

## 《 905 》 UNIFORMITY OF DOSAGE UNITS

### Change to read:

[ NOTE— In this chapter, *unit* and *dosage unit* are synonymous. ]

To ensure the consistency of dosage units, each unit in a batch should have a drug substance content within a narrow range around the label claim. Dosage units are defined as dosage forms containing a single dose or a part of a dose of drug substance in each unit. • The uniformity of dosage units specification is not intended to apply to suspensions, emulsions, or gels in unit-dose containers intended for topical administration. •<sub>6</sub>

The term “uniformity of dosage unit” is defined as the degree of uniformity in the amount of the drug substance among dosage units. Therefore, the requirements of this chapter apply to each drug substance being comprised in dosage units containing one or more drug substances, unless otherwise specified in the individual monograph.

The uniformity of dosage units can be demonstrated by either of two methods, *Content Uniformity* or *Weight Variation* (see [Table 1](#)). The test for *Content Uniformity* is based on the assay of the individual content of drug substance(s) in a number of individual dosage units to determine whether the individual content is within the limits set. The *Content Uniformity* method may be applied in all cases. The test for *Content Uniformity* is required for those dosage forms described in (C1)–(C6) below:

(C1)	coated tablets, other than film-coated tablets containing 25 mg or more of a drug substance that comprises 25% or more (by weight) of one tablet;
(C2)	transdermal systems;
(C3)	suspensions or emulsions or gels in unit-dose • single-unit • <sub>6</sub> containers or in soft capsules that are intended for systemic administration only (not for those drug products that are intended for • topical • <sub>6</sub> administration);
(C4)	inhalations (other than solutions for inhalation packaged in glass or plastic ampuls and intended for use in nebulizers) packaged in premeasured dosage units. For inhalers and premeasured dosage units labeled for use with a named inhalation device, also see <i>Aerosols, Nasal Sprays, Metered-Dose Inhalers, and Dry Powder Inhalers</i> 《 601 》 ;
(C5)	solids (including sterile solids) that are packaged in single-unit containers and that contain active or inactive added substances, except that the test for <i>Weight Variation</i> may be applied in the special • cases • <sub>6</sub> stated in • <sub>6</sub> (W3) below; and
(C6)	suppositories.

The test for *Weight Variation* is applicable for the following dosage forms:

(W1)	solutions for inhalation that are packaged in glass or plastic ampuls and intended for use in nebulizers, and oral solutions packaged in unit-dose containers and into soft capsules;
(W2)	solids (including sterile solids) that are packaged in single-unit containers and contain no added substances, whether active or inactive;
(W3)	solids (including sterile solids) that are packaged in single-unit containers, with or without added substances, whether active or inactive, that have been prepared from true solutions and freeze-dried in the final containers and are labeled to indicate this method of preparation; and
(W4)	hard capsules, uncoated tablets, or film-coated tablets, containing 25 mg or more of a drug substance comprising 25% or more, by weight, of the dosage unit or, in the case of hard capsules, the capsule contents, except that uniformity of other drug substances present in lesser proportions is demonstrated by meeting <i>Content Uniformity</i> requirements.

The test for *Content Uniformity* is required for all dosage forms not meeting the above conditions for the *Weight Variation* test. • Where compliance with the *Content Uniformity* test is required, then, by application of the provision for use of alternative methods provided in the *General Notices* section of this Pharmacopeia, it is possible for manufacturers to ensure this compliance by application of the *Weight Variation* test where the concentration relative standard deviation (RSD) of the drug substance in the final dosage units is not more than 2%. This RSD determination may be based on the manufacturer's process validation and product development data. •<sub>6</sub> The concentration RSD is the RSD of the concentration per dosage unit (w/w or w/v), where concentration per dosage unit equals the assay result per dosage unit divided by the individual dosage unit weight. See the RSD formula in [Table 2](#). • Where the *Weight Variation* test is used in this way, the product must, if tested, nevertheless comply with the official compendial test for *Content Uniformity*. •<sub>6</sub>

