6.02 Uniformity of Dosage Units

Change 1. Content Uniformity, 3. Criteria and Table 6.02-2 as follows:

1. Content Uniformity

Select not less than 30 units, and proceed as follows for the dosage form designated.

Where different procedures are used for assay of the preparation and for the content uniformity test, it may be necessary to establish a correction factor to be applied to the results of the latter.

(i) Solid dosage forms: Assay 10 units individually using an appropriate analytical method. Calculate the acceptance value (see Table 6.02-2).

(ii) Liquid or Semi-Solid dosage forms: Assay 10 units individually using an appropriate analytical method. Carry out the assay on the amount of well-mixed material that is removed from an individual container in conditions of normal use and express the results as delivered dose. Calculate the acceptance value (see Table 6.02-2.).

1.1. Calculation of Acceptance Value

Calculate the acceptance value by the formula:

$|M - \bar{X}.| + ks$,

in which the terms are as defined in Table 6.02-2.

3. Criteria

Apply the following criteria, unless otherwise specified.

(i) Solid, Semi-Solid and Liquid dosage forms: The requirements for dosage uniformity are met if the acceptance value of the first 10 dosage units is less than or equal to $L1$ %. If the acceptance value is greater than $L1$ %, test the next 20 dosage units and calculate the acceptance value. The requirements are met if the final acceptance value of the 30 dosage units is less than or equal to $L1$% and no individual content of the dosage unit is less than $(1 - L2 \times 0.01)M$ nor more than $(1 + L2 \times 0.01)M$ in *Calculation of Acceptance Value* under *Content Uniformity* or under *Mass Variation*. Unless otherwise specified, $L1$ is 15.0 and $L2$ is 25.0.

Table 6.02-2

Variable	Definition	Conditions	Value
$\bar{X}$	mean of individual contents (x1, x2, …, xn) expressed as a percentage of the label claim		
$x_1, x_2, \cdots, x_n$	individual contents of the dosage units tested, expressed as a percentage of the label claim		
n	sample size (number of dosage units in a sample)		
k	acceptability constant	If n=10, then	2.4
		If n=30, then	2.0
s	sample standard deviation		$\sqrt{\sum_{i=1}^{n}(x_i-\bar{X})^2 / (n-1)}$
RSD	relative standard deviation (the sample standard deviation expressed as a percentage of the mean)		$100s/\bar{X}$
M (case 1) To be applied when $T \leqq 101.5$	reference value	If 98.5 % $\leqq \bar{X} \leqq$ 101.5 %, then	$M = \bar{X}$ ($AV = ks$)
		If $\bar{X} <$ 98.5 %, then	M = 98.5 % ($AV = 98.5 - \bar{X} + ks$)
		If $\bar{X} >$ 101.5 %, then	M = 101.5 % ($AV = \bar{X} - 101.5 + ks$)
M (case 2) To be applied when $T >$ 101.5	reference value	If 98.5 % $\leqq \bar{X} \leqq T$, then	$M = \bar{X}$ ($AV = ks$)
		If $X <$ 98.5 %, then	M = 98.5 % ($AV = 98.5 - \bar{X} + ks$)
		If $\bar{X} > T$, then	$M = T$ % ($AV = \bar{X} - T + ks$)
Acceptance Value (AV)			general formula: $\lvert M - \bar{X} \rvert + ks$ [Calculations are specified above for the different cases.]
$L1$	maximum allowed acceptance value		$L1$ = 15.0 unless otherwise specified.
$L2$	maximum allowed range for deviation of each dosage unit tested from the calculated value of M	On the low side, no dosage unit result can be less than 0.75M while on the high side, no dosage unit result can be greater than 1.25M (This is based on an L2 value of 25.0.)	$L2$ = 25.0 unless otherwise specified.
T	Target content per dosage unit at time of manufacture, expressed as the percentage of the label claim. Unless otherwise stated, T is 100.0%, or T is the manufacturer's approved target content per dosage unit.		

Add the following to 9.22 Standard Solutions:

Standard Hydrogen Peroxide Stock Solution To an amount of hydrogen peroxide(30) and water to make a solution so that each mL contains 0.30 g of hydrogen peroxide (H_2O_2:34.01). Pipet 1 mL of this solution, add water to make exactly 10 mL, pipet 1 mL of this solution, transfer it to a flask containing 10 mL of water and 10 mL of dilute sulfuric acid, and titrate<2.50> with 0.02 mol/L potassium permanganate VS until the color of the solution changes to slightly red. Perform a blank determination, and make any necessary correction.

