

Application Form for Sakura Tablet

**Mock-Up for the Manufacture Method, Specifications,
and Test Method Columns of Drug Product (Sample Description)**

Research on the construction of steady and efficient processes
for the manufacture, development, and approval review of drugs

First Section Meeting

Application Form for Sakura tablet_V2_01_0900310 for translation

[Manufacturing method]

[Scale of manufacturing process]:

Manufacture, packaging, labeling, storage, and testing of Sakura Tablet

Critical steps

<First Step> Blending process

<Second Step> Second blending process

<Third Step> Compression process

<First Step> Blending process

Blend <<30 w/w%>> amokinol, <<53 w/w%>> calcium hydrogen phosphate hydrate, <<10 w/w%>> D-mannitol, and <<5 w/w%>> sodium starch glycolate. Determine the blending endpoint according to [Process control 1]. [Process control 2]

<Second Step> Second blending process

To the mixture obtained from the First Step, add 2 w/w% magnesium stearate with respect to the composition of the Sakura Tablet, and blend the mixture using a tumbling mixer for <<1 to 15 min>>.

<Third Step> Compression process

Compress the mixture obtained from the Second Step at 6 - 10 kN using a rotary type tableting machine (with a punch of 6 mm in diameter) [Process control 3]

<Fourth Step> Coating process

Transfer the compressed uncoated tablets that were manufactured in the Third Step into a coating pan, and spray coat them with a coating solution.

<Fifth Step> Packaging, labeling, and storage processes

Thereafter, fill “a polypropylene film” with the tablets that were already coated in the step mentioned above and package them into “aluminium foil” and seal it by heating with a blister packaging machine. Cut the sealed products to make PTP sheets and transfer them into “a carton box” and perform labeling appropriately. Store these labeled boxes and perform appropriate testing.

[Control item in the Second Step (Raw material)]

Specific surface area of magnesium stearate (Brunauer, Emmett, and Teller (BET) method)

[Process control 1]

Relative standard deviation: Less than 3% (near-infrared (NIR) method)

When the blend uniformity is tested according to the test method (NIR method) as determined under the uniformity of dosage units (RTRT) of [Specifications & test methods], the relative standard deviation is less than 3%.

[Process control 2]

Content: 98 to 102% (high-performance liquid chromatography (HPLC) method)

When the content is tested according to the test method (HPLC method) as observed in the assay (RTRT) of [Specifications & test methods], the content is equivalent to 98 to 102%.

[Process control 3]

When the mean weight of the tablet (following tablet compression) is measured, the content is 100 ± 3 mg.

[Specifications & test methods]

[Test name]: Content

[Specifications & test methods]

Sakura Tablet contains not less than 95.0 and not more than 105.0% of the labeled amount of amokinol ($C_{xx}H_{xx}N_xO_x$: XXX.XX).

[Specifications & test methods]

[Test name]: Description

[Specifications & test methods]

Sakura Tablet occurs as light red film-coated tablets.

[Specifications & test methods]

[Test name]: Identification

[Specifications & test methods]

Weigh XX g of powdered Sakura Tablet, equivalent to X mg of amokinol ($C_{xx}H_{xx}N_xO_x$). Add X mL of a mixture of acetonitrile and water (1:1), shake well for XX min, and filter. Discard the first 10 mL of the filtrate, and use the subsequent filtrate as the sample solution. Separately, to X mg of amokinol reference standard add X mL of a mixture of acetonitrile and water (1:1), shake well for XX min, filter, and use the filtrate as the standard solution. Determine the absorption spectrum of the sample and standard solutions as directed under Ultraviolet-visible Spectrophotometry, and compare the spectrum with the Reference Spectrum: both spectra exhibit similar intensities of absorption at the same wave number.

[Specifications & test methods]

[Test name]: Purity, related substances

[Specifications & test methods]

Weigh accurately not less than 20 tablets of Sakura Tablets and grind to powder. Weigh accurately a quantity of powdered Sakura Tablet, equivalent to X.XXX g of amokinol according to the labeled amount, add the mobile phase to make exactly 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, and use this solution as the standard solution. Perform the test with 20 μ L each of the sample and standard solutions as directed under the Liquid Chromatography according to the following conditions. Determine the peak areas (A_T and A_S) of amokinol in the sample solution and the standard solution by the Automatic integration method: the amount of each related substance is not more than 0.2%, and the total amount of related substances is not more than 1.0%.