**Table 1. Application of Content Uniformity (CU) and Weight Variation (WV) Tests for Dosage Forms**

			Dose & Ratio of Drug Substance

<b>Dosage Form</b>	<b>Type</b>	<b>Subtype</b>	<b>Dose &amp; Ratio of Drug Substance or mg or <math>\geq 25\%</math></b>	<b>Ratio of Drug Substance or mg or <math>&lt; 25\%</math></b>
Tablets	Uncoated		WV	CU
	Coated	Film	WV	CU
		Others	CU	CU
Capsules	Hard		WV	CU
	Soft	Suspension, emulsion, or gel	CU	CU
		Solutions	WV	WV
Solids in single-unit containers	Single component		WV	WV
	Multiple components	Solution freeze-dried in final container	WV	WV
		Others	CU	CU
Suspension, emulsion, or gel for systemic use only, packaged in single-unit containers			CU	CU
Solutions for inhalation packaged in glass or plastic ampuls and intended for use in nebulizers, and oral solutions packaged in unit-dose containers and into soft capsules			WV	WV
Inhalations (other than solutions for inhalation packaged in glass or plastic ampuls and intended for use in nebulizers packaged in premeasured dosage units)			CU	CU
Transdermal systems			CU	CU
Suppositories			CU	CU
Others			CU	CU

**Change to read:**

### CONTENT UNIFORMITY

Select not fewer than 30 units, and proceed as follows for the dosage form designated. Where the amount of drug substance in a single dosage unit differs from that required in the *Assay*, adjust the degree of dilution of the solutions and/or the volume of aliquots so that the concentration of the drug substances in the final solution is of the same order as that obtained in the *Assay* procedure; or, in the case of a titrimetric assay, use a titrant of a different concentration, if necessary, so that an adequate volume of titrant is required (see *Titrimetry* § 541 ); see also *Procedures* under *Tests and Assays* in the *General Notices and Requirements*. If any such modifications are made in the *Assay* procedure set forth in the individual monograph, make the appropriate corresponding changes in the calculation formula and titration factor.

Where a special *Procedure for content uniformity* is specified in the test for *Uniformity of dosage units* in the individual monograph, make any necessary correction of the results obtained as follows.

1. Prepare a composite specimen of a sufficient number of dosage units to provide the amount of specimen called for in the *Assay* in the individual monograph plus the amount required for the special *Procedure for content uniformity* in the monograph by finely powdering tablets or mixing the contents of capsules or oral solutions, suspensions, emulsions, gels, or solids in single-unit containers to obtain a homogeneous mixture. If a homogeneous mixture cannot be obtained in this manner, use suitable solvents or other procedures to prepare a solution containing all of the drug substance, and use appropriate aliquot portions of this solution for the specified procedures.
2. Assay separate, accurately measured portions of the composite specimen of capsules or tablets or suspensions or inhalations or solids in single-unit containers, both (a) as directed in the *Assay*, and (b) using the special *Procedure for content uniformity* in the monograph.
3. Calculate the weight of drug substance equivalent to 1 average dosage unit, by (a) using the results obtained by the *Assay* procedure, and by (b) using the results obtained by the special procedure.
4. Calculate the correction factor,  $F$ , by the formula:

$$F = W/P$$

in which *W* is the weight of drug substance equivalent to 1 average dosage unit obtained by the Assay procedure, and *P* is the weight of drug substance equivalent to 1 average dosage unit obtained by the special procedure. If

$$\frac{100|W - P|}{W}$$

is greater than 10, the use of a correction factor is not valid.

- 5. The correction factor is to be applied only if *F* is not less than 1.030 nor greater than 1.100, or not less than 0.900 nor greater than 0.970. If *F* is between 0.970 and 1.030, no correction is required.
- 6. If *F* lies between 1.030 and 1.100, or between 0.900 and 0.970, calculate the weight of drug substance in each dosage unit by multiplying each of the weights found using the special procedure by *F*.

