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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~~ safety, health, and ~~health~~environmental practices and determine the applicability of regulatory limitations prior to use.*

1.4 *This international standard was developed in accordance with internationally recognized principles on standardization established in the Decision on Principles for the Development of International Standards, Guides and Recommendations issued by the World Trade Organization Technical Barriers to Trade (TBT) Committee.*

2. Referenced Documents

2.1 *ASTM Standards*:[2]

E2363 Terminology Relating to Process Analytical Technology in the Pharmaceutical Industry

[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.

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] Available from the Pharmaceuticals and Medical Devices ~~Agency, Japan, http://jpdb.nihs.go.jp.~~Agency (PMDA), Shin-Kasumigaseki Building, 3-3-2 Kasumigaseki, Chiyoda-ku, Tokyo 100-0013, Japan, https://www.pmda.go.jp.

[4] Available from the European ~~Council,~~ Directorate for the Quality of Medicines and Health Care (EDQM), Council of Europe, 7 allée Kastner, CS 30026, F-67081 Strasbourg, France, http://www.edqm.eu.

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

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 – α) = 95 %, where α is a risk that is allocated to the two parameters being estimated.

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.

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

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 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:*~~*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

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	$\lvert M - \bar{X} \rvert + 2.4\ s \leq 15.0$, where M is defined below.
S_2	20	(*1*) $\lvert M - \bar{X} \rvert + 2.0\ s \leq 15.0$, 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.

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*.

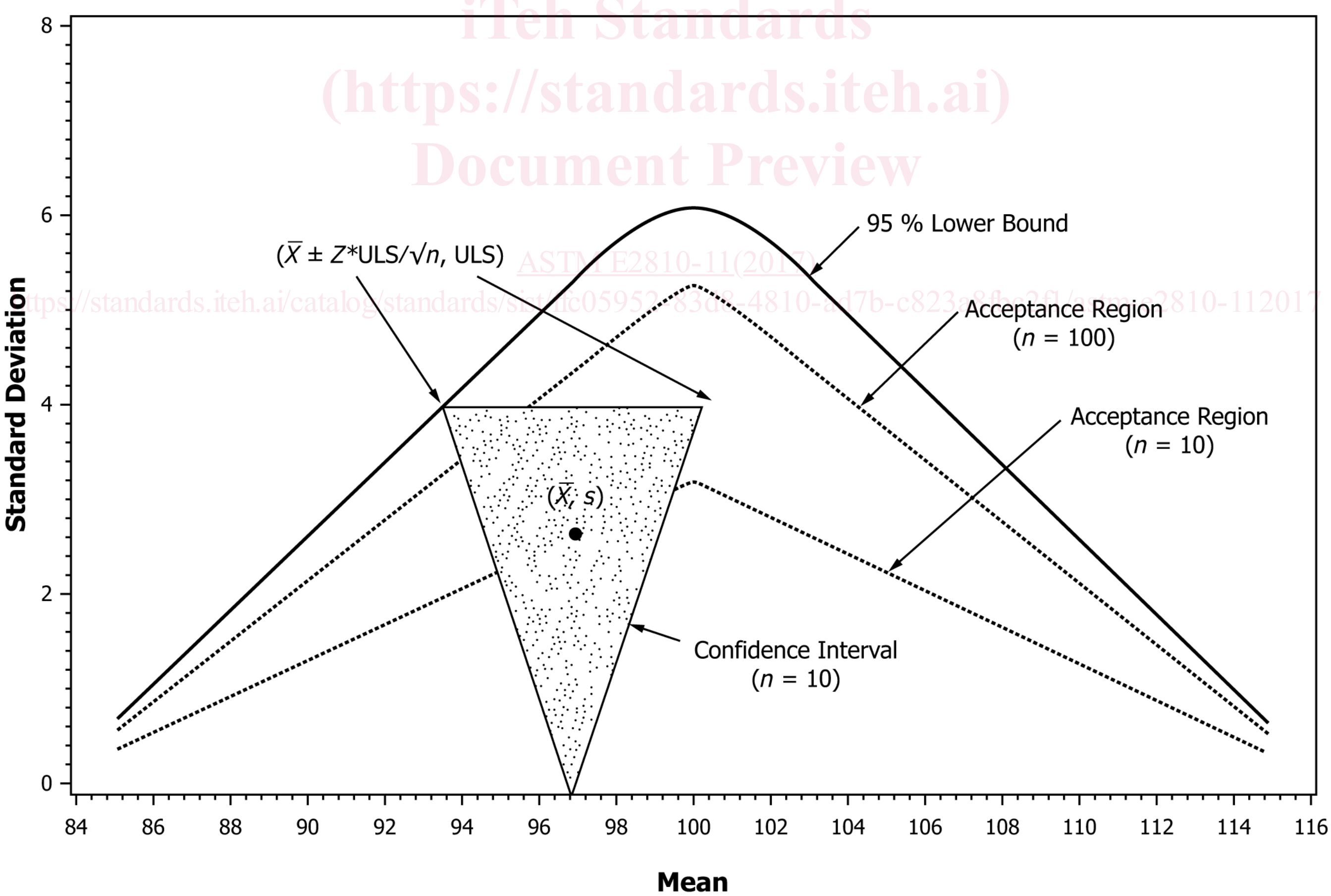
5.1.2 The first step is to determine the acceptable parameter region. On a two-dimensional content space consisting of the true mean (μ) on the horizontal axis and standard deviation (σ) on the vertical axis the upper boundary of this region is defined by a contour, a curve that is concave downward and 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* % 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**).



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