(Equation 1)

Operating conditions:

- Detector: An ultraviolet absorption photometer (wavelength, 210 nm)
- Column: A stainless steel column 4.6 mm in inside diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μ 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 min.
- System suitability:

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Test for required detectability: Pipet 10 mL of the standard solution, and add the mobile phase to make exactly 100 mL. Confirm that the peak area of amokinol obtained from 20 μ L of this solution is equivalent to 7% to 13% of that of the standard solution.

System performance: Dissolve X.XXX g each of amokinol and YYY in XX mL of the mobile phase. When the procedure is run with 20 μ L of this solution under the above operating conditions, amokinol and YYY are eluted in this order with the resolution between the peaks being not less than XX.

System repeatability: When the test is repeated 6 times with 20 μ L of the standard solution under the above operating conditions: the relative standard deviation of the peak area of amokinol is not more than 2.0%.

[Specifications & test methods]

[Test name]: Uniformity of dosage units (RTRT)

[Specifications & test methods]

This test is performed as a real-time release testing, which is subsequently to be established as the release specification.

The blend uniformity in the blending process <First Step> and the tablet weight in the compression process <Third Step> conform to the designated process control values.

Note: The blend uniformity in the blending process <First Step> is tested according to the following test method.

Perform the test as directed under Near-infrared Spectrophotometry (NIR) using the probe in diffuse reflection mode through a glass plate glass made of borosilicate glass from the outside of the operating blending equipment, and determine the blend uniformity according to the relative standard deviation of the assay values obtained at 6 consecutive points.

(Equation 2)

Operating conditions:

Measurement method: Diffuse reflectance
Light source: High-energy air-cooled NIR source
Detector: High-sensitive InGaAs detector
Scanning range: 7500 - 4000 cm^{-1}
Scanning frequency: 16-fold
Resolution: 8 cm^{-1}
Conditions for the pretreatment of spectrum: Multiplicative Scatter Correction (MSC)
Analytical method: Partial least squares (PLS)

System suitability:

System performance:

When the content is determined using the blending powder in which the content of the drug substance has been verified to be almost 100% according to a control evaluation procedure, the content is equivalent to 98.0% to 102.0% according to the labeled amount.

In this study, the following calibration and validation processes are performed; furthermore, a calibration curve obtained for the periodic revalidation implemented is used, where appropriate.

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Calibration:

Use at least 5 samples of blending powder with different contents but with the same excipient rate as that of Sakura Tablet, which are prepared to contain drug substance in the range of 70% to 130% according to the labeled amount. Use MSC and PLS for the pretreatment of the spectrum and the analytical method respectively, to construct calibration curve.

Validation:

Validate the calibration curve obtained using the production lots that reflect the production on commercial-scale.

Periodic revalidation:

Validate the calibration curve using commercial-scaled production lots at appropriately predetermined intervals.

The control evaluation procedure to be used for the system suitability, calibration, and validation follows the Assay (RTRT) used in HPLC provided in the [Specifications & test methods] section.

[Specifications & test methods]

[Test name] Uniformity of dosage units

[Specifications & test methods]

This test can be substituted with the uniformity of dosage units (RTRT), which is a real-time release test, and is not performed at the time of release.

In case of any changes to the manufacturing process, perform the test according to the following method until the verification for each process control procedure is entirely completed: it meets the requirement of the Content uniformity test.

Furthermore, if the RTR is not applicable in a particular case in which no effect on the quality of Sakura Tablets has been verified in the results of risk assessment, perform the test according to the following method: it meets the requirement of the Content uniformity test. .

To 1 tablet of Sakura Tablet add 50 mL of a mixture of acetonitrile and water (1:1), and shake the mixture until the tablet is disintegrated. Expose the solution to ultrasonic vibration for 10 min, and add a mixture of acetonitrile and water (1:1) to make exactly 100 mL. Filter this solution through a membrane filter (pore size, 0.45 μ m), and use the filtrate as the sample solution. Separately, weigh accurately about X.XX g of amokinol reference standard, and 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 the sample and standard solutions as directed under Ultraviolet-visible Spectrophotometry, using a mixture of acetonitrile and water (1:1) as the control solution; determine the absorbance (A_T and A_S) of the sample solution and the standard solution at the wave length of 284 nm.

