Dissolution Acceptance Limits Based on Parametric Tolerance Intervals

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Abstract
ASTM Standard E2709 provides an approach for establishing confidence in passing the USP <711> dissolution test procedure for immediate-release dosage forms. An ISPE Good Practice Guide on process validation uses this approach to calculate acceptance limits for sample standard deviations. The resulting acceptance limits are extremely conservative, however, due to a poorly-shaped joint confidence region for the lot mean and standard deviation. A parametric tolerance interval approach provides wider acceptance limits with much better statistical properties by using a better partition of the parameter space. The improvement in acceptance limits can be considerable. As an example, consider establishing 90% confidence of 95% probability of passing USP <711>. For a sample size of 6 dosage units, the tolerance interval approach provides acceptance limits that are 1.5 to 2.1 times greater than those in the ISPE Good Practice Guide. For a sample size of 90 dosage units, the tolerance interval approach provides acceptance limits that are 1.13 to 1.35 times greater than those in the ISPE Good Practice Guide. An example is provided to show that the improved acceptance limits provide a meaningful reduction in decision errors.

Keywords: ASTM Standard E2709; Dissolution; USP 711; Tolerance intervals; Acceptance limits; Lot release

1. Introduction

Dissolution is a key quality characteristic for immediate-release pharmaceutical dosage forms. The dissolution of an individual dosage unit, such as a tablet or capsule, is typically measured at several time points and progresses from 0% of labelled content at time zero to about 100% of labelled content as time progresses. The observed dissolution of an individual dosage unit includes both actual differences among dosage units and analytical variation. United States Pharmacopeia (USP) general chapter <711>, *Dissolution*, provides a three-stage dissolution test procedure (USP and National Formulary 2011) that is not intended to serve as a lot-release procedure (USP General Notices and Requirements 2010). ASTM Standard E2709, on the other hand, provides an approach for establishing confidence in passing tests such as USP <711> and states that the resulting acceptance limits can be used as elements of lot release (ASTM International 2014). An ISPE Good Practice Guide on process validation applies the E2709 approach to USP <711> and provides tables of acceptance limits for sample standard deviations (ISPE 2019). The acceptance limits in the ISPE Good Practice Guide's Tables 14.2 and 14.3 provide 90% and 95% confidence, respectively, of 95% probability of passing USP <711>. Unfortunately, the acceptance limits are extremely conservative due to the use of a poorly-shaped joint confidence region for the lot mean and standard deviation.

Much better acceptance limits are obtained by partitioning the parameter space for lot means and standard deviations into a region with higher probabilities of passing USP <711> and a region with lower probabilities. Parametric tolerance interval (PTI) and Bayesian approaches can be used to obtain such a partition. In the context of establishing confidence in passing the USP <905> test procedure for uniformity of dosage units (often referred to as content uniformity), Bergum (2015) and Stepinac and Saeed (2017) used PTI approaches to develop acceptance limits while Lewis and Fan (2016) used a Bayesian approach. Lewis and Fan also showed that a PTI approach provides an approximation to their Bayesian approach. Consequently, we focus our attention on a PTI approach for establishing confidence in passing USP <711>.

The remainder of this article is organized as follows. Section 2 summarizes the USP <711> dissolution test procedure and provides an empirical approximation to the probability of passing it. Section 3 describes the E2709 approach for establishing confidence in passing USP <711> and illustrates its use. Section 4 describes a PTI approach that follows the spirit of E2709 and compares its acceptance limits to those in the ISPE Good Practice Guide. Section 5 provides operating characteristic curves for the PTI approach and an example demonstrating their use.

Several of the results in this article are based on Monte Carlo simulations. All Monte Carlo simulations were conducted using Version 9.3 or 9.4 of the SAS® System for Windows (Copyright © 2002-2010, SAS Institute Inc., SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA). The simulations are based on independent observations from a normal distribution.

2. The USP <711> Dissolution Test Procedure

The USP <711> dissolution test for immediate-release dosage forms specifies a three-stage procedure that compares the percent of active pharmaceutical ingredient dissolved at a specified time point to a value Q, such as Q = 80% dissolved at 30 minutes. Stage 1 is based on the dissolution of six dosage units. Stage 1's requirements are met if each of the six observations is greater than or equal to Q + 5%. If Stage 1's requirements are not met one proceeds to Stage 2, which is based on the six observations from Stage 1 and the dissolution of six additional dosage units. Stage 2's requirements are met if the average of the 12 observations is greater than or equal to Q and none of the results observations is less than Q − 15%. If Stage 2's requirements are not met one proceeds to Stage 3, which is based on the twelve observations from Stages 1 and 2 and the dissolution of 12 additional dosage units. Stage 3's requirements are met if the average of the 24 observations is greater than or equal to Q, no more than two observations are less than Q − 15%, and none of the observations is less than Q − 25%. USP <711> is passed if any of the three stages' requirements are met and failed if none of the three stages' requirements are met.

