on a weight basis)	97 to 103 mg
RSD	Less than 2%

2.3.P.3.4.1.2 Dissolution Test

The effects of each factor on the dissolution rate were studied for the drug products manufactured according to the allocation of the drug substance particle size, specific surface of magnesium stearates, lubricant blending time and compression pressure as factors. 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 (%) = 108.9 - 11.96 $\times \log_{10}$(d(0.9)) drug substance particle size - 7.556 $\times 10^{-5} \times$ specific surface area of magnesium stearate (cm^2/g) - 0.1849 $\times$ lubricant blending time (min) - $3.783 \times 10^{-2} \times$ compression pressure (N)

For the particle size of the drug substance, the volume distribution was measured using a dry method without preparing the sample using a laser diffraction scattering method. For the specific surface area of magnesium stearate, nitrogen molecules were adsorbed on a surface of powder particles at low temperature, and the specific surface area was determined from the adsorption amount (BET method). The items and ranges for process control that applies to the dissolution test are shown in Table 2.3.P.3.4.1.2. By controlling each process using this system, dissolution of the drug product is believed to be controllable. Therefore, dissolution test in the specification could be omitted.

Table 2.3.P.3.4.1.2-1 Process Control Items and Control Range

Process control items	Control range
Drug substance particle size	XX-XX $\log_{10}$(d(0.9))
Specific surface area of magnesium stearate	XX-XX cm2/g
Lubricant blending time	XX-XX min
Compression pressure	XX-XX N

2.3.P.3.4.1.3 Content

For assay of the active ingredient, process control by HPLC has been set in the blending process. In the pilot scale, the weight of each ten tablets from 20 sampling points was determined over the manufacturing process. The process control ranges from these tests are shown in Table 2.3.P.3.4.1.3-1.

Utilizing above strategies, conclusion was drawn for this particular drug product that conventional assay studies required as part of release test can be abbreviated and used for release assessment by utilizing the assay value (refer to following calculation) that will be calculated using active ingredient assay amount in blended powder obtained during blending process, drug product weight following compression process and correction value to be taken from theoretical weight.

Content (%) = Blended powder content $\times$ drug product weight $\div$ theoretical tablet weight

Table 2.3.P.3.4.1.3-1 Process Control Items and Control Range

Process control items	Control range
Content of blended powder (blending process)	98 to 102%
Tablet weight (compression process)	97 to 103 mg

2.3.P.3.4.2. Validation of Test Methods (Analytical Procedures)

For the NIR monitoring method used in the blending homogeneity test, the calibration model was constructed and validated.

[1] Construction of Calibration Model

The blended powders containing the active ingredient at 5 levels ranging from 70 to 130% of the labeled amount were used. Samples were taken from 10 sampling points at each level of blended powder. This procedure was repeated 3 times on different blended powders, and a total of 150 samples were used for construction of a calibration curve. The determination of observed values used the assay (HPLC) in drug product homogeneity in the specifications and test methods as the controlled evaluation for validation. The results of the constructed calibration curve confirmed a good linearity and correlation with observed values in a range of ±30% of theoretical content value.

A fiber probe was used in the NIR measurement. Y software of XX Company was used to construct the calibration curves. For analysis, the method of Partial Least Squares (PLS) was used and optimization calculation was performed.

The optimized results are shown in Table 2.3.P.3.4.2-1.

Table 2.3.P.3.4.2-1 Test Results of the Calibration Curves

Items	Results
Range of wavelength for the analysis	6100 - 5500 cm^{-1}
Pre-treatment for spectrum measurement	MSC
PLS component number	5
Multiple correlation coefficient	0.985
RMSECV (standard deviation)	0.67

It was confirmed that the loading spectra used in the calibration model were similar to the spectra of the drug substance, so this model was justified.

[2] Test of the Calibration Model (Validation)

Fifty samples were used for the validation. As in calibration, the validation was performed on blended powder samples prepared at 5 levels ranging from 70 to 130% of the active ingredient, and the results were, as shown in Table 2.3.P.3.4.2-2, favorable.

Table 2.3.P.3.4.2-2 Test Results of Calibration Curves

Items	Results
Multiple correlation coefficient	0.981
RMSEP (standard error)	0.75

[3] Test of commercial production facilities

A total of 30 values measured on 10 samples each of 3 batches of blended powdered manufactured in a commercial manufacturing scale were incorporated into the calibration curve constructed in [1], and the curve was corrected. NIR measured values obtained from the batches manufactured in a commercial manufacturing scale and the results of HPLC showed a good correlation.