Each mL of 0.02 mol/L potassium permanganate VS

=1.701 mg of H_2O_2

Standard Hydrogen Peroxide Solution To exactly 10 mL of Standard Hydrogen Peroxide Stock Solution add water to make exactly 100 mL. Prepare before use. Each mL contains 30 mg of hydrogen peroxide (H_2O_2:34.01).

Standard Chromium Solution for Atomic Absorption Spectrophotometry Weigh exactly 0.283 g of potassium dichromate (standard reagent), dissolve in water to make exactly 1000 mL. Each mL contains 0.10 mg of chromium (Cr).

Standard Iron Solution (2) for Atomic Absorption Spectrophotometry To exactly 2 mL of Standard Iron Stock Solution add water to make exactly 250 mL. Pipet 10 mL of this solution, add water to make exactly 100 mL. Prepare before use. Each mL contains 8 μg of iron (Fe).

Add the following to 9.43 Filter Papers, Filters for filtration, Test Papers,Crucibles, etc.:

Peroxide test strip A strip which is prepared so that it be able to assay the concentration of hydrogen peroxide in the range of 0 to 25 ppm. The test strips have the suitable color scale covering the range from 0 to 25 ppm hydrogen peroxide.

Add the following:

Gelatin

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This monograph is harmonized with the European Pharmacopoeia and the U. S. Pharmacopeia. The parts of the text that are not harmonized are marked with symbols (♦ ♦).

Gelatin is a purified protein obtained from collagen of animals by partial alkaline and/or acid hydrolysis, or by thermal hydrolysis. The hydrolysis leads to gelling or non-gelling grades.

It is the gelling grade.

The label states the gel strength (Bloom value).

♦**Description** Gelatin occurs as colorless or white to light yellow-brown sheets, shreds, granules or powder.

It is freely soluble in hot water, and practically insoluble in ethanol (95).

It does not dissolve in water, but slowly swells and softens when immersed in it, gradually absorbing water 5 to 10 times its own mass.

Gelatin derived from an acid-treated collagen exhibits an isoelectric point between pH 7.0 and 9.0, and Gelatin derived from an alkali-treated collagen exhibits an isoelectric point between pH 4.5 and 5.0.♦

Identification (1) Dissolve 1.00 g of Gelatin in freshly boiled and cooled water at about 55 ºC to make 100 mL, and use this solution as the sample solution. To 2 mL of the sample solution keeping at about 55 ºC add 0.05 mL of copper (II) sulfate TS. Mix and add 0.5 mL of 2 mol/L sodium hydroxide TS: a violet color is produced.

(2) In a test tube about 15 mm in diameter, place 0.5 g of Gelatin, add 10 mL of water, and allow to stand for 10 minutes. Heat at 60ºC for 15 minutes, then keep the tube upright at 0ºC for 6 hours, and invert the tube: the contents do not flow out immediately.

Gel strength (Bloom value) Determine the mass (g) necessary to produce the force which, applied to a plunger 12.7 mm in diameter, makes a depression 4 mm deep in a gel having a concentration of 6.67% and matured at 10ºC.

(i) Apparatus Texture analyzer or gelometer with a cylindrical piston 12.7 ± 0.1 mm in diameter with a plane pressure surface and a sharp bottom edge, and with a bottle 59±1 mm in internal diameter and 85 mm high (jelly cup).

(ii) Procedure Place 7.5 g of Gelatin in a jelly cup, add 105 mL of water, close the cup, and allow to stand for 1 to 4 hours. Heat in a water bath at 65 ± 2ºC for 15 minutes. While heating, stir gently with a glass rod. Ensure that the solution is uniform and any condensed water on the inner walls of the cup is incorporated. Allow to cool at room temperature for 15 minutes and transfer the cup to a thermostatically controlled bath at 10.0 ± 0.1ºC, and fitted with a device to ensure that the platform on which the cup stands is perfectly horizontal. Close the cup, and allow to stand for 17 ± 1 hours. Remove the sample cup from the bath and quickly wipe the water from the exterior of the cup. Center the cup on the platform of the apparatus so that the plunger contacts the sample as nearly at its midpoint as possible, and start the measurement with 4 mm depression distance and 0.5 mm/second test speed: 80 to 120% of the labeled nominal value.

pH <*2.54*> pH at 55ºC of the sample solution obtained in Identification (1) is 3.8 - 7.6.