**Uncoated, Coated, or Molded Tablets, Capsules, Oral Solutions in \* Unit-Dose Containers, Suspensions or Emulsions or Gels in Single-Unit Containers (that are intended for systemic administration only), \*<sub>6</sub> and Solids (including Sterile Solids) in Single-Unit Containers—** Assay 10 units individually as directed in the Assay in the individual monograph, unless otherwise specified in the *Procedure for content uniformity* in the individual monograph. Calculate the acceptance value as directed below.

For oral solutions \* in unit-dose containers, and for suspensions, emulsions, or gels in single-unit containers that are intended for systemic administration only, \*<sub>6</sub> conduct the Assay on the amount of well-mixed material that drains from an individual container in not more than 5 seconds, or for highly viscous products, conduct the Assay on the amount of well-mixed material that is obtained by quantitatively removing the contents from an individual container, and express the results as the delivered dose.

**Calculation of Acceptance Value—** Calculate the acceptance value by the formula:

$$|M - \overline{X}| + ks$$

in which the terms are as defined in [Table 2](#).

Table 2			
Variable	Definition	Conditions	Value
$\overline{X}$	Mean of individual contents ( $x_1, x_2, \dots, x_n$ ), expressed as a percentage of the label claim		

Variable	Definition	Conditions	Value
$x_1, x_2, \dots, x_n$	Individual contents of the units tested, expressed as a percentage of the label claim		
$n$	Sample size (number of units in a sample)		
$k$	Acceptability constant	If $n = 10$ , then $k =$	2.4
		If $n = 30$ , then $k =$	2.0
$s$	Sample standard deviation		$\left[ \frac{\sum_{i=1}^n (x_i - \bar{X})^2}{n-1} \right]^{\frac{1}{2}}$

Variable	Definition	Conditions	Value
<i>RSD</i>	Relative standard deviation (the sample standard deviation expressed as a percentage of the mean)		$\frac{100s}{\bar{X}}$
<i>M</i> (case 1) to be applied when $T \leq 101.5$	Reference value	If $98.5\% \leq \bar{X} \leq 101.5\%$ , 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	$M = 101.5\%$ $(AV = \bar{X} - 101.5 + ks)$
<i>M</i> (case 2) to be applied when $T > 101.5$	Reference value	If $98.5 \leq \bar{X} \leq T$ , then	$M = \bar{X}$ $(AV = ks)$
		If $\bar{X} < 98.5\%$ , then	$M = 98.5\%$ $(AV = 98.5 - \bar{X} + ks)$
		If $\bar{X} > T$ , then	$M = T\%$ $(AV = \bar{X} - T + ks)$

Variable	Definition	Conditions	Value
Acceptance value ( <i>AV</i> )			<p>general formula:</p> $\left  M - \overline{X} \right  + ks$ <p>(Calculations are specified above for the different cases.)</p>
<i>L1</i>	Maximum allowed acceptance value		<i>L1</i> = 15.0 unless otherwise specified in the individual monograph
<i>L2</i>	Maximum allowed range for deviation of each dosage unit tested from the calculated value of <i>M</i>	<p>On the low side, no dosage unit result can be less than <math>\bullet [1 - (0.01)(L2)]M</math>, <math>\bullet_6</math> while on the high side no dosage unit result can be greater than <math>\bullet [1 + (0.01)(L2)]M</math> <math>\bullet_6</math> (This is based on an <i>L2</i> value of 25.0.)</p>	<i>L2</i> = 25.0 unless otherwise specified in the individual monograph
<i>T</i>	<p>Target <math>\bullet</math> content per dosage unit at the time of manufacture, expressed as a percentage of the label claim. <math>\bullet_6</math> For purposes of this Pharmacopeia, unless otherwise specified in the individual monograph, <i>T</i> is <math>\bullet</math> the average of the limits specified in the potency definition in the individual monograph. <math>\bullet_6</math></p>		

**Suppositories, Transdermal Systems, and Inhalations Packaged in Premetered Dosage Units—** [ NOTE— Acceptance value calculations are not required for these dosage forms. ] Assay 10 units individually as directed in the Assay in the individual monograph, unless otherwise specified in the *Procedure for content uniformity*.