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 96.4% to 102.3% of the labeled amount and its RSD values were 1.4% to 1.8%. Therefore all batches met the criteria of Content Uniformity 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)	97.9 (96.4-102.1)	99.1 (97.4-101.0)	100.3 (96.5-102.3)
Relative standard deviation (%)	1.6	1.8	1.8
Determined value	4.4	3.3	4.4

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 102.5% 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	89.8	87.3	88.5
Dissolution test results Mean (min-max)	92.8 (88.4 - 94.2)	90.3 (89.0 - 102.5)	91.5 (90.5 - 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 (Sakura Tablet, Film-coated Tablet)

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: Not more than 0.2% Total related substances: Not more than 1.0%
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% (Q)
Content (assay)		Based on the content of the blended powder in the blending process and on the weight in the compression process.	
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)

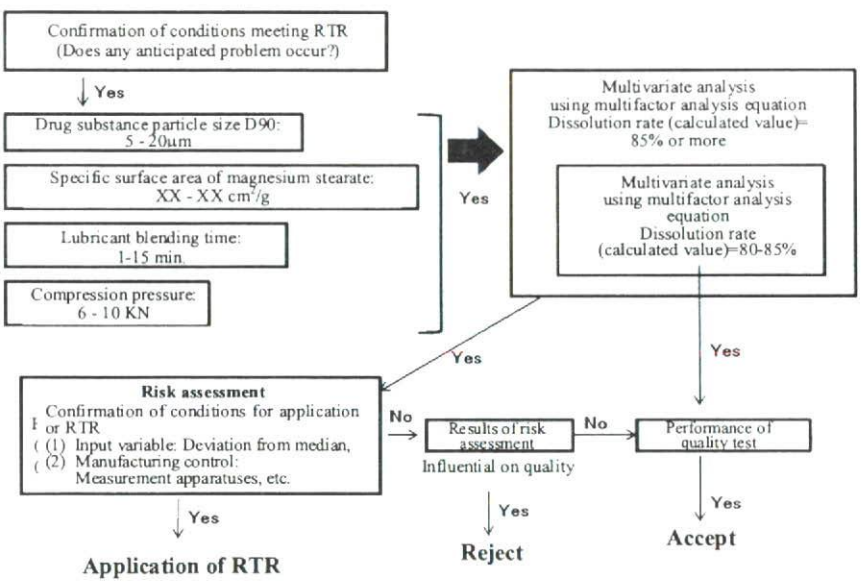
Note) Only dissolution test, content uniformity and assay are described because real release testings are set for those items. Other analytical procedures must be described.

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. The real-time release procedures are described for each item of real-time release tests. The quality test methods performed according to the control strategies such as the results of risk assessment and change in manufacturing site and in stability testing are described.

2.3.P.5.2.1 Dissolution Test

The real-time release procedures are performed according to the following flow chart.

Dissolution test (decision tree)



(1) After 3rd process of amokinol drug substance (pulverization of amokinol), drug substance particle size, specific surface area of magnesium stearate in the control of raw materials for Sakura tablets, blending time at 2nd blending process, and compression pressure at 3rd process (compression process) are confirmed to meet the in-process control values.

(2) The dissolution rate is calculated from the following equation, and the rate which is 85% or more is considered acceptable.

Dissolution rate (%) to the labeled amount of amokinol (CxxHxxNxOx) = $108.9 - 11.96 \times$ drug substance particle size $[\log_{10}(d(0.9))] - 7.556 \times 10^{-5}$ x specific surface area of magnesium stearate (cm^2/g) $- 0.1849 \times$ lubricant blending time (minutes) $- 3.783*10^{-2} \times$ compression pressure (N)

When the dissolution rate is 80-85%, the dissolution rate is calculated from the second dissolution test, and the rate which is 80% (Q) or more is considered acceptable.

Take 1 tablet of Sakura Tablets, and perform the test at 50 rpm as directed in the Paddle Method, using 900 mL of 0.1% sodium lauryl sulfate TS. Take not less than 20 mL of the dissolved solution at 30 minutes after starting the test, and filter through a membrane filter (not more than 0.45 □m in pore size). Discard the first X mL of the filtrate, pipet subsequent V mL, add 0.1% sodium lauryl sulfate TS to make exactly V' mL of a solution containing about XX □g of amokinol (CxxHxxNxxOx) per mL according to the labeled amount, and use this solution as the sample solution.

Separately, weigh accurately about X.XX g of amokinol reference standard, add XX mL of 0.1% sodium lauryl sulphate TS to make exactly XX mL. Pipet 1 mL of this solution, add 0.1% sodium lauryl sulfate TS to make exactly XX mL, and use this solution as the standard solution. Perform the test with the sample solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine peak areas, A_T and A_S, of amokinol in each solution by the automatic integration method.

Dissolution rate (%) to the labeled amount of amokinol (CxxHxxNxOx) = $W_S \times A_T/A_S \times V'/V \times 1/C \times$ X.XXX

W_S: Amount (mg) of amokinol reference standard

C: Labeled amount (mg) of amokinol (CxxHxxNxOx) per tablet

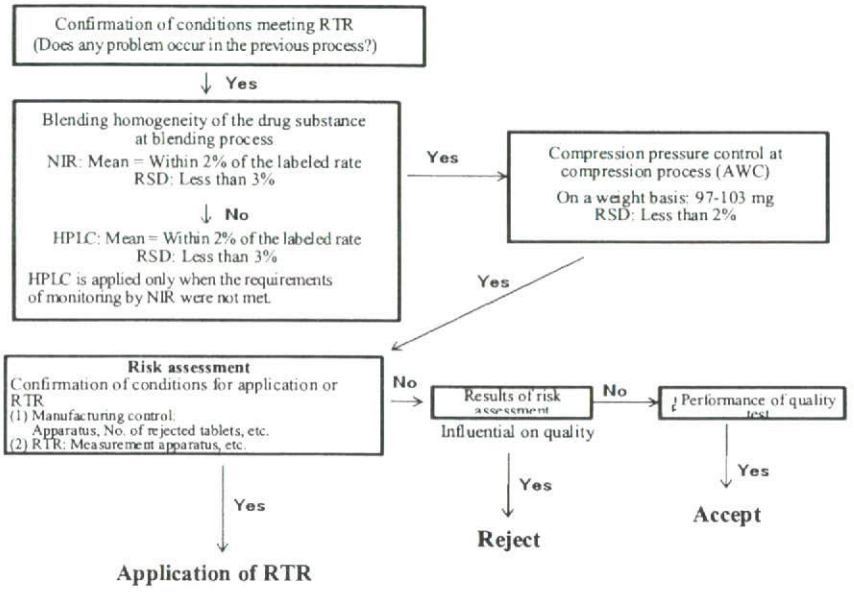
Operating conditions
Detector: An ultraviolet absorption photometer (wavelength: 210 nm).
Column: A stainless steel column about 4.6 mm in inside diameter and 15cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 □m in particle diameter).
Column temperature: A constant temperature of about 40°C.
Mobile phase: A mixture of acetonitrile and water (1:1).
Flow rate: Adjust the flow rate so that the retention time of amokinol is about X minutes.

System suitability
System performance: Proceed with 20 □L of the standard solution under the above operating conditions. Amokinol and the internal standard solution are eluted in this order, and a resolution between their peaks is not less than XX.
System reproducibility: Repeat the test six times with 20 □L of the standard solution under the above operating conditions. The relative standard deviation of the peak area of amokinol is not more than 1.0%.

2.3.P.5.2.2 Content Uniformity

The real-time release procedures are performed according to the following flow chart.

Content uniformity test (decision tree))



The blending homogeneity at the 1st process (blending process) and tablet weight at the 3rd process (compression process) are confirmed to meet the in-process control values.
When the results obtained by NIR cannot be employed in blending homogeneity monitoring at blending process, and the test is performed on samples taken from 6 sampling points according to the content of blended powder (HPLC) described in 2.3.P.3.3.1.

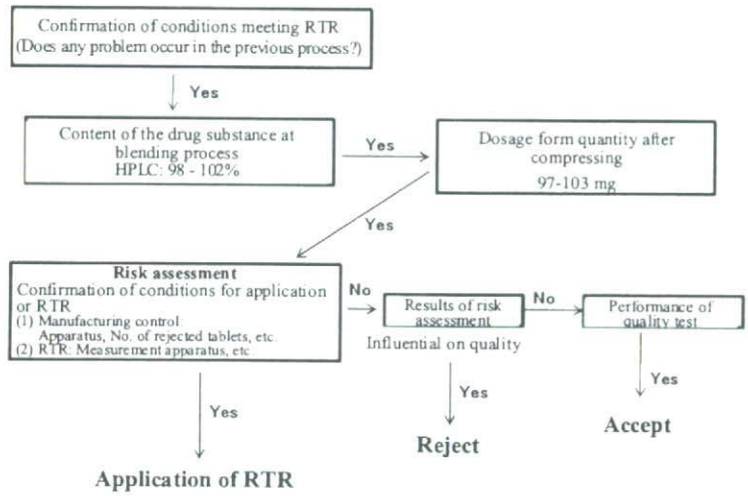
When it is judged from the results of risk assessment that quality test is necessary, the content uniformity test is performed by the following method: the requirements are met.
Take 1 tablet of Sakura tablets, add 50 mL of a mixture of acetonitrile and water (1:1), shake until the tablet is disintegrated, radiate ultrasound for 10 minutes, and add a mixture of acetonitrile and water (1:1) to male exactly 100 mL. Filtrate this solution through a membrane filter (0.45 □m in pore size), and use the filtrate as the sample solution. Separately, weigh accurately about X.XX g of amokinol reference standard, dissolve in a mixture of acetonitrile and water (1:1) to make exactly V mL. Pipet 5 mL of this solution, add a mixture of acetonitrile and water (1:1) to make exactly 100 mL, and use this solution as the standard solution. Perform the test with these solutions as directed under the Ultraviolet Visible Spectrophotometry and determine absorbance of A_T and A_S at 284 nm using a mixture of acetonitrile and water (1:1) as the blank.

Amount (mg) of amokinol = $W_S \times A_T/A_S \times$ X.XXX
W_S: Amount (mg) of amokinol reference standard

2.3.P.5.2.3 Content (assay)

The real-time release procedures are performed according to the following flow chart.

Content (decision tree)



The amount of amokinol is calculated by the following equation.

Amount (%) to labeled amount of amokinol (CxxHxxNxxOx) = Content (%) of amokinol in blended powder at 1st process (blending process) × tablet weight (mg) after 3rd process (compression)/*C*
C: Labeled amount (mg) of amokinol (CxxHxxNxOx) per tablet

When it is judged from the results of risk assessment that the quality test is necessary, the amount of amokinol is measured by the following assay method.

Weigh accurately, and powder not less than 20 Sakura tablets. Weigh accurately a portion of powder, equivalent to about X.XXX g of amokinol according to the labeled amount, add exactly XX mL of the internal standard solution, and shake thoroughly for XX minutes. Centrifuge this solution, to XX mL of the supernatant add the mobile phase to make XX mL, and use this solution as the sample solution.

Separately, weigh accurately about X.XXX g of amokinol reference standard, dissolve in the mobile phase to make exactly XX mL. Pipet XX mL of this solution, add the mobile phase to make XX mL, and use this solution as the standard solution. Perform the test with 20 □L each of the sample solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine peal areas, QT and QS, of amokinol in each solution.

Amount (mg) of amokinol (CxxHxxNxOx) = $W_S \times Q_T/Q_S \times$ X.XXX
W_S: Amount (mg) of amokinol reference standard
Internal standard solution = A solution in a mixture of acetonitrile and water (1:1) (1 in 2000)

Operating conditions
Detector: An ultraviolet absorption photometer (wavelength: 210 nm).
Column: A stainless steel column about 4.6 mm in inside diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 □m in particle diameter).

Column temperature: A constant temperature of about 40°C.
Mobile phase: A mixture of acetonitrile and water (1:1).
Flow rate: Adjust the flow rate so that the retention time of amokinol is about X minutes.

System suitability
System performance: Proceed with 20 ㎕ of the standard solution under the above operating conditions. Amokinol and the internal standard are eluted in this order, and a resolution between their peaks is not less than XX.
System reproducibility: Repeat the test six times with 20 ㎕ of the standard solution under the above operating conditions. The relative standard deviation of the peak area of amokinol is not more than 1.0%.

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

Note: Only dissolution test is decribed

2.3.P.5.3.1 Dissolution Test

Analytical validation is as summarized in Table 2.3.P.5.3-1, and has been shown by the results of linearity, accuracy, and precision to be suitable as analytical method.

Table 2.3.P.5.3.1-1 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.5.3.2 Content Uniformity

2.3.P.5.3.3 Content (Assay)

2.3.P.5.4 Batch Analyses

2.3.P.5.5 Characterisation of Impurities

2.3.P.5.6 Justification of Specification and Test Methods

Note: Only dissolution test is decribed

2.3.P.5.6.1 Dissolution Test

It has been decided to control drug substance particle size, specific surface area of magnesium stearate, blending time at 2nd blending process, compression pressure as real-time release in place of the dissolution test. When the dissolution rate (%) calculated from these 4 items is not less than 85%, the real-time release was considered acceptable taking into account the separately established quality test specification, dissolution rate (%) = 80%Q. When the calculated dissolution rate is 80-85% and the results of risk assessment indicates that this is not considered to affect the quality, the separately established quality tests is performed on the batch in issue.