Purity ♦**(1)** Heavy metals <*1.07*> - Proceed with 0.5g of Gelatin according to Method 2, and perform the test. Prepare the control solution with 2.5 mL of Standard Lead Solution (not more than 50 ppm).♦

(2) Iron - To 5.00 g of Gelatin, in a glass-stoppered flask, add 10 mL of hydrochloric acid, close the flask, and place in a water bath at 75 – 80 ºC for 2 hours. If necessary for proper solubilization, the gelatin may be allowed to swell after addition of the acid and before heating, the heating time may be prolonged and a higher temperature may be used. After cooling, adjust the content of the flask to 100.0 g with water, and use this solution as the sample solution. Separately, place 5.00 g each of Gelatin in three glass-stoppered flasks, proceed with them in the same manner as the sample solution, then add 10 mL, 20 mL and 30 mL of Standard Iron Solution (2) for Atomic Absorption Spectrophotometry exactly to each flask separately. Adjust the content of these flasks to 100.0 g each with water, and use these solutions as the standard solutions. Perform the test with the sample solution and the standard solutions as directed in the standard addition method under Atomic Absorption Spectrophotometry <*2.23*> according to the following conditions, and determine the content of iron: not more than 30 ppm.

Gas: Combustible gas – Acetylene
Supporting gas – Air
Lamp: Iron hollow cathode lamp
Wavelength: 248.3 nm

(3) Chromium – Use the sample solution obtained in (2) as the sample solution. Separately, place 5.00 g each of Gelatin in three glass-stoppered flasks, proceed with them in the same manner as the sample solution, then add 0.25 mL, 0.50 mL and 0.75 mL of Standard Chromium Solution for Atomic Absorption Spectrophotometry exactly to each flask separately. Adjust the content of these flasks to 100.0 g each with water, and use these solutions as the standard solutions. Perform the test with the sample solution and the standard solutions as directed in the standard addition method under Atomic Absorption Spectrophotometry <*2.23*> according to the following conditions, and determine the content of chromium: not more than 10 ppm.

Gas: Combustible gas – Acetylene
Supporting gas – Air
Lamp: Chromium hollow cathode lamp

Wavelength: 357.9 nm

(4) Zinc – Use the sample solution obtained in (2) as the sample solution. Separately, place 5.00 g each of Gelatin in three glass-stoppered flasks, proceed with them in the same manner as the sample solution, then add 7.5 mL, 15 mL and 22.5 mL of Standard Zinc Solution for Atomic Absorption Spectrophotomety exactly to each flask separately. Adjust the content of these flasks to 100.0 g each with water, and use these solutions as the standard solutions. Perform the test with the sample solution and the standard solutions as directed in the standard addition method under Atomic Absorption Spectrophotomety <*2.23*> according to the following conditions, and determine the content of zinc: not more than 30 ppm.

Gas: Combustible gas – Acetylene
Supporting gas – Air
Lamp: Zinc hollow cathode lamp
Wavelength: 213.9 nm

♦**(5)** Arsenic <*1.11*> - Take 15.0 g of Gelatin in a flask, add 60 mL of diluted hydrochloric acid (1 in 5), and dissolve by heating. Add 15 mL of bromine TS, heat until the excess of bromine is expelled, neutralize with ammonia TS, add 1.5 g of disodium hydrogen phosphate dodecahydrate, and allow to cool. To this solution add 30 mL of magnesia TS, allow to stand for 1 hour, and collect the precipitates. Wash the precipitates with five 10-mL portions of diluted ammonia TS (1 in 4), and dissolve in diluted hydrochloric acid (1 in 4) to make exactly 50 mL. Perform the test with 5 mL of this solution: the solution has no more color than the following color standard.