**Change to read:****WEIGHT VARIATION**

Select not fewer than 30 dosage units, and proceed as follows for the dosage form designated. The result of the *Assay*, obtained as directed in the individual monograph, is designated as result *A*, expressed as % of label claim (see *Calculation of the Acceptance Value*). Assume that the concentration (weight of drug substance per weight of dosage unit) is uniform. [ NOTE— Specimens other than these test units may be drawn from the same batch for assay determinations. ]

**Uncoated or Film-Coated Tablets—** Accurately weigh 10 tablets individually. Calculate the drug substance content, expressed as % of label claim, of each tablet from the weight of the individual tablet and the result of the *Assay*. Calculate the acceptance value.

**Hard Capsules—** Accurately weigh 10 capsules individually, taking care to preserve the identity of each capsule. Remove the contents of each capsule by a suitable means. Accurately weigh the emptied shells individually, and calculate for each capsule the net weight of its contents by subtracting the weight of the shell from the respective gross weight. Calculate the drug substance content, expressed as % of label claim, of each capsule from the net weight of the individual capsule content and the result of the *Assay*. Calculate the acceptance value.

**Soft Capsules—** Accurately weigh 10 intact capsules individually to obtain their gross weights, taking care to preserve the identity of each capsule. Then cut open the capsules by means of a suitable clean, dry cutting instrument such as scissors or a sharp open blade, and remove the contents by washing with a suitable solvent. Allow the occluded solvent to evaporate from the shells at room temperature over a period of about 30 minutes, taking precautions to avoid uptake or loss of moisture. Weigh the individual shells, and calculate the net contents. Calculate the drug substance content, expressed as % of label claim, in each capsule from the net weight of product removed from the individual capsules and the result of the *Assay*. Calculate the acceptance value.

**Solids (including Sterile Solids) in Single-Unit Containers—** Proceed as directed for *Hard Capsules*, treating each unit as described therein. Calculate the acceptance value.

**Oral Solutions Packaged in • Unit-Dose •<sub>6</sub> Containers—** Accurately weigh the amount of liquid that drains in not more than 5 seconds from each of 10 individual containers. If necessary, compute the equivalent volume after determining the density. Calculate the drug substance content, expressed as % of label claim, in the liquid drained from each unit from the net weight of the individual container content and the result of the *Assay*. Calculate the acceptance value.

**Calculation of Acceptance Value—** Calculate the acceptance value as shown in *Content Uniformity*, except that the individual contents of the units are replaced with the individual estimated contents defined below.

$x_1, x_2, \dots, x_n$	=	individual estimated contents of the units tested, where $x_i = w_i \times A / \bar{w}$
$w_1, w_2, \dots, w_n$	=	individual weights of the units tested • for weight variation, • <sub>6</sub>
<i>A</i>	=	content of drug substance (% of label claim) determined as described in the <i>Assay</i> , and
$\bar{w}$	=	mean of individual weights ( $w_1, w_2, \dots, w_n$ ) • of the units used in the <i>Assay</i> . • <sub>6</sub>

**Solutions for Inhalation Packaged in Glass or Plastic Ampuls and Intended for Use in Nebulizers—** [ NOTE— Acceptance value calculations are not required for these dosage forms. ] Accurately weigh 10 containers individually, taking care to preserve the identity of each container. Remove the contents of each container by a suitable means. Accurately weigh the emptied containers individually, and calculate for each container the net weight of its contents by subtracting the weight of the container from the respective gross weight. From the results of the *Assay*, obtained as directed in the individual monograph, calculate the drug substance content, expressed as % of label claim, in each of the containers.

**Change to read:****CRITERIA**

Apply the following criteria, unless otherwise specified in the individual monograph.

**Uncoated, Coated, or Molded Tablets, Capsules, Oral Solutions in • Unit-Dose Containers, Suspensions or Emulsions or Gels in Single-Unit Containers (that are intended for systemic administration only), •<sub>6</sub> and Solids (including Sterile Solids) in Single-Unit Containers—** 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 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 any dosage unit is less than  $\bullet [1 - (0.01)(L2)] M \bullet_6$  nor more than  $\bullet [1 + (0.01)(L2)] M \bullet_6$  as specified in the *Calculation of Acceptance Value* under *Content Uniformity* or under *Weight Variation*. Unless otherwise specified in the individual monograph,  $L1$  is 15.0 and  $L2$  is 25.0.

#### **Suppositories—**

**Limit A** (if the average of the limits specified in the potency definition in the individual monograph is 100.0 percent or less) — Unless otherwise specified in the individual monograph, the requirements for dosage uniformity are met if the amount of the drug substance in each of the 10 dosage units as determined from the *Content Uniformity* method lies within the range of 85.0% to 115.0% of the label claim, and the RSD is less than or equal to 6.0%.

If 1 unit is outside the range of 85.0% to 115.0% of label claim, and no unit is outside the range of 75.0% to 125.0% of label claim, or if the RSD is greater than 6.0%, or if both conditions prevail, test 20 additional units. The requirements are met if not more than 1 unit of the 30 is outside the range of 85.0% to 115.0% of label claim, and no unit is outside the range of 75.0% to 125.0% of label claim and the RSD of the 30 dosage units does not exceed 7.8%.

**Limit B** (if the average of the limits specified in the potency definition in the individual monograph is greater than 100.0 percent)—

1. If the average value of the dosage units tested is 100.0 percent or less, the requirements are as in *Limit A*.
2. If the average value of the dosage units tested is greater than or equal to the average of the limits specified in the potency definition in the individual monograph, the requirements are as specified under *Limit A*, except that the words "label claim" are replaced by the words "label claim multiplied by the average of the limits specified in the potency definition in the monograph divided by 100".
3. If the average value of the dosage units tested is between 100 percent and the average of the limits specified in the potency definition in the individual monograph, the requirements are as specified under *Limit A*, except that the words "label claim" are replaced by the words "label claim multiplied by the average value of the dosage units tested (expressed as a percent of label claim) divided by 100".

#### **Transdermal Systems and Inhalations Packaged in Premetered Dosage Units—**

**Limit A** (if the average of the limits specified in the potency definition in the individual monograph is 100.0 percent or less) — Unless otherwise specified in the individual monograph, the requirements for dosage uniformity are met if the amount of the drug substance in not fewer than 9 of the 10 dosage units as determined from the *Content Uniformity* method (or, in the case of solutions for inhalation packaged in glass or plastic ampuls and intended for use in nebulizers, from either the *Content Uniformity* or the *Weight Variation* method) lies within the range of 85.0% to 115.0% of label claim, and no unit is outside the range of 75.0% to 125.0% of label claim, and the RSD of the 10 dosage units is less than or equal to 6.0%.

If 2 or 3 dosage units are outside the range of 85.0% to 115.0% of label claim, but not outside the range of 75.0% to 125.0% of label claim, or if the RSD is greater than 6.0% or if both conditions prevail, test 20 additional units. The requirements are met if not more than 3 units of the 30 are outside the range of 85.0% to 115.0% of label claim and no unit is outside the range of 75.0% to 125.0% of label claim, and the RSD of the 30 dosage units does not exceed 7.8%.

**Limit B** (if the average of the limits specified in the potency definition in the individual monograph is greater than 100.0 percent)—

1. If the average value of the dosage units tested is 100.0 percent or less, the requirements are as in *Limit A*.
2. If the average value of the dosage units tested is greater than or equal to the average of the limits specified in the potency definition in the individual monograph, the requirements are as specified under *Limit A*, except that the words "label claim" are replaced by the words "label claim multiplied by the average of the limits specified in the potency definition in the monograph divided by 100".
3. If the average value of the dosage units tested is between 100 percent and the average of the limits specified in the potency definition in the individual monograph, the requirements are as specified under *Limit A*, except that the words "label claim" are replaced by the words "label claim multiplied by the average value of the dosage units tested (expressed as a percent of label claim) divided by 100".

• (Official January 1, 2007) •<sub>6</sub>

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*Expert Committee* : (PDF05) Pharmaceutical Dosage Forms 05

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