Suppose the dissolution of individual dosage units is modelled as independent observations from a normal distribution with mean μ and standard deviation σ. Then the probability, P, of passing USP <711> only depends on $\delta = \mu - Q$ and σ. There is no closed-form solution for the relationship, but lower bounds have been derived (see Chow *et al.* 2002, for example). The ISPE Good Practice Guide uses a lower bound for P given δ and σ, while we use a nonlinear empirical approximation for σ given P and δ. As shown in Section 4,

the nonlinear approximation can also be used in a PTI approach for establishing confidence in passing USP <711>.

The nonlinear approximation is based on a zero-intercept version of model 4.5.6 in Ratkowsky (1990) and takes the form

$$\sigma = \beta\delta + \gamma\left(\sqrt{\theta^2 + \varepsilon^2} - \sqrt{(\delta - \theta)^2 + \varepsilon^2}\right) \quad (1)$$

where the parameters β, γ, θ and ε depend on the value of P. Estimated parameter values for P = 80%, 90%, 95%, 99% and 99.9% are shown in Table 1 and the corresponding probability contours are shown in Figure 1. To assess the accuracy of the nonlinear approximation, Monte Carlo simulation was used to estimate the probability of passing USP <711> for (δ, σ) pairs on the probability contours shown in Figure 1. The results indicate small systematic deviations from the nominal probability, as shown in Figure 2 for P = 90%, 95% and 99%. Although we don't show results here, good approximations to probability contours for USP <711> can also be obtained using a series of five or more line segments.

Table 1: Parameter Values for the Nonlinear Empirical Approximation to Probability Contours for USP <711>

	Probability of Passing USP <711>				
Parameter	*80%*	*90%*	*95%*	*99%*	*99.9%*
β	5.3625	2.7594	2.0044	1.3448	0.9860
γ	4.8255	2.2872	1.5787	0.9924	0.6965
θ	0.9134	1.8928	2.6020	3.6897	4.5635
ε	0.6846	0.8443	0.8956	0.8438	0.6715