Color standard: Proceed with 15 mL of Standard Arsenic Solution, instead of Gelatin, in the same manner (not more than 1 ppm). ♦

(6) Peroxides –

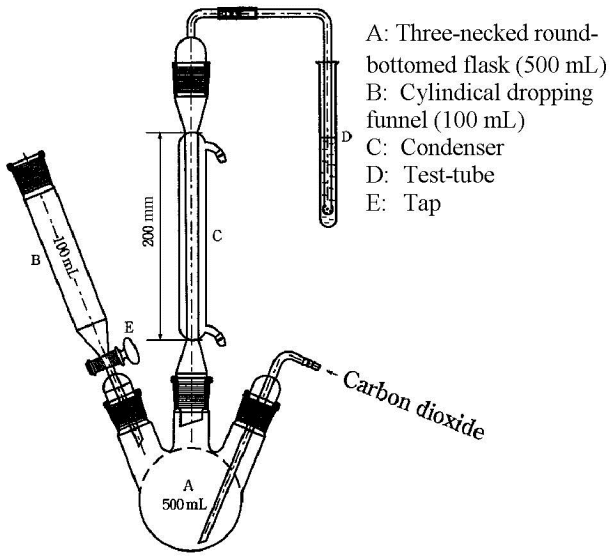
(i) Enzyme reaction: Peroxidase transfers oxygen from peroxides to an organic redox indicator which is converted to a blue oxidation product. The intensity of the color obtained is proportional to the quantity of peroxide and can be compared with a color scale provided with the test strips, to determine the peroxide concentration.

(ii) Procedure: Weigh 20.0 ± 0.1 g of Gelatin in a beaker, add 80.0 ± 0.2 mL of water, and stir to moisten all the gelatin. Allow to stand at room temperature for 1 – 3 hours. Cover the beaker with a watch-glass, and heat the beaker for 20 ± 5 minutes in a water bath at 65 ± 2 ºC for dissolving the sample. Stir the contents of the beaker with a glass rod to achieve a homogeneous solution, and use this as the sample solution. Dip a peroxide test strip for 1 second into the sample solution, such that the reaction zone is properly wetted. Remove the test strip, shake off excess liquid, and compare the reaction zone after 15 seconds with the color scale provided. Multiply the concentration read from the color scale by a factor of 5 to calculate the concentration of peroxide in the test substance: not more than 10 ppm.

(iii) Suitability test: To exactly 10 mL of Standard Hydrogen Peroxide Solution add water to make exactly 300 mL. Pipet 2 mL of this solution, add water to make exactly 1000 mL (2 ppm). Dip a peroxide test strip for 1 second into this solution, such that the reaction zone is properly wetted. Remove the test strip, shake off excess liquid and compare the color of the reaction zone after 15 seconds with the color scale: the color of the zone is equivalent to 2 ppm of the color scale.

(7) Sulfur dioxide –

(i) Apparatus Use as shown in the figure.



(ii) Procedure Introduce 150 mL of water into the three-necked round-bottomed flask and pass carbon dioxide through the whole system at a rate of 100 mL per minute. Place 10 mL of hydrogen peroxide-sodium hydroxide TS in the test-tube. After 15 minutes, remove the cylindrical dropping funnel without interrupting the stream of carbon dioxide, and introduce through the opening into the three-necked round-bottomed flask about 25.0 g of Gelatin with the aid of 100 mL of water. Pour 80 mL of 2 mol/L hydrochloric acid TS into the funnel, open the tap to introduce the hydrochloric acid into the three-necked round-bottomed flask ♦and close the tap while several mL of the hydrochloric acid remains, in order to avoid losing sulfur dioxide,♦ Place the three-necked round-bottomed flask in a water bath, and heat the mixture for 1 hour. Transfer the contents of the test-tube with the aid of a little water to a 200 mL wide- necked conical flask. Heat the flask in a water bath for 15 minutes and cool. Add 0.1 mL of bromophenol blue TS and titrate <*2.50*> with 0.1 mol/L sodium hydroxide VS until the color changes from yellow to violet-blue lasting for at least 20 seconds. Perform a blank determination and make any necessary correction. Calculate the amount of sulfur dioxide from the following expression: it is not more than 50 ppm.

Amount (ppm) of sulfur dioxide = $V / M \times 1000 \times 3.203$

M: Amount (g) of Gelatin taken
V: Amount (mL) of 0.1 mol/L sodium hydroxide VS consumed

Conductivity <*2.51*> Perform the test at 30 ± 1.0ºC with the sample solution obtained in Identification (1), without temperature compensation: not more than 1 $mS \cdot cm^{-1}$.

Loss on drying <*2.41*> Not more than 15.0%. (5g, 105ºC, 16 hours)

Microbial limit <*4.05*> The acceptance criteria of TAMC and TYMC are 10^3 CFU/g and 10^2 CFU/g, respectively. *Salmonella* and *Escherichia coli* are not observed.

Containers and storage ♦Containers – Tight containers. ♦ Storage – Protect from heat and moisture.