Uniformity of Dosage Units (BP 2011 & USP 34)

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June 14, 2011

Outline :

- Definition
- Harmonized general chapter
- USP 34 <905> Uniformity of Dosage Units
- BP 2011 Appendix XII C. Consistency of Formulated Preparations

  4. Uniformity of Dosage Units
- Definition of "T" and " $\overline{W}$ "
- Example

To ensure the consistency of the dosage units

- Each units in a batch should have a drug substance content within a narrow range around the label claim

Definition:

"The degree of uniformity in the amount of the drug substance among dosage units"

Can be demonstrated by either of 2 methods

1. Content Uniformity (CU)

2. Mass/Weight Variation (MW), (WV)

Pharmacopoeia

- US Pharmacopeia (USP): USP 34
- British Pharmacopoeia (BP): BP 2011

USP 28-NF 23

- Harmonized general chapter <905> on page 2505-2510 with an implementation date April 1, 2006

- Approved by the Pharmacopeial Discussion Group (PDG)

- USP postponed the implementation date to January 1, 2007: USP 29

PDG:- The United States Pharmacopeia
  - The Japanese Pharmacopeia
  - The European Pharmacopeia

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.

- The requirements are met if the final acceptance value of the 30 dosage units is less than or equal to L1% and all individual dosage units fall within the range calculated using L2 factor.

Statistical basis of the new content uniformity criteria

General idea of statistical tolerance intervals:

- To use the available data to form an interval that covers a specified proportion of the distribution underlying the data.

- To form an interval about the label claim within which a specified proportion of units would fall.

- An interval is a 95% tolerance interval for 90% of the distribution if 95% of such interval with repeated sampling would cover at least 90% of the distribution.

Uniformity of Dosage Units (BP 2011, USP 34)

Dosage Form	Type	Subtype	Dose&Ratio of Drug Substance	
			≥25 mg and ≥25%	<25 mg or <25%
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
Solutions in unit-dose containers and into soft capsules			WV	WV
Others			CU	CU [8]

Mass/Weight Variation (MV/WV)

Assay for the drug substance(s) on a representative sample $\longrightarrow$ result (%la.)

Select $\geq$ 30 dosage units

$\longrightarrow$ Accurately weigh 10 units individually

$\longrightarrow$ Cal. the drug substance (in %la.) of each unit from the weight of individual unit and the result of the Assay

$\longrightarrow$ Cal. The acceptance value (AV)

**Assume that the concentration (wt. of drug substance per wt. of dosage unit) is uniform.

Calculation of individual estimated contents
$$X_i = w_i \times A/\overline{W}$$

$X_1, X_2, ..., X_n$	=	Individual estimated contents of the units tested
$W_1, W_2, ..., W_n$	=	Individual weights of the units tested
A	=	Content of drug substance (% of label claim) obtained using an appropriate analytical method
$\overline{W}$	=	Mean of individual weights ($W_1, W_2, ..., W_n$)

Content Uniformity (CU)

Select $\geq$ 30 dosage units and proceed as follows

for the dosage form designated

$\longrightarrow$ Assay 10 unit individually

$\longrightarrow$ Cal. the drug substance (in %la.) of each unit

$\longrightarrow$ Cal. The acceptance value

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.

Requirement of uniformity of dosage units

Acceptance value (AV) of the first 10 units is $\leq$ L1%

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

If AV is > L1%, test the next 20 units,

Calculate the AV

AV of 30 units is $\leq$ L1%

No individual content of any dosage unit is

< [1-(0.01)(L2)]M nor > [1+(0.01)(L2)]M

L1 = 15.0, L2 = 25.0

$\overline{X}$	Mean of individual contents (X_1, X_2,…, X_n), expressed as a percentage of the label claim
X_1, X_2,…, 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 or If n = 30, then k = 2.0
S	Sample standard deviation
RSD	Relative standard deviation (The sample standard deviation expressed as a percentage of the mean)
M	Reference value
AV	Acceptance value
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 Range:[1-(0.01)(L2)]M to [1+(0.1)(L2)]M, L2 = 25.0 unless otherwise specified.
T	Target content per dosage unit at the time of manufacture, expressed as a percentage of the label claim. For purposes of this Pharmacopeia, unless otherwise stated in the individual monograph, T is 100.0%, and for manufacturing purposes, T is the manufacturer's approved target test amount value at the time manufacture.

Calculation of Acceptance Value (AV)

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

if n = 10, then k = 2.4

if n = 30, then k = 2.0

M (case 1) when T ≤ 101.5

Conditions	Value	
If 98.5% ≤ $\overline{X}$ ≤ 101.5%	M = $\overline{X}$	AV = ks
If $\overline{X}$ < 98.5%	M = 98.5%	AV = 98.5 − $\overline{X}$ + ks
If $\overline{X}$ > 101.5%	M = 101.5%	AV = $\overline{X}$ -101.5 + ks

Acceptance Value (AV)

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

if n = 10, then k = 2.4

if n = 30, then k = 2.0

M (case 2) when T > 101.5

Conditions	Value	
If 98.5% $\leq \overline{X} \leq$ T%	M = $\overline{X}$	AV = ks
If $\overline{X}$ < 98.5%	M = 98.5%	AV = 98.5 $- \overline{X}$ + ks
If $\overline{X}$ > T%	M = T%	AV = $\overline{X}$-T + ks

Definition of "T"