(Equation 3)

[Specifications & test methods]

[Test name]: Dissolution (RTRT)

[Specifications & test methods]

This test is performed as the real-time release testing, which is subsequently to be established as the release specification.

When the particle size of amokinol, specific surface area of magnesium stearate in the control of raw materials for the manufacture of Sakura Tablets [Magnesium stearate], blending time in the Second blending process <Second Step>, and the mean tablet compression force in the Compression process <Third Step> conform to the designated process control values, and when the dissolution rate calculated using the following equation is not less than 85%, it meets the requirements.

(Equation 4)

Note: The specific surface area of magnesium stearate is tested according to the following test method.

Specific surface area of magnesium stearate

Note) The details of the test method for evaluating specific surface area of magnesium stearate content have been provided below.

[Specifications & test methods]

[Test name]: Dissolution

[Specifications & test methods]

This test can be substituted with the Dissolution (RTRT), which is a real-time release test, and is not performed at the time of release.

In cases of any changes to manufacturing process, perform the following dissolution test until the verification for each process control procedure is entirely completed. The value Q is specified to be 80%.

Furthermore, if the RTR method is not applicable in a particular case in which no effect on the quality of Sakura Tablets have not been verified in the risk assessment results, perform the following dissolution test. The value Q is specified to be 80%.

Perform the test with 1 tablet of Sakura Tablet using 900 mL of 0.1% sodium lauryl sulfate TS as the test solution according to paddle method at 50 rpm. Half an hour after the initiation of the test, filter not less than 20 mL of the dissolved solution through a membrane filter (pore size < 0.45 μm). Discard the first X mL of the filtrate, pipet the subsequent V mL, add 0.1% sodium lauryl sulfate TS to make exactly V' mL, which contains XX μg of amokinol (C_{XXHX_xN_xO_x}) 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, and add XX mL of 0.1% sodium lauryl sulfate 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 and standard solutions as directed under the Liquid Chromatography according to the following operating conditions. Determine the peak areas (A_T and A_S) of amokinol in the sample solution and the standard solution by the Automatic integration method.

(Equation 5)

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Operating conditions:

- Detector: An ultraviolet absorption photometer (wavelength, 210 nm)
- Column: A stainless steel column 4.6 mm in inside diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (particle diameter, 5 μ m).
- 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 min.
- System suitability:
- System performance: When the procedure is run with 20 μ L of the standard solution under the above operating conditions, amokinol and internal standard substance are eluted in this order with the resolution between the peaks being not less than XX.
- System repeatability: When the test is repeated 6 times with 20 μ 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%.

[Specifications & test methods]

[Test name]: Water

[Specifications & test methods]

Weigh accurately 10 tablets of Sakura Tablets and grind to powder. To powdered Sakura Tablets add 10 mL of methanol, shake well until it is disintegrated, and filter. Pipet 1 mL of the filtrate, and measure its water content as directed under Coulometric titration. Perform a blank determination, and make any necessary correction. The water content of the drug product is not more than 3%.

(Equation 6)

[Specifications & test methods]

[Test name]: Assay (RTRT)

[Specifications & test methods]

This test is performed as a real-time release test, which is subsequently to be established as the release specification.

The amount of amokinol is calculated using the following equation.

(Equation 7)

Note: The content of amokinol in the blended powder in the blending process is determined according to the following test method.

Weigh accurately XX mg of the blended powder, add exactly XX mL of the internal standard solution, and shake well for XX min. Centrifuge this solution, separate XX mL of the supernatant liquid, 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, and dissolve in the mobile phase to make exactly XX mL. To exactly XX mL of this solution, add the mobile phase to make XX mL, and use this solution as the standard. Perform the test with 20 μ L each of the sample solution and the standard solution as directed under Liquid Chromatography according to the following conditions. Determine

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the peak areas (Q_T and Q_S) of amokinol in the sample solution and the standard solution by the Automatic integration method.