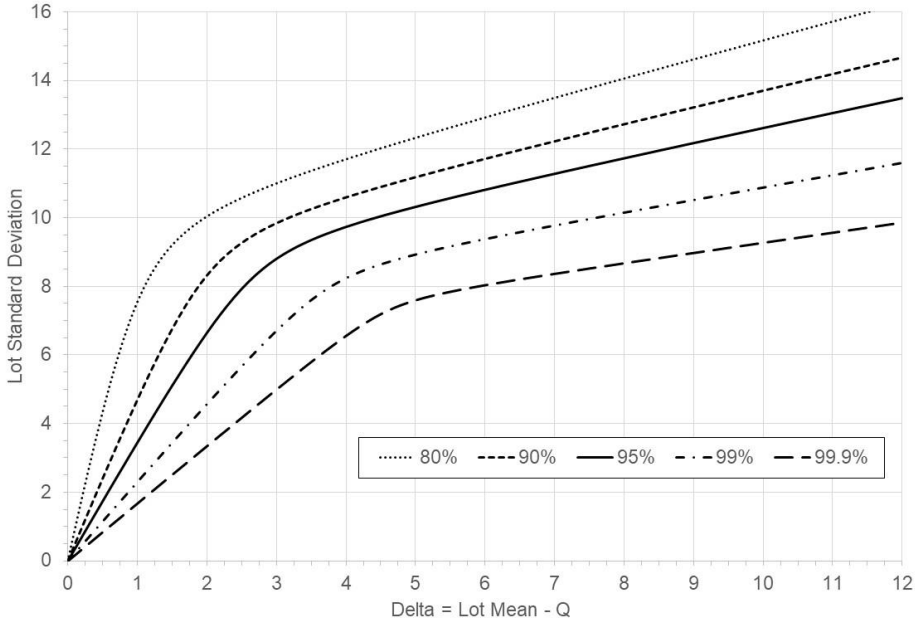

Figure 1: Nonlinear Approximation to Probability Contours for USP <711>

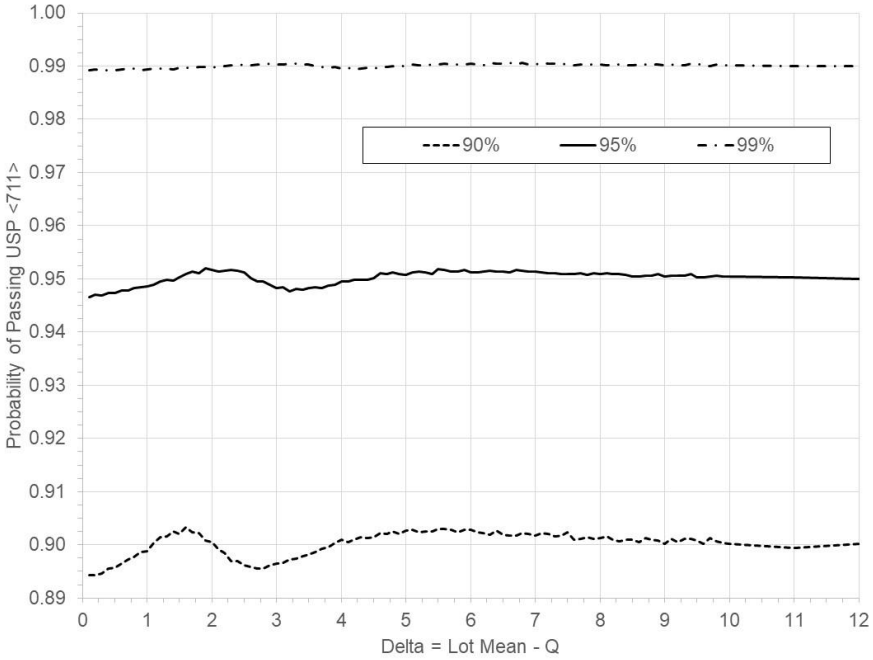

Figure 2: Accuracy of the Nonlinear Approximation to Probability Contours for USP <711>

3. The ASTM E2709 Approach to Acceptance Limits

ASTM Standard E2709 provides a general approach for establishing confidence in the probability of passing test procedures such as USP <711>. It is based on statistical methodology developed by Bergum (1990). The ISPE Good Practice Guide applies the E2709 approach to USP <711> and obtains acceptance limits for sample standard deviations given specified values of sample means. The ISPE Good Practice Guide assumes independent normally distributed observations for individual dosage units and provides acceptance limits for 90% and 95% confidence of 95% probability of passing USP <711> in its Tables 14.2 and 14.3. The E2709 approach has three steps:

(1) Specify a desired level of confidence for a lower bound for P, such as 90% confidence that P is at least 95%, and a sample size. Denote the confidence level by $100(1-\alpha)$%, the lower bound by LB and the sample size by n.

(2) Construct a $100(1-\alpha)$% joint confidence region for $\delta = \mu - Q$ and σ based on n dosage units. The ISPE Good Practice Guide uses a one-sided version of a triangular confidence region in E2709, since larger values of δ have higher probabilities of passing USP <711>.

(3) Let $\bar{y} = \sum_{i=1}^{n} y_i/n$, $\bar{d} = \bar{y} - Q$, and $s = \sqrt{\sum_{i=1}^{n}(y_i - \bar{y})^2/(n-1)}$. For a specified value of $\bar{d}$, the acceptance limit for s is the largest value of s for which the upper-left vertex of the confidence region is below the contour line for LB.

The upper-left vertex of the joint confidence region is (δ^*, σ^*) where

$$\delta^* = \bar{d} - z_{\sqrt{1-\alpha}}\sigma^*/\sqrt{n}$$

$$\sigma^* = \sqrt{(n-1)s^2/\chi^2_{n-1,1-\sqrt{1-\alpha}}}$$

and where $\chi^2_{n-1,1-\sqrt{1-\alpha}}$ is the $1-\sqrt{1-\alpha}$ quantile of a chi-squared distribution with $n-1$ degrees of freedom, and $z_{\sqrt{1-\alpha}}$ is the $\sqrt{1-\alpha}$ quantile of the standard normal distribution.

The E2709 approach is illustrated in Figure 3 for 90% confidence, a lower bound *LB* = 95%, n = 12, $\bar{d}$ = 5%, and s = 4.19%. The probability contour for *LB* is based on the nonlinear approximation given by equation (1). The upper-left vertex of the 90% joint confidence region is (1.95, 6.47), which nearly abuts the 95% probability contour. Consequently, the acceptance limit for establishing 90% confidence of 95% probability of passing USP <711> is $s \leq 4.19\%$ when $\bar{d}$ = 5% and n = 12. Table 2 provides some additional acceptance limits for s and Figure 4 illustrates the acceptance limits for 90% confidence of 95% probability of passing USP <711>. The acceptance limits approach the nonlinear approximation to the 95% probability contour as n increases, because the size of the 90% joint confidence region for (δ, σ) decreases as n increases.

The ISPE Good Practice Guide contains a more extensive tabulation of acceptance limits in its Tables 14.2 and 14.3. The acceptance limits in Table 14.2 provide 90% confidence of 95% probability of passing USP <711> and those in Table 14.3 provide 95% confidence of 95% