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ORIGINAL ARTICLE

Content uniformity acceptance limit for a validation batch—suppositories, transdermal systems, and inhalations

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Abstract
Background: The USP test for 'Uniformity of Dosage Units' specified by USP Chapter <905> is required of every drug product sold in the United States. Dosage-unit uniformity is determined either by weight variation or by assay of individual units. The USP acceptance criteria for content uniformity states that the relative standard deviation (RSD) of a sample of 30 units should not exceed 7.8%. *Purpose*: This article provides a methodology for deriving an upper acceptance limit on the RSD of dosage units from a validation batch of suppositories, transdermal systems, or inhalations such that future batches will have a 95% chance of passing the USP content uniformity RSD acceptance criterion (the RSD of 30 dosage units does not exceed 7.8%).

Key words: *Acceptance limit; content uniformity; inhalations; relative standard deviation; suppositories; transdermal systems; validation*

Introduction

This article provides a methodology for deriving an upper acceptance limit on the relative standard deviation (RSD) of dosage units from a validation batch of suppositories, transdermal systems, or inhalations. The acceptance limit is derived such that one can be 95% confident that future batches will have a 95% chance of passing USP content-uniformity RSD acceptance criterion for suppositories, transdermal systems, and inhalations packaged in premetered dosage units given in USP Chapter <905>[1].

The USP test for 'Uniformity of Dosage Units' specified by USP Chapter <905> is required of every drug product sold in the United States. Dosage-unit uniformity is determined either by weight variation or by assay of individual units. The methodology offered only pertains to the RSD acceptance criterion for uniformity of dosage units as described in Table 1. (For inhalers and premetered dosage units labeled for use with a named inhalation device, see also Metered-Dose Inhalers and Dry Powder Inhalers, USP Chapter <601>.)

The acceptance criteria in Table 1 apply if the average of the limits specified in the potency definition in the individual monograph is 100% or less. If the average of the limits specified in the potency definition in the individual monograph is greater than 100%, then the criteria are as follows:

1. If the average value of the dosage units tested is 100% or less, the acceptance criteria are those described in Table 1.
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 acceptance criteria are the same as those in Table 1 except 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% and the average of the limits specified in the potency definition in the individual monograph,

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Table 1. Uniformity of dosage units acceptance criteria for suppositories, transdermal systems, and inhalations—USP Chapter <905>.

Number tested	Pass if
10 units	1. each of the 10 dosage units lies within the range 85.0–115.0% of the label claim 2. the RSD is less than or equal to 6.0%
Additional 20 units	1. no more than one unit of the 30 units is outside the range of 85.0–115% of label claim and no unit is outside the range of 75.0–125.0% of label claim 2. the RSD of the 30 dosage units does not exceed 7.8%

the same criteria apply 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 percent of label claim) divided by 100'.

Method

The USP acceptance criteria for content uniformity states that the RSD of a sample of 30 units should be less than 7.8%. For a batch to have a 95% chance of passing the RSD criterion, the following probability statement must hold:

$$P_\theta\left[\frac{s}{\bar{x}}\le 0.078\right]=0.95\Rightarrow P_\theta\left[\frac{\sqrt{30}\bar{x}}{s}>\frac{\sqrt{30}}{0.078}\right]=0.95 \Rightarrow P_\theta\left[\frac{\sqrt{30}\,\bar{x}}{s}\le\frac{\sqrt{30}}{0.078}\right]=0.05, \quad (1)$$

where $\theta = \mu/\sigma$ can be determined from the noncentral *t*-distribution such that the probability statement in Equation (1) is true[2]. The population RSD (σ/μ) is the inverse of θ.

After solving for θ in Equation (1), the population RSD (θ^{-1}) is calculated to be 6.43%.

To be 95% confident that Statement 1 holds, it is required that 6.43% be the 95% upper confidence bound on the population RSD for a preliminary sample of size *n*. The exact upper $(1-\alpha)\times 100\%$ confidence limit on the population RSD, RSD_{upper} as outlined by Verrill[3] satisfies the equation

$$NCt_{n-1,\ \sqrt{n}\Big/\frac{\%RSD_{\text{upper}}}{100},\,1-\alpha}=\frac{\sqrt{n}\bar{x}}{s_n}, \quad (2)$$

where $NCt_{n-1,\ \sqrt{n}\Big/\frac{\%RSD_{\text{upper}}}{100},\,1-\alpha}$ is the $(1-\alpha)\times 100$th percentile of a noncentral *t*-distribution with degrees of freedom df = $n - 1$ and noncentrality parameter $\delta=\sqrt{n}\Big/\left(\frac{\%RSD_{\text{upper}}}{100}\right)$, $\bar{x}_n$ is the sample mean; and s_n is the sample SD. Given $\%RSD_{\text{upper}}/100 = 0.0643$, one then can determine for a given *n*, $NCt_{n-1,\sqrt{n}/0.0643,0.95}\times 100\%$, the required upper bound on the sample %RSD so that Statement 1 holds with 95% certainty.

It is noted that for small %RSDs, the sample %RSD/100 is approximately equal to $s_{\log}$, the SD of the natural logs of the sample values, and that $\frac{(n-1)\,s^2_{\log}}{\sigma^2_{\log}}$ is distributed approximately chi-squared with $(n - 1)$ df. It then follows that the required upper limit for a %RSD from a sample of size n can be computed as $\frac{\sqrt{\chi^2_{0.05,n-1}}\times 0.0643}{\sqrt{n-1}}\times 100\%$. This alternative approach gives identical values of the upper limit for the sample %RSD rounded to 0.01.

Application

The following example illustrates an application of the methodology for setting acceptance limits on content uniformity RSD for a validation batch. To be 95% confident that future batches have at least a 95% chance of passing

Table 2. Acceptance limits on sample content uniformity %RSD of a validation batch for various sample sizes.

Sample size, *n*	Upper limit on sample, %RSD[a]
5	2.71
10	3.91
15	4.40
20	4.69
25	4.88
30	5.02
35	5.13
40	5.22
45	5.29
50	5.35
55	5.40
60	5.45
65	5.49
70	5.52
75	5.55
80	5.58

[a]With these limits on the sample %RSD, one can be 95% confident that future batches will have a 95% chance of passing USP content uniformity RSD acceptance criterion (the RSD of 30 dosage units does not exceed 7.8%).

the USP content-uniformity RSD acceptance criteria based on a sample of 30 units, the sample RSD for content uniformity for a validation batch based on a sample of 50 units should be less than $s/\bar{x} = \sqrt{50}/132.181$ or 5.35%. Table 2 provides acceptance limits on the sample content uniformity %RSD for validation batches for different sample sizes. The table shows that the upper acceptance limit for the sample %RSD increases as sample size increases. Sample %RSD approaches the true %RSD and is estimated with increasing precision as sample size increases, thereby allowing for a higher acceptance limit on the sample %RSD.

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