(Equation 8)

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 4.6 mm in inside diameter of and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (particle diameter, 5 μ m).

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 min.

System suitability:

System performance: When the procedure is run with 20 μ L of the standard solution under the above operating conditions, amokinol and internal standard substance are eluted in this order with the resolution between the peaks being not less than XX.

System repeatability: When the test is repeated 6 times with 20 μ 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%.

[Specifications & test methods]

[Test name]: Assay

[Specifications & test methods]

This test can be substituted with the Assay (RTRT), which is a real-time release test, and is not performed at the time of release.

In case of any changes to manufacturing process, the amount of amokinol is calculated according to the following assay method until the verification for each process control procedure is entirely completed.

Furthermore, if the RTR is not applicable in a particular case, in which no effect on the quality of Sakura Tablets have not been verified in the results of the risk assessment, the amount of amokinol is calculated according to the following assay method.

Weigh accurately not less than 20 Sakura Tablets and grind to powder . Weigh accurately a quantity equivalent to X.XXX g of amokinol according to the labeled amount, add exactly XX mL of the internal standard solution, and shake well for XX min. Centrifuge this solution, separate XX mL of the supernatant liquid, 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, and dissolve in the mobile phase to make exactly XX mL. To exactly 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 μ L each of the sample and standard solutions as directed under Liquid Chromatography according to the following conditions. Determine the peak areas (Q_T and Q_S) of amokinol in the sample solution and the standard solution by the Automatic integration method.

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(Equation 9)

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 4.6 mm in inside diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 µm 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 min.

System suitability:

System performance: When the procedure is run with 20 µL of the standard solution under the above operating conditions, amokinol and internal standard substance are eluted in this order with the resolution between peaks being not less than XX.

System repeatability: When the test is repeated 6 times with 20 µL 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%.

**Application for Marketing Approval Attachment
(Proprietary name: Sakura Tablet 30 mg)**

Equation 1 (Purity)

Amount of each related substance (mg) = $W_S \times A_T/A_S \times X.XXX$

W_S : Amount (mg) of amokinol reference standard

Equation 2 (Uniformity of dosage units: RTRT)

Relative standard deviation (%) = $X/s \times 100$

$$s = \sqrt{\sum_{i=1}^n (x_i - \bar{X})^2 / (n - 1)}$$

\bar{X} : Mean of individual contents (x_1, x_2, \dots, x_n)

x_1, x_2, \dots, x_n : Individual contents of the dosage units tested.

n : Sample size (Total number of the samples tested)

s : Standard deviation of the sample

Equation 3 (Uniformity of dosage units)

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

W_S : Amount (mg) of amokinol reference standard

Equation 4 (Dissolution: RTRT)

Dissolution rate (%) with respect to the labeled amount of amokinol ($C_{XX}H_{XX}N_XO_X$)
= $108.9-11.96 \times$ Particle size of amokinol [$\log_{10}(d(0.9))$]- $7.556 \times 10^{-5} \times$ Specific surface area of magnesium stearate (cm^2/g)- $0.1849 \times$ Lubricant blending time (min)- $3.783 \times 10^{-2} \times$ Mean tablet compression force (N)

Equation 5 (Dissolution)

Dissolution rate (%) with respect to the labeled amount of amokinol ($C_{XX}H_{XX}N_XO_X$)
= $W_S \times A_T/A_S \times V/V \times 1/C \times X.XXX$

W_S : Amount (mg) of amokinol reference standard

C : Labeled amount (mg) of amokinol ($C_{XX}H_{XX}N_XO_X$) in 1 Sakura Tablet

Equation 6 (Water)

Water content (%) in amokinol

= [Water content (μg) in the sample - Water content (μg) in the blank determination solution] /
Weight (mg) of 10 Sakura Tablets

Equation 7 (Assay: RTRT)

Content (%) of amokinol ($C_{XX}H_{XX}N_XO_X$) with respect to the labeled amount

= Content (%) of amokinol in the blended powder in the blending process <First Step> \times Tablet weight (mg) following compression <Third Step> / C

C : Labeled amount (mg) of amokinol ($C_{XX}H_{XX}N_XO_X$) in 1 Sakura Tablet

Equation 8 (Assay: RTRT)

$$\text{Amount (mg) of amokinol (C}_{xx}\text{H}_{xx}\text{N}_x\text{O}_x) = W_s \times Q_T/Q_S \times X.XXX$$