2.3.P.5.6.1.1 Justification of Specification and Methods of 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.5.4-1.

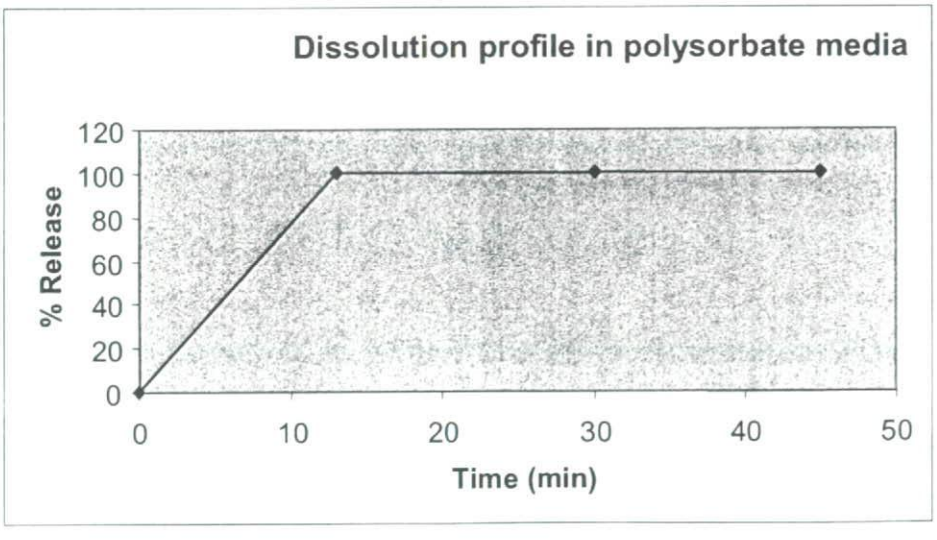


Figure 2.3.P.5.4-1 Dissolution Profiles in the Polysorbate 80 Added Test Fluids

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.5.4-2.

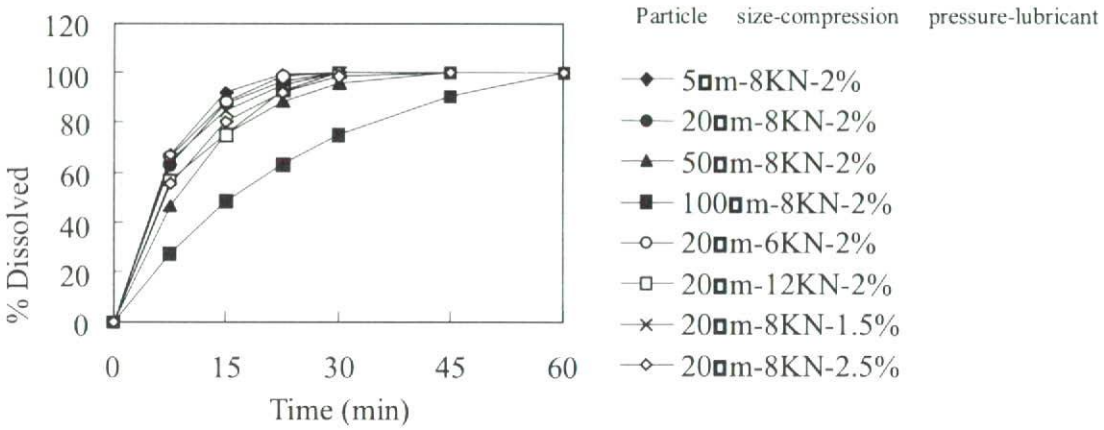


Figure 2.3.P.5.4-2 Dissolution Profiles in 0.1% Sodium Lauryl Sulphate Test Fluid

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.

2.3.P.5.6.2 Content Uniformity

2.3.P.5.6.3 Content (Assay)

MODULE 3: Quality

Generic name: Amokinol

3.2.P.2 PHARMACEUTICAL DEVELOPMENT

Sakura Tablet

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

3.2.P.2.2 Drug Product

3) Initial Risk Assessment

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

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

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

Material attributes and processes that are likely to affect tablet quality attributes 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 PHA

The risk assessment in this development stage were qualitatively evaluated by team members 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 members. When the rating given by the team members differed, the higher risk rating was employed.

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

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

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 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 PHA 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 PHA

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