Designation: E2810 – 11$^{\varepsilon 2}$

Standard Practice for Demonstrating Capability to Comply with the Test for Uniformity of Dosage Units[1]

This standard is issued under the fixed designation E2810; the number immediately following the designation indicates the year of original adoption or, in the case of revision, the year of last revision. A number in parentheses indicates the year of last reapproval. A superscript epsilon (ε) indicates an editorial change since the last revision or reapproval.

ε[1] NOTE—Editorial corrections made throughout in February 2013.
ε[2] NOTE—Editorial corrections made throughout in December 2013.

1. Scope

1.1 This practice provides a general procedure for evaluating the capability to comply with the Uniformity of Dosage Units (UDU) test. This test is given in General Chapter <905> Uniformity of Dosage Units of the USP, in 2.9.40 Uniformity of Dosage Units of the Ph. Eur., and in 6.02 Uniformity of Dosage Units of the JP, and these versions are virtually interchangeable. For this multiple-stage test, the procedure computes a lower bound on the probability of passing the UDU test, based on statistical estimates made at a prescribed confidence level from a sample of dosage units.

1.2 This methodology can be used to generate an acceptance limit table, which defines a set of sample means and standard deviations that assures passing the UDU test for a prescribed lower probability bound, confidence level, and sample size.

1.3 *This standard does not purport to address all of the safety concerns, if any, associated with its use. It is the responsibility of the user of this standard to establish appropriate safety and health practices and determine the applicability of regulatory limitations prior to use.*

2. Referenced Documents

2.1 *ASTM Standards:*[2]

E2363 Terminology Relating to Process Analytical Technology in the Pharmaceutical Industry

E2709 Practice for Demonstrating Capability to Comply with an Acceptance Procedure

2.2 *Other Documents:*

JP Japanese Pharmacopoeia[3]

Ph. Eur. European Pharmacopoeia [4]

USP United States Pharmacopeia[5]

3. Terminology

3.1 *Definitions*—See Terminology E2363 for a more extensive listing of terms in ASTM Committee E55 standards.

3.2 *Definitions of Terms Specific to This Standard:*

3.2.1 *acceptable parameter region, n*—the set of values of parameters characterizing the distribution of test results for which the probability of passing the lot acceptance procedure is greater than a prescribed lower bound.

3.2.2 *acceptance limit, n*—the boundary of the acceptance region, for example, the maximum sample standard deviation for a given sample mean.

3.2.2.1 *Discussion*—The coefficient of variation (relative standard deviation) may be substituted for the standard deviation where applicable.

3.2.3 *acceptance region, n*—the set of values of parameter estimates (that is, sample mean and standard deviation) where confidence limits attain a prescribed lower bound on the probability of passing a lot acceptance procedure.

3.2.4 *confidence level, C, n*—the prescribed overall level for calculating the uncertainty region of the parameters from the sample estimates.

3.2.4.1 *Discussion*—The preset confidence level is stated as a percentage, for example, $100\,(1 - \alpha) = 95\ \%$, where α is a risk that is allocated to the two parameters being estimated.

[1] This practice is under the jurisdiction of ASTM Committee E55 on Manufacture of Pharmaceutical and Biopharmaceutical Products and is the direct responsibility of Subcommittee E55.03 on General Pharmaceutical Standards.

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[2] For referenced ASTM standards, visit the ASTM website, www.astm.org, or contact ASTM Customer Service at service@astm.org. For *Annual Book of ASTM Standards* volume information, refer to the standard's Document Summary page on the ASTM website.

[3] Available from the Pharmaceuticals and Medical Devices Agency, Japan, http://jpdb.nihs.go.jp.

[4] Available from the European Council, Strasbourg, France, http://www.edqm.eu.

[5] Available from U.S. Pharmacopeia (USP), 12601 Twinbrook Pkwy., Rockville, MD 20852-1790, http://www.usp.org.

3.2.5 *lower probability bound, LB, n*—the nominal probability of passing the UDU test for a given set of parameter estimates.

3.2.6 *multiple-stage acceptance procedure, n*—a procedure that involves more than one stage of sampling and testing a given quality characteristic with one or more acceptance criteria per stage.

3.2.7 *representative sample, n*—a sample that consists of a number of units that are drawn based on rational criteria such as random sampling and intended to assure that the sample accurately portrays the material being sampled

3.2.8 *sampling plan, n*—scheme for selecting dosage units from locations within a batch for testing purposes.

3.2.8.1 *Discussion*—In this standard, a single dosage unit is selected from each batch location.

3.2.9 *uniformity of dosage units, UDU, n*—the degree of uniformity in the amount of the drug substance among dosage units.

3.2.9.1 *Discussion*—The requirements of the UDU test apply to each drug substance in dosage units containing one or more drug substances, unless otherwise specified. The uniformity improves as the variability decreases.

4. Significance and Use

4.1 The methodology was originally developed (**1-4**)[6] for use in drug content uniformity and dissolution but has general application to any multistage test with multiple acceptance criteria. Practice E2709 summarizes the statistical aspects of this methodology. This practice applies the general methodology of Practice E2709 specifically to the UDU test.

4.1.1 While other methods can be used to estimate the probability of passing the UDU test, they are outside the scope of this practice.

4.2 The UDU test procedure describes a two-stage sampling test, where at each stage one can pass or continue testing, and the decision to fail is deferred until the second stage. At each stage there are acceptance criteria on the test results as outlined in Table 1.

4.3 The UDU test is a market standard. The USP General Notices include the following statement about compendial standards. "The similarity to statistical procedures may seem to suggest an intent to make inference to some larger group of units, but in all cases, statements about whether the compendial standard is met apply only to the units tested." Therefore, the UDU procedure is not intended for inspecting uniformity of finished product for lot/batch release or as a lot inspection procedure.

4.3.1 The UDU test defines a product requirement to be met at release and throughout the shelf-life of the product.

4.3.2 Passing the UDU test once does not provide statistical assurance that a batch of drug product meets specified statistical quality control criteria.

4.4 This practice provides a practical specification that may be applied when uniformity of dosage units is required. An

[6] The boldface numbers in parentheses refer to a list of references at the end of this standard.

TABLE 1 Uniformity of Dosage Units Test Procedure

NOTE 1—All measurements of dosage units and criteria values are in percentage label claim (%LC). At each stage calculate the sample average, $\bar{X}$, and the sample standard deviation, s.

Stage	Number Tested	Pass Stage If:
S_1	10	$\lvert M - \bar{X}\rvert + 2.4\ s \le 15.0$, where M is defined below.
S_2	20	(*1*) $\lvert M - \bar{X}\rvert + 2.0\ s \le 15.0$, using all 30 results ($S_1 + S_2$). (*2*) No dosage unit is outside the maximum allowed range of 0.75 * M to 1.25 * M.

M is defined as follows:

If T is less than or equal to 101.5 %LC, and
- (*1*) If $\bar{X}$ is less than 98.5 %LC, then M = 98.5 %LC.
- (*2*) If $\bar{X}$ is between 98.5 and 101.5 %LC, then $M = \bar{X}$.
- (*3*) If $\bar{X}$ is greater than 101.5 %LC, then M = 101.5 %LC.

If T is greater than 101.5 %LC, and
- (*1*) If $\bar{X}$ is less than 98.5 %LC, then M = 98.5 %LC.
- (*2*) If $\bar{X}$ is between 98.5 and T, then $M = \bar{X}$.
- (*3*) If $\bar{X}$ is greater than T, then $M = T$.

T is the target content per dosage unit at the time of manufacture, expressed as %LC. Unless otherwise specified in the individual monograph, T is 100.0 %LC.

acceptance region for the mean and standard deviation of a set of test results from the lot is defined such that, at a prescribed confidence level, the probability that a future sample from the lot will pass the UDU test is greater than or equal to a prespecified lower probability bound. Having test results fall in the acceptance region provides assurance that a sample would pass the UDU test with at least the specified lower bound probability. This procedure does not account for any decrease in potency during the shelf life, which could affect the ability to meet the UDU test requirements.

4.5 This practice can be used as an element for process demonstration or validation, continuous process verification, in-process testing, or lot release (acceptance). As the circumstances and available information vary in these different application areas, this practice does not prescribe a specific target, sample size, lower probability bound, or confidence level. These must be prospectively selected by the user and may be different from those used in the acceptance limit tables provided in this practice.

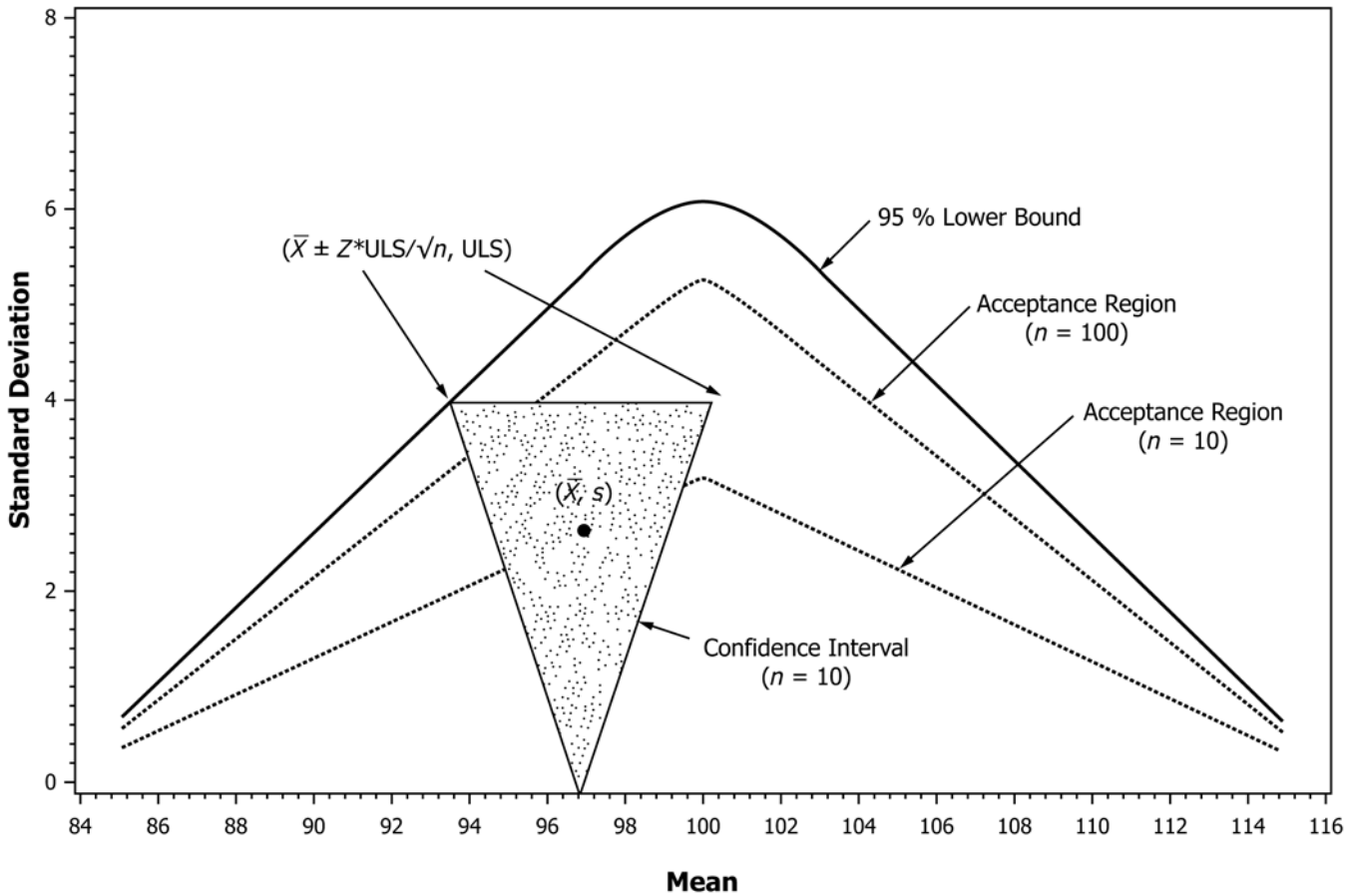
5. Procedure

5.1 *Generating The Acceptance Limit Table:*

5.1.1 The general procedure that generates the acceptance limit tables is described in Practice E2709 and the specific procedure for application to the UDU test is described in the literature (**4**). A simplified description on the construction and use of these tables is given in this section. A computer program is required to generate the tables given a target *T* as a percentage of label claim (LC), a lower probability bound *LB*, a confidence level *C*, and a sample size *n*.

5.1.2 The first step is to determine the acceptable parameter region. On a two-dimensional content space consisting of the true mean (μ) on the horizontal axis and standard deviation (σ) on the vertical axis the upper boundary of this region is defined by a contour, a curve that is concave downward and depicted by the solid curve in Fig. 1. The contour is determined by the *LB* probability and the Target under the assumption that the dosage unit content is normally distributed. The acceptable parameter region is the set of points on or below the contour. Any (μ, σ) pair in the acceptable region would pass the UDU test with a probability of at least the *LB*.

5.1.3 The second step is to generate the *acceptance limit curve*. The sample mean ($\bar{X}$) and sample standard deviation (*s*) estimate the population parameters μ and σ within *C* %



NOTE 1—All points below the lower bound contour have higher than a 95 % chance of passing UDU test if mean and standard deviation are known. All points below the acceptance region contours pass the associated acceptance limit table for $n = 100$ and $n = 10$.
ULS is the upper confidence limit for σ.
Z is a standard normal critical value.

FIG. 1 Example of Simultaneous Confidence Interval with 95 % Lower Bound and Acceptance Regions

confidence limits as chosen by the user. The joint confidence region for μ and σ (**5**) has the shape of an inverted triangle around a ($\bar{X}$, s) pair as depicted in Fig. 1 with the lowest vertex at ($\bar{X}$, 0). A value of $\bar{X}$ is selected starting with $s = 0$, then the confidence region is expanded by increasing s until one of the upper vertices just touches the *acceptable parameter region*. The size of the confidence region is determined by C and n. This value of s defines a point on the acceptance limit curve at ($\bar{X}$, s). Additional selections of $\bar{X}$ then generate the *acceptance limit* curve, as depicted as dotted lines in Fig. 1. Acceptance limit curves are shown for $n = 10$ and $n = 100$, illustrating that the acceptance limits approach the acceptable parameter region with increasing sample size.

5.1.4 Computer programs have been developed for generating acceptance limit tables, but these may not be available to all practitioners. This practice contains four acceptance limit tables for many practical use situations.

5.2 *Using the Acceptance Limit Tables in This Practice:*

5.2.1 In each table acceptance limits on the standard deviation are given for means ranging 90–110 % of LC in increments of 0.2 %LC for sample sizes ranging from $n = 10$ to $n = 500$. In all tables the target is set at $T = 100$ %LC, so the acceptance limits for standard deviations are symmetrical around 100 %LC. This target is also required for interchangeability across the ICH regions (**6**).

TABLE 2 Acceptance Limits on Sample Standard Deviation (%LC) for $T = 100$ %LC, $C = 95$ %, $LB = 90$ %LC

Sample Average	Sample Size (n)										
(%LC)	10	30	40	50	60	80	100	120	150	200	500
100.0	2.91	4.36	4.65	4.84	4.99	5.19	5.33	5.43	5.54	5.66	5.93
99.8 or 100.2	2.88	4.31	4.59	4.79	4.94	5.14	5.28	5.38	5.50	5.62	5.91
99.6 or 100.4	2.84	4.26	4.54	4.74	4.89	5.09	5.24	5.34	5.45	5.58	5.88
99.4 or 100.6	2.81	4.21	4.49	4.69	4.83	5.04	5.18	5.29	5.40	5.53	5.84
99.2 or 100.8	2.77	4.16	4.43	4.63	4.77	4.98	5.13	5.23	5.35	5.48	5.79
99.0 or 101.0	2.74	4.10	4.38	4.57	4.72	4.92	5.07	5.17	5.29	5.43	5.74
98.8 or 101.2	2.70	4.05	4.32	4.52	4.66	4.86	5.01	5.11	5.23	5.37	5.69
98.6 or 101.4	2.67	4.00	4.27	4.46	4.60	4.80	4.94	5.05	5.17	5.30	5.63
98.4 or 101.6	2.63	3.95	4.21	4.40	4.54	4.74	4.88	4.99	5.10	5.24	5.56
98.2 or 101.8	2.60	3.89	4.16	4.34	4.48	4.68	4.82	4.92	5.04	5.17	5.49
98.0 or 102.0	2.56	3.84	4.10	4.28	4.42	4.62	4.75	4.86	4.97	5.10	5.43
97.8 or 102.2	2.53	3.79	4.05	4.22	4.36	4.55	4.69	4.79	4.90	5.03	5.35
97.6 or 102.4	2.49	3.74	3.99	4.17	4.30	4.49	4.62	4.72	4.84	4.97	5.28
97.4 or 102.6	2.46	3.68	3.93	4.11	4.24	4.43	4.56	4.66	4.77	4.90	5.21
97.2 or 102.8	2.42	3.63	3.88	4.05	4.18	4.36	4.50	4.59	4.70	4.83	5.13
97.0 or 103.0	2.39	3.58	3.82	3.99	4.12	4.30	4.43	4.53	4.63	4.76	5.06
96.8 or 103.2	2.35	3.53	3.77	3.93	4.06†	4.24	4.37	4.46	4.56†	4.69†	4.99
96.6 or 103.4	2.32	3.48	3.71	3.87	4.00	4.18	4.30	4.39	4.50	4.62	4.91
96.4 or 103.6	2.28	3.42	3.65†	3.81	3.94	4.11	4.23	4.33	4.43	4.55	4.84
96.2 or 103.8	2.24	3.37	3.60	3.76	3.88	4.05	4.17	4.26	4.36	4.48	4.77
96.0 or 104.0	2.21	3.32	3.54	3.70	3.82	3.99	4.10	4.19	4.29	4.41	4.69
95.8 or 104.2	2.17	3.26	3.48	3.64	3.76	3.92	4.04	4.13	4.23	4.34	4.62
95.6 or 104.4	2.14	3.21	3.43	3.58	3.70	3.86	3.98	4.06	4.16	4.27	4.54
95.4 or 104.6	2.10	3.16	3.37	3.52	3.63	3.80	3.91	3.99	4.09	4.20	4.47
95.2 or 104.8	2.07	3.11	3.31	3.46	3.57	3.73	3.84†	3.93	4.02	4.13	4.39
95.0 or 105.0	2.03	3.05	3.26	3.40	3.51	3.67	3.78	3.86	3.95	4.06	4.32
94.8 or 105.2	2.00	3.00	3.20	3.35	3.45	3.61	3.71	3.79	3.88	3.99	4.24
94.6 or 105.4	1.96	2.95	3.15	3.29	3.39	3.54	3.65	3.73	3.82	3.92	4.17
94.4 or 105.6	1.93	2.89†	3.09	3.23	3.33	3.48	3.58	3.66	3.75	3.85	4.10
94.2 or 105.8	1.89	2.84	3.03	3.17	3.27	3.42	3.52	3.59	3.68	3.78	4.02
94.0 or 106.0	1.86	2.79	2.98	3.11	3.21	3.35	3.45	3.53	3.61	3.71	3.95
93.8 or 106.2	1.82	2.74	2.92	3.05	3.15	3.29	3.39	3.46	3.54	3.64	3.87
93.6 or 106.4	1.79	2.68	2.86	2.99	3.09	3.23	3.32	3.39	3.47	3.57	3.80
93.4 or 106.6	1.75	2.63	2.81	2.93	3.03	3.16	3.25	3.33	3.40	3.50	3.72
93.2 or 106.8	1.72	2.58	2.75	2.87	2.97	3.10	3.19	3.26	3.34	3.43	3.65
93.0 or 107.0	1.68	2.52	2.69	2.81	2.90	3.03	3.12	3.19	3.27	3.36	3.57
92.8 or 107.2	1.65	2.47	2.64	2.75	2.84	2.97	3.06	3.13	3.20	3.28	3.50
92.6 or 107.4	1.61	2.42	2.58	2.70	2.78	2.91	2.99	3.06	3.13	3.21	3.42
92.4 or 107.6	1.57	2.36	2.52	2.64	2.72	2.84	2.93	2.99	3.06	3.14	3.35
92.2 or 107.8	1.54	2.31	2.47	2.58	2.66	2.78	2.86	2.92	2.99	3.07	3.27
92.0 or 108.0	1.50	2.26	2.41	2.52	2.60	2.71	2.80	2.86	2.92	3.00	3.20
91.8 or 108.2	1.47	2.20	2.35	2.46	2.54	2.65	2.73	2.79	2.86	2.93	3.12
91.6 or 108.4	1.43	2.15	2.30	2.40	2.48†	2.59	2.66	2.72	2.79	2.86	3.05
91.4 or 108.6	1.40	2.10	2.24	2.34	2.42	2.52	2.60	2.65	2.72	2.79	2.97
91.2 or 108.8	1.36	2.04	2.18	2.28	2.35	2.46	2.53	2.59	2.65	2.72	2.89
91.0 or 109.0	1.33	1.99	2.13	2.22	2.29	2.39	2.47	2.52	2.58	2.65	2.82
90.8 or 109.2	1.29	1.94	2.07	2.16	2.23	2.33	2.40	2.45	2.51	2.58	2.74
90.6 or 109.4	1.26	1.89	2.01	2.10	2.17	2.27	2.33	2.39	2.44	2.51	2.67
90.4 or 109.6	1.22	1.83	1.96	2.04	2.11	2.20	2.27	2.32	2.37	2.44	2.59
90.2 or 109.8	1.19	1.78†	1.90	1.98	2.05	2.14	2.20	2.25	2.30	2.37	2.52
90.0 or 110.0	1.15	1.73	1.84	1.93	1.99	2.08	2.14	2.18	2.24†	2.30	2.44

† Editorially corrected.

5.2.1.1 At the confidence level of $C = 95$ % used often in the regulatory arena, three levels of the probability lower bound are provided: $LB = 90$ % (Table 2), $LB = 95$ % (Table 3) and $LB = 99$ % (Table 4). These provide 90 %, 95 %, and 99 % coverage, respectively, of the population of dosage units under consideration. The usual coverage is 95 %.

5.2.1.2 Table 5 is provided at $C = 90$ % and $LB = 95$ % for comparison with Table 3 to demonstrate the effect of a lower confidence level.

NOTE 1—Tables can also be generated for other choices for ranges of means, such as 85.1 to 114.9 %LC, or for other sample sizes.

5.2.2 A representative sample of n dosage units is taken from the batch and the active content is measured on each unit, taken as a random sample or as a systematic sample (selecting and testing one unit at equally spaced time intervals of manufacture across the batch). Other sampling plans, such as testing more than one unit at each of several locations, are outside the scope of this practice.

5.2.3 The sample average ($\bar{X}$) and sample standard deviation (s) are calculated. Enter the table row with the sample average and the table column with the sample size to find the acceptance limit on the standard deviation. If the sample standard deviation is at or below the acceptance limit then it can be asserted at the C % confidence level that the batch will

TABLE 3 Acceptance Limits on Sample Standard Deviation (%LC) for $T = 100$ %LC, $C = 95$ %, $LB = 95$ %LC

Sample Average	Sample Size (n)										
(%LC)	10	30	40	50	60	80	100	120	150	200	500
100.0	2.81	4.18	4.46	4.64	4.78	4.98	5.11	5.21	5.31	5.43	5.69
99.8 or 100.2	2.77	4.13	4.41	4.59	4.73	4.93	5.07	5.16	5.27	5.39	5.67
99.6 or 100.4	2.74	4.08	4.35	4.54	4.68	4.88	5.02	5.12	5.23†	5.35	5.64
99.4 or 100.6	2.70	4.04	4.30	4.49	4.63	4.83	4.96	5.07	5.18	5.30	5.60
99.2 or 100.8	2.67	3.99	4.26	4.43	4.57	4.77	4.91	5.01	5.12	5.25	5.55
99.0 or 101.0	2.64	3.94	4.20	4.39	4.51	4.71	4.85	4.95	5.07	5.20	5.49
98.8 or 101.2	2.60	3.88	4.15	4.33	4.47	4.65	4.79	4.89	5.01	5.14	5.44
98.6 or 101.4	2.57	3.84	4.09	4.27	4.41	4.59	4.73	4.83	4.94	5.07	5.38
98.4 or 101.6	2.54	3.79	4.03	4.21	4.35	4.54	4.67	4.77	4.88	5.01	5.31
98.2 or 101.8	2.50	3.74	3.99	4.16	4.29	4.48	4.61	4.70	4.82	4.94	5.25
98.0 or 102.0	2.47	3.68	3.93	4.11	4.23	4.42	4.55	4.65	4.75	4.88	5.18
97.8 or 102.2	2.43	3.64	3.88	4.05	4.18	4.36	4.49	4.58	4.68	4.81	5.11
97.6 or 102.4	2.40	3.58	3.83	3.99	4.12	4.29	4.42	4.52	4.63	4.74	5.05
97.4 or 102.6	2.37	3.54	3.77	3.93	4.06	4.24	4.36	4.45	4.56	4.68	4.97
97.2 or 102.8	2.33	3.49	3.71	3.88	4.00	4.18	4.30	4.39	4.49	4.62	4.90
97.0 or 103.0	2.30	3.43	3.67	3.82	3.95	4.11	4.24	4.33	4.43	4.55	4.83
96.8 or 103.2	2.26	3.39	3.61	3.77	3.88	4.06	4.17	4.27	4.37	4.48	4.76
96.6 or 103.4	2.23	3.33	3.55	3.71	3.83	4.00	4.12	4.20	4.30	4.41	4.69
96.4 or 103.6	2.20	3.29	3.50	3.65	3.77	3.93	4.05	4.14	4.23	4.35	4.62
96.2 or 103.8	2.16	3.23	3.44	3.60	3.71	3.88	3.99	4.07	4.17	4.28	4.55
96.0 or 104.0	2.13	3.18	3.40	3.54	3.66	3.81	3.93	4.01	4.10	4.21	4.47
95.8 or 104.2	2.09	3.13	3.34	3.49	3.59	3.76	3.86	3.95	4.04	4.15	4.41
95.6 or 104.4	2.06	3.08	3.29	3.43	3.54	3.69	3.80	3.88	3.98	4.08	4.34
95.4 or 104.6	2.03	3.03	3.23	3.38	3.48	3.63	3.74	3.82	3.91	4.02	4.26
95.2 or 104.8	1.99	2.98	3.18	3.31	3.42	3.57	3.67	3.75	3.85	3.94	4.19
95.0 or 105.0	1.96	2.93	3.13	3.26	3.36	3.52	3.61	3.70	3.78	3.88	4.12
94.8 or 105.2	1.92	2.87	3.07	3.20	3.31	3.45	3.56	3.63	3.72	3.81	4.05
94.6 or 105.4	1.89	2.83	3.02	3.15	3.24	3.39	3.49	3.57	3.65	3.75	3.98
94.4 or 105.6	1.86	2.78	2.96	3.09	3.19	3.33	3.43	3.50	3.58	3.68	3.91
94.2 or 105.8	1.82	2.72	2.91	3.03	3.13	3.27	3.36	3.44	3.51	3.61	3.83
94.0 or 106.0	1.79	2.67	2.85	2.98	3.07	3.21	3.30	3.37	3.45	3.54	3.77
93.8 or 106.2	1.75	2.63	2.80	2.92	3.01	3.14	3.24	3.31	3.39	3.47	3.70
93.6 or 106.4	1.72	2.57	2.74	2.86	2.96	3.09	3.17	3.25	3.32	3.41	3.62
93.4 or 106.6	1.69	2.52	2.69	2.81	2.90	3.03	3.11	3.18	3.25	3.34	3.55
93.2 or 106.8	1.65	2.47	2.64	2.75	2.84	2.96	3.05	3.11	3.19	3.27	3.48
93.0 or 107.0	1.62	2.42	2.59	2.70	2.78	2.90	2.99	3.05	3.12	3.21	3.40
92.8 or 107.2	1.58	2.37	2.52	2.64	2.72	2.84	2.92	2.99	3.05	3.14	3.33
92.6 or 107.4	1.55	2.32	2.47	2.58	2.67	2.78	2.86	2.93	2.99	3.07	3.27
92.4 or 107.6	1.52	2.26	2.42	2.52	2.61	2.72	2.80	2.86	2.93	3.00	3.20
92.2 or 107.8	1.48	2.21	2.36	2.47	2.54	2.66	2.74	2.79	2.86	2.93	3.13
92.0 or 108.0	1.45	2.16	2.31	2.41	2.48	2.59	2.68	2.73	2.80	2.87	3.05
91.8 or 108.2	1.41	2.11	2.26	2.35	2.43	2.53	2.61	2.66	2.73	2.80	2.97
91.6 or 108.4	1.38	2.06	2.20	2.30	2.37	2.47	2.55	2.60	2.67	2.73	2.90
91.4 or 108.6	1.35	2.01	2.15	2.24	2.31	2.41	2.49	2.54	2.60	2.67	2.83
91.2 or 108.8	1.31	1.96	2.09	2.18	2.25	2.35	2.43	2.47	2.54	2.60	2.76
91.0 or 109.0	1.28	1.91	2.04	2.13	2.19	2.29	2.36	2.41	2.47	2.53	2.69
90.8 or 109.2	1.24	1.86	1.98	2.07	2.13	2.23	2.30	2.34	2.40	2.46	2.62
90.6 or 109.4	1.21	1.81	1.93	2.01	2.07	2.17	2.23	2.28	2.34	2.39	2.55
90.4 or 109.6	1.18	1.75	1.87	1.95	2.02	2.11	2.17	2.21	2.27	2.33	2.48
90.2 or 109.8	1.14	1.70	1.82	1.90	1.96	2.05	2.11	2.16	2.20	2.26	2.41
90.0 or 110.0	1.11	1.66	1.76	1.85	1.90	1.99	2.04	2.09	2.13	2.20	2.33

† Editorially corrected.