W_s : Amount (mg) of amokinol reference standard

Equation 9 (Assay)

$$\text{Amount (mg) of amokinol (C}_{xx}\text{H}_{xx}\text{N}_x\text{O}_x) = W_s \times Q_T/Q_S \times X.XXX$$

W_s : Amount (mg) of amokinol reference standard

Attachment

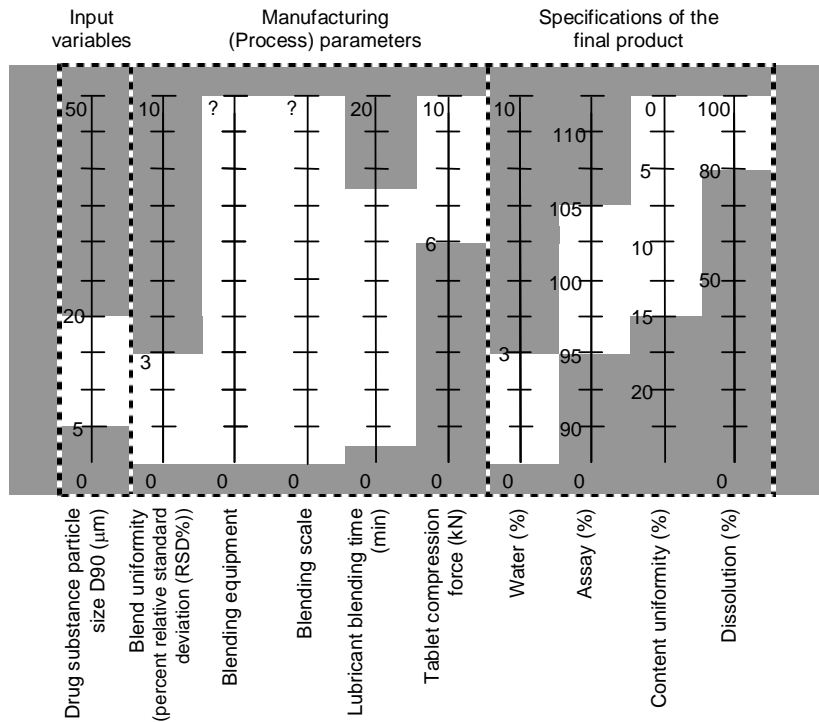


Figure 1 (Design Space and Specifications of Sakura Tablet 30 mg)

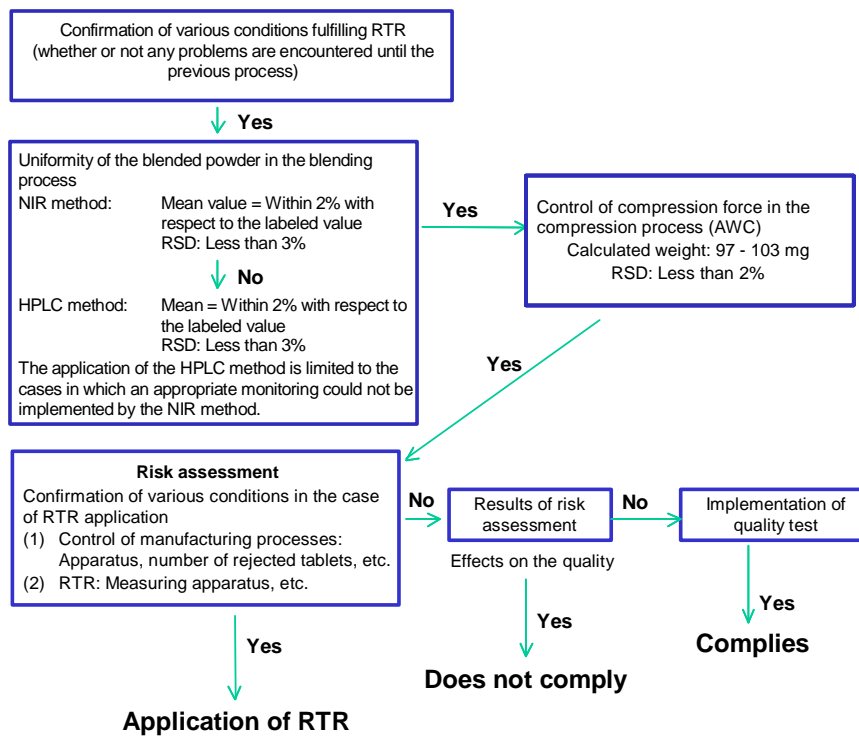


Figure 2 (Procedure for the Application of the RTR for Content Uniformity)