BP	Definition	USP	Definition
2005 2007	Target test sample amount at time of manufacture.	28 29 30	Target test sample amount at time of manufacture. For purposes of this Pharmacopeia, unless otherwise specified in the individual monograph, T is 100.0%, and for manufacturing purposes, T is the manufacturer's approved target test amount value at the time of manufacture.
2008	Target test sample amount at time of manufacture.	31 32	Target content per dosage unit at the time of manufacture, expressed as a percentage of the label claim. For purposes of this Pharmacopeia, unless otherwise specified in the individual monograph, T is the average of the limits specified in the potency definition in the individual monograph.
2009 2010 2011	Target content per dosage unit at time of manufacture, expressed as a percentage of the label claim. T is equal to 100 Percent unless an overage for stability reasons has been approved, in which case it is greater than 100 percent	32 (2nd supp.) 33 34	Target content per dosage unit at the time of manufacture, expressed as a percentage of the label claim. For purposes of this Pharmacopeia, unless otherwise stated in the individual monograph, T is 100.0%, and for manufacturing purposes, T is the manufacturer's approved target test amount value at the time of manufacture.

Definition of w_i & $\overline{W}$: $X_i = w_i \times A/\overline{W}$

BP	Definition	USP	Definition
2005 2007	$w_1, w_2, ..., w_n$ = individual masses of the dosage units tested $\overline{W}$ = mean of individual masses $(w_1, w_2, ..., w_n)$	28 29 30	$w_1, w_2, ..., w_n$ = individual weights of the units tested $\overline{W}$ = mean of individual weights $(w_1, w_2, ..., w_n)$
2008	$w_1, w_2, ..., w_n$ = individual masses of the dosage units tested $\overline{W}$ = mean of individual masses $(w_1, w_2, ..., w_n)$	31 32	$w_1, w_2, ..., w_n$ = individual weights of the units tested, for weight variation $\overline{W}$ = mean of individual weights $(w_1, w_2, ..., w_n)$ of the units used n the Assay
2009 2010 2011	$w_1, w_2, ..., w_n$ = individual masses of the dosage units tested $\overline{W}$ = mean of individual masses of the units used in the assay	32 (2nd supp.) 33 34	$w_1, w_2, ..., w_n$ = individual weights of the units tested $\overline{W}$ = mean of individual weights $(w_1, w_2, ..., w_n)$

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Frequently asked questions

Q: What is meant by the term "special procedure" as found under Content Uniformity in the official chapter?

A: Typically, CU determination is made on individual dosage units using the procedure found in the Assay.

For certain products, a separate procedure is given in the monograph for CU determination.

e.g. Clopidogrel Tablets

Theophylline Extended-Release Capsules

Frequently asked questions

Q: What is the max. allowable acceptance value for CU testing at level 2, where a total of 30 dosage units have been tested?

A: CU testing can be performed in 2 stages:

1st stage (10 units) and 2nd stage (total 30 units)

L1 = limit for the acceptance value for both stages

L2 = to calculate the allowed limits for individual dosage unit content

Frequently asked questions

Q: If uncoated tablet contains 2 drug substances but only one of them meets the requirement for WV, how can the requirement be met?

A: In the case of a two-component tablet, uniformity of dosage units test requirement will be met by the WV for the component $\geq$ 25 mg of drug substance comprising $\geq$ 25% of the weight of the dosage unit mass. The other component will require the CU.

Example:

T value	100.0%
L1	15.0
L2	25.0
Average of 10 values (%la.), $\overline{X}$	102.0
Standard deviation of 10 values	4.6
M value: (If $\overline{X}$ >101.5% then M = 101.5)	101.5
AV = $\overline{X}$ − 101.5 + ks = (102.0-101.5) + 2.4(4.6)	11.54
Result	Pass

Criteria : AV of the first 10 units is $\leq$ L1%

Example:

T value	100.0%
L1	15.0
L2	25.0
Average of 10 values (%la.), $\overline{X}$	107.0
Standard deviation of 10 values	4.6
M value: (If $\overline{X}$ > 101.5% then M = 101.5)	101.5
AV = $\overline{X}$ − 101.5 + ks = 107.0-101.5+ 2.4(4.6)	16.54
Result	Fail
Perform the next 20 units, total = 30 units , Average ($\overline{X}$)	106.5
Standard deviation of 30 values	5.2
Min. value = 94.7%la. and max. value = 127.1% la.	
M value: (If $\overline{X}$ > 101.5% then M = 101.5)	101.5
AV = $\overline{X}$ − 101.5 + ks = 106.5 − 101.5 + 2.0(5.2)	15.4
Min. allowed range: [1-(0.01)(L2)]M	76.1
Max. allowed range: [1+(0.01)(L2)]M	126.9
Result	Fail

USP 28 to USP34

<905> Uniformity of Dosage Units

- Content Uniformity

- Weight variation

BP 2005 and BP 2007

Appendix XII N. Uniformity of Dosage Units

(Ph.Eur. Method 2.9.40)

- Content Uniformity

- Mass Variation

Appendix XII G. Uniformity of Weight (Mass)

(Ph.Eur. Method 2.9.5)

Appendix XII H. Uniformity of Content

(Ph.Eur. Method 2.9.6)

Appendix XII L. Uniformity of Weight (Mass) of Delivered Doses from Multi-dose Containers

(Ph.Eur. Method 2.9.27)

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BP 2008 to BP 2011

Appendix XII C. Consistency of Formulated Preparations

1. Uniformity of Weight (Mass) *(Ph.Eur. Method 2.9.5)*

2. Uniformity of Weight (Mass) of Delivered Doses from Multidose containers *(Ph.Eur. Method 2.9.27)*

3. Uniformity of Content *(Ph.Eur. Method 2.9.6)*

4. Uniformity of Dosage Units *(Ph.Eur. Method 2.9.40)*

Thank you