TABLE 4 Acceptance Limits on Sample Standard Deviation (%LC) for T = 100 %LC, C = 95 %, LB = 99 %LC

Sample Average (%LC)	Sample Size (n)										
	10	30	40	50	60	80	100	120	150	200	500
100.0	2.62	3.88	4.13	4.31	4.43	4.61	4.73	4.82	4.92	5.03	5.27
99.8 or 100.2	2.59	3.84	4.09	4.26	4.39	4.57	4.69	4.78	4.88	4.99	5.25†
99.6 or 100.4	2.56	3.79†	4.04	4.21	4.34	4.52	4.64	4.73	4.84	4.95	5.22
99.4 or 100.6	2.53	3.75†	3.99	4.16	4.29	4.47	4.59	4.68	4.78	4.90	5.17
99.2 or 100.8	2.49	3.70	3.94	4.11	4.23	4.41	4.54	4.63	4.73	4.85	5.13
99.0 or 101.0	2.46	3.65	3.89	4.06	4.18	4.36	4.48	4.57	4.68	4.79	5.07
98.8 or 101.2	2.43	3.61	3.84	4.01	4.13	4.31	4.43	4.52	4.62	4.74	5.02
98.6 or 101.4	2.40	3.56	3.79	3.95	4.08	4.25	4.37	4.46	4.56	4.68	4.96
98.4 or 101.6	2.37	3.51	3.74	3.90	4.02	4.19	4.31	4.40	4.50	4.62	4.90
98.2 or 101.8	2.34	3.47	3.69	3.85	3.97	4.14	4.26	4.34	4.44	4.56	4.83
98.0 or 102.0	2.31	3.42	3.64	3.80	3.92	4.08	4.20	4.29	4.38†	4.50	4.77
97.8 or 102.2	2.27	3.37	3.59	3.75	3.86	4.03	4.14	4.23	4.32	4.44	4.70
97.6 or 102.4	2.24	3.33	3.54	3.70	3.81	3.97	4.09	4.17	4.27	4.38	4.64
97.4 or 102.6	2.21	3.28	3.49	3.64	3.76	3.92	4.03	4.11	4.21	4.31	4.58
97.2 or 102.8	2.18	3.23	3.45	3.59	3.70	3.86	3.97	4.05	4.15	4.25	4.51
97.0 or 103.0	2.15	3.19	3.40	3.54	3.65	3.81	3.91	4.00	4.09	4.19	4.45
96.8 or 103.2	2.12	3.14	3.35	3.49	3.60	3.75	3.86	3.94	4.03	4.13	4.38
96.6 or 103.4	2.08	3.09	3.30	3.44	3.54	3.69	3.80	3.88	3.97	4.07	4.32
96.4 or 103.6	2.05	3.05	3.24	3.38	3.49	3.64	3.74	3.82	3.91	4.01	4.25
96.2 or 103.8	2.02	3.00	3.20	3.33	3.43	3.58	3.68	3.76	3.85	3.95	4.19
96.0 or 104.0	1.99	2.95	3.14	3.28	3.38	3.53	3.63	3.70	3.79	3.88	4.12
95.8 or 104.2	1.96	2.91	3.10	3.23	3.33	3.47	3.57	3.64	3.73	3.82	4.06
95.6 or 104.4	1.93	2.86	3.05	3.18	3.27	3.41	3.51	3.58	3.67	3.76	3.99
95.4 or 104.6	1.89	2.81	2.99	3.12	3.22	3.36	3.45	3.52	3.61	3.70	3.92
95.2 or 104.8	1.86	2.76	2.94	3.07	3.16	3.30	3.40	3.47	3.55	3.64	3.86
95.0 or 105.0	1.83	2.72	2.89	3.02	3.11	3.25†	3.34	3.41	3.48	3.58†	3.79
94.8 or 105.2	1.80	2.67	2.84	2.97	3.06	3.19	3.28	3.35	3.43	3.51	3.73
94.6 or 105.4	1.77	2.62	2.79	2.91	3.00	3.13	3.22	3.29	3.36	3.45	3.66
94.4 or 105.6	1.73	2.58	2.74	2.86	2.95	3.08	3.16	3.23	3.30	3.39	3.60
94.2 or 105.8	1.70	2.53	2.69	2.81	2.90	3.02	3.11	3.17	3.24	3.33	3.53
94.0 or 106.0	1.67	2.48	2.64	2.76	2.84	2.96	3.05	3.11	3.18	3.26	3.46
93.8 or 106.2	1.64	2.43	2.59	2.70	2.79	2.91	2.99	3.05	3.12	3.20	3.40
93.6 or 106.4	1.61	2.39	2.54	2.65	2.73†	2.85	2.93	2.99	3.06	3.14	3.33
93.4 or 106.6	1.58	2.34	2.49	2.60	2.68	2.79	2.87	2.93	3.00	3.08	3.27
93.2 or 106.8	1.54	2.29	2.44	2.55	2.62	2.74	2.82	2.87	2.94	3.02	3.20
93.0 or 107.0	1.51	2.24	2.39	2.49	2.57	2.68	2.76	2.82	2.88	2.95	3.14
92.8 or 107.2	1.48	2.20	2.34	2.44	2.52	2.63	2.70	2.76	2.82	2.89	3.07
92.6 or 107.4	1.45	2.15	2.29	2.39	2.46	2.57	2.64	2.70	2.76	2.83	3.00
92.4 or 107.6	1.42	2.10	2.24	2.34	2.41	2.51	2.58	2.64	2.70	2.77	2.94
92.2 or 107.8	1.38	2.06	2.19	2.28	2.36	2.46	2.53	2.58	2.64	2.71	2.87
92.0 or 108.0	1.35	2.01	2.14	2.23	2.30	2.40	2.47	2.52	2.58	2.64	2.81
91.8 or 108.2	1.32	1.96	2.09	2.18	2.25	2.34	2.41	2.46	2.52	2.58	2.74
91.6 or 108.4	1.29	1.91	2.04	2.13	2.19	2.29	2.35	2.40	2.46	2.52	2.67
91.4 or 108.6	1.26	1.87	1.99	2.07	2.14	2.23	2.29	2.34	2.39	2.46	2.61
91.2 or 108.8	1.23	1.82	1.94	2.02	2.08	2.17	2.24	2.28	2.34	2.39	2.54
91.0 or 109.0	1.19	1.77	1.89	1.97	2.03	2.12	2.18	2.22	2.27	2.33	2.48
90.8 or 109.2	1.16	1.73	1.84	1.92	1.98	2.06	2.12	2.16	2.21	2.27	2.41
90.6 or 109.4	1.13	1.68	1.79	1.86	1.92	2.00	2.06	2.11	2.15	2.21	2.34
90.4 or 109.6	1.10	1.63	1.74	1.81	1.87	1.95	2.00	2.04	2.09	2.15	2.28
90.2 or 109.8	1.07	1.58	1.69	1.76	1.81	1.89	1.95	1.99	2.03	2.08	2.21
90.0 or 110.0	1.03	1.54	1.64	1.71	1.76	1.84	1.89	1.93	1.97	2.02	2.15