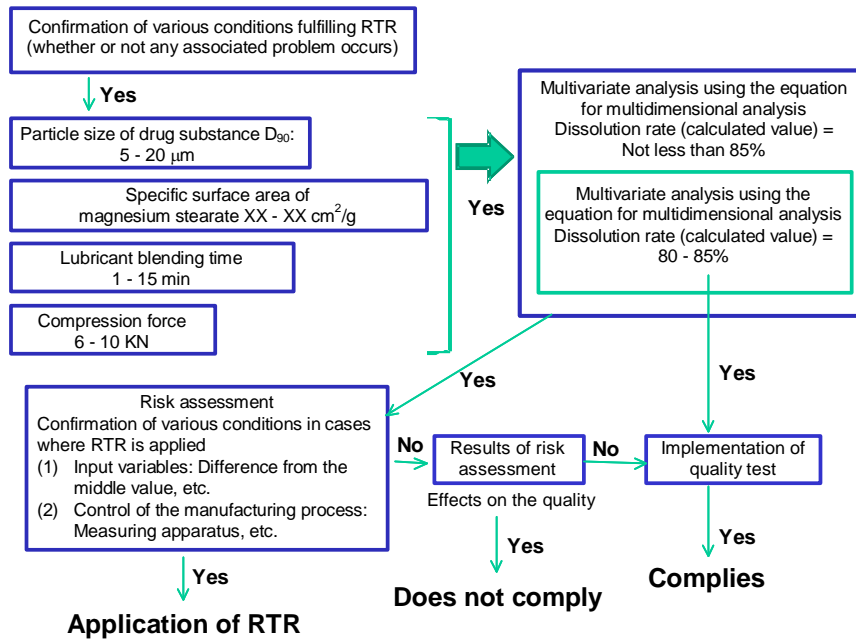


Figure 3 (Procedure for Applying the RTR to the Dissolution)

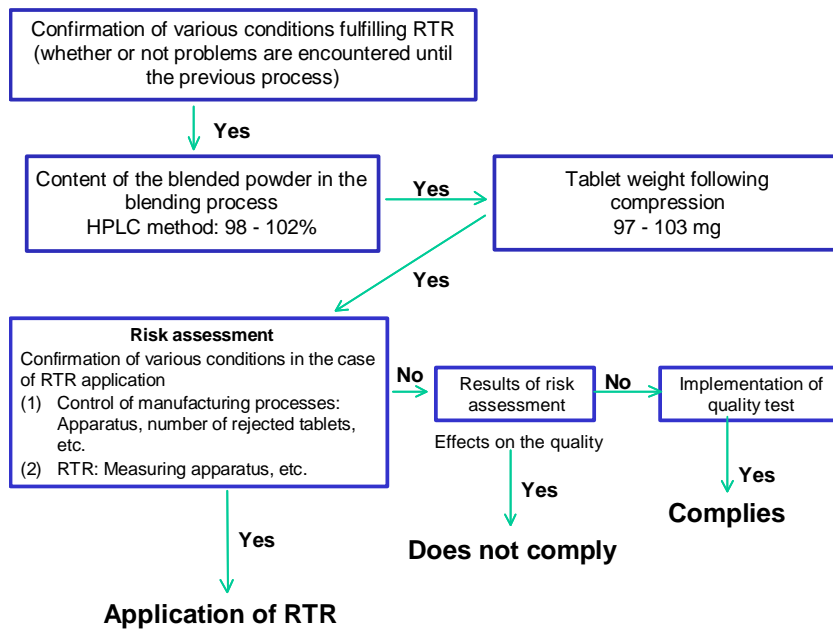


Figure 4 (Procedure for the Application of the RTR to the Content)