† Editorially corrected.

have an LB % chance of passing the UDU test. Some interpolation may be required for sample sizes and sample means not listed in the table.

5.2.3.1 *Example 1*—A sample of $n = 60$ dosage units provided dosage content statistics of $\bar{X} = 98.6$ %LC and $s = 3.91$ %LC. Since s was below the upper limit of 4.41 %LC (using Table 3), we can state with 95 % confidence there is at least a 95 % probability that a future sample taken from the batch will meet the UDU test.

5.2.3.2 *Example 2*—A sample of $n = 70$ dosage units provided dosage content statistics of $\bar{X} = 97.8$ %LC and $s = 4.29$ %LC. Since $n =$ was not provided in the Table 3, we must interpolate between entry $n = 60$ with the upper limit 4.18 %LC and entry $n = 80$ with the upper limit 4.36 %LC as follows:

$$\text{acceptance limit} = 4.18 + [(4.36 - 4.18)(80 - 70)/(80 - 60)]$$
$$= 4.18 + [(0.18)(10)/(20)] = 4.27\,\%LC$$

Since $s = 4.29$ %LC was above the upper limit of 4.27 %LC, we cannot state with 95 % confidence there is at least a 95 % probability that a future sample taken from the batch will meet the UDU test.

5.2.3.3 *Example 3*—A sample of $n = 60$ dosage units provided dosage content statistics of $\bar{X} = 98.6$ %LC and

TABLE 5 Acceptance Limits on Sample Standard Deviation (%LC) for *T* = 100 %LC, *C* = 90 %, *LB* = 95 %LC

Sample Average (%LC)	Sample Size (*n*)										
	10	30	40	50	60	80	100	120	150	200	500
100.0	3.21	4.47	4.71	4.88	5.00	5.16	5.27	5.35	5.44	5.54	5.76
99.8 or 100.2	3.17	4.42	4.67	4.83	4.95	5.12	5.23	5.32	5.41	5.51	5.74
99.6 or 100.4	3.13	4.37	4.61	4.78	4.90	5.07	5.19	5.27	5.36	5.47	5.71
99.4 or 100.6	3.09	4.32	4.56	4.72	4.85	5.02	5.14	5.22	5.32	5.42	5.67
99.2 or 100.8	3.06	4.27	4.50	4.67	4.79	4.96	5.08	5.17	5.26	5.37	5.63
99.0 or 101.0	3.02	4.21	4.45	4.61	4.73	4.91	5.02	5.11	5.21	5.32	5.58
98.8 or 101.2	2.98	4.16	4.39	4.55	4.67	4..84	4.96	5.05	5.15	5.26	5.52
98.6 or 101.4	2.94	4.11	4.34	4.50	4.62	4.78	4.90	4.99	5.08	5.20	5.46
98.4 or 101.6	2.90	4.05	4.28	4.44	4.55	4.72	4.84	4.93	5.02	5.13	5.40
98.2 or 101.8	2.86	4.00	4.22	4.38	4.50	4.66	4.78	4.86	4.96	5.07	5.33
98.0 or 102.0	2.82	3.95	4.17	4.32	4.44	4.60	4.71	4.80	4.89	5.00	5.26
97.8 or 102.2	2.78	3.89	4.11	4.26	4.37	4.54	4.65	4.73	4.82	4.93	5.19
97.6 or 102.4	2.75	3.84	4.05	4.20	4.31	4.47	4.58	4.67	4.76	4.86	5.12
97.4 or 102.6	2.71	3.79	4.00	4.14	4.25	4.41	4.52	4.60	4.69	4.80	5.05
97.2 or 102.8	2.67	3.73	3.94	4.08	4.19	4.35	4.45	4.53	4.63	4.73	4.98
97.0 or 103.0	2.63	3.68	3.88	4.03	4.13	4.29	4.39	4.47	4.56	4.66	4.91
96.8 or 103.2	2.59	3.62	3.82	3.97	4.07	4.22	4.33	4.40	4.49	4.59	4.84
96.6 or 103.4	2.55	3.57	3.77	3.91	4.01	4.16	4.26	4.34	4.42	4.52	4.76
96.4 or 103.6	2.51	3.52	3.71	3.85	3.95	4.10	4.20	4.27	4.36	4.46	4.69
96.2 or 103.8	2.47	3.46	3.65	3.79	3.89	4.03	4.13	4.21	4.29	4.39	4.62
96.0 or 104.0	2.43	3.41	3.60	3.73	3.83	3.97	4.07	4.14	4.22	4.32	4.55
95.8 or 104.2	2.40	3.35	3.54	3.67	3.77	3.91	4.00	4.08	4.16	4.25	4.48
95.6 or 104.4	2.36	3.30	3.48	3.61	3.71	3.84	3.94	4.01	4.09	4.18	4.40
95.4 or 104.6	2.32	3.24	3.43	3.55	3.65	3.78	3.87	3.95	4.02	4.11	4.33
95.2 or 104.8	2.28	3.19	3.37	3.49	3.58	3.72	3.81	3.88	3.96	4.04	4.26
95.0 or 105.0	2.24	3.13	3.31	3.43	3.52	3.66	3.75	3.81	3.89	3.97	4.19
94.8 or 105.2	2.20	3.08	3.25	3.37	3.46	3.59	3.68	3.75	3.82	3.91	4.11
94.6 or 105.4	2.16	3.03	3.20	3.31	3.40	3.53	3.61	3.68	3.75	3.84	4.04
94.4 or 105.6	2.12	2.97	3.14	3.25	3.34	3.47	3.55	3.61	3.69	3.77	3.97
94.2 or 105.8	2.09	2.92	3.08	3.20	3.28	3.40	3.49	3.55	3.62	3.70	3.90
94.0 or 106.0	2.05	2.86	3.02	3.13	3.22	3.34	3.42	3.48	3.55	3.63	3.82
93.8 or 106.2	2.01	2.81	2.97	3.08	3.16	3.27	3.36	3.42	3.48	3.56	3.75
93.6 or 106.4	1.97	2.75	2.91	3.02	3.10	3.21	3.29	3.35	3.42	3.49	3.68
93.4 or 106.6	1.93	2.70	2.85	2.96	3.04	3.15	3.23	3.28	3.35	3.42	3.61
93.2 or 106.8	1.89	2.65	2.79	2.90	2.97	3.08	3.16	3.22	3.28	3.36	3.53
93.0 or 107.0	1.85	2.59	2.74	2.84	2.91	3.02	3.10	3.15	3.21	3.29	3.46
92.8 or 107.2	1.81	2.54	2.68	2.78	2.85	2.96	3.03	3.09	3.15	3.22	3.39
92.6 or 107.4	1.77	2.48	2.62	2.72	2.79	2.89†	2.96	3.02	3.08	3.15	3.32
92.4 or 107.6	1.74	2.43	2.56	2.66	2.73	2.83	2.90	2.95	3.01	3.08	3.24
92.2 or 107.8	1.70	2.37	2.51	2.60	2.67	2.77	2.84	2.89	2.94	3.01	3.17
92.0 or 108.0	1.66	2.32	2.45	2.54	2.61	2.70	2.77	2.82	2.88	2.94	3.10
91.8 or 108.2	1.62	2.26	2.39	2.48	2.55	2.64	2.71	2.75	2.81	2.87	3.02
91.6 or 108.4	1.58	2.21	2.33	2.42	2.48	2.58	2.64	2.69	2.74	2.80	2.95
91.4 or 108.6	1.54	2.16	2.27	2.36	2.42	2.51	2.58	2.62	2.67	2.73	2.88
91.2 or 108.8	1.50	2.10	2.22	2.30	2.36	2.45	2.51	2.55	2.61	2.66	2.81
91.0 or 109.0	1.46	2.05	2.16	2.24	2.30	2.39	2.44	2.49	2.54	2.60	2.73
90.8 or 109.2	1.42	1.99	2.10	2.18	2.24	2.32	2.38	2.42	2.47	2.53	2.66
90.6 or 109.4	1.38	1.94	2.04	2.12	2.18	2.26	2.31	2.36	2.40	2.46	2.59
90.4 or 109.6	1.34	1.88	1.99	2.06	2.12	2.19	2.25	2.29	2.34	2.39	2.51
90.2 or 109.8	1.31	1.83	1.93	2.00	2.05	2.13	2.18	2.22	2.27	2.32	2.44
90.0 or 110.0	1.27	1.77	1.87	1.94	1.99	2.07	2.12	2.16	2.20	2.25	2.37

† Editorially corrected.

s = 3.91 %LC at time of manufacture. At the end of shelf life the dosage units are predicted to have lost potency such that the effective $\bar{X}$ = 96.2 %LC. Since s = 3.91 %LC was above the upper limit of 3.71 %LC (using Table 3), we cannot state with 95 % confidence there is at least a 95 % probability that a future sample taken from the batch will meet the UDU test throughout the shelf life.

5.3 *Selection of Sample Size:*

5.3.1 To select the size of sample to be taken, the probability that sample statistics ($\bar{X}$, s) will lie within acceptance limits should be evaluated over a range of sample sizes for selected values of population parameters (μ, σ) of practical interest (for example, based on product history or development lots). For selected values of the population parameters, the probability of passing the UDU test should be higher than the lower bound. The probability of passing the acceptance limit depends on the sample size. The larger the sample size n that is chosen, the larger will be the acceptance region and the tighter the distribution of the statistics. For expected values of the population parameters, choose n so that the probability of passing acceptance limits is greater than a desired value.

6. Keywords

6.1 acceptance limits; acceptance sampling inspection; multiple-stage sampling test; uniformity of dosage units

REFERENCES

(1) Bergum, J.S., "Constructing Acceptance Limits for Multiple Stage Tests," *Drug Development and Industrial Pharmacy*, Vol 16, No. 14, 1990, pp. 2153–2166.

(2) Bergum, J.S., and Utter, M.L., "Process Validation," *Encyclopedia of Bio-pharmaceutical Statistics*, Marcel Dekker: New York, NY, 2000, pp. 422–439.

(3) Bergum, J.S., and Utter, M.L., "Statistical Methods for Uniformity and Dissolution Testing," *Pharmaceutical Process Validation*, 3rd ed., edited by R.A. Nash and A.H. Watchter, Marcel Dekker: New York, NY, 2003, pp. 667–697.

(4) Bergum, J.S., and Li, H., "Acceptance Limits for the New ICH USP 29 Content Uniformity Test," *Pharmaceutical Technology*, October 2007, pp. 90–100.

(5) Lindgren, B.W., *Statistical Theory*, Macmillan, New York, NY, 1968.

(6) ICH Q4B Annex 6(R1), "Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions on Uniformity of Dosage Units General Chapter," *International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use*, September 27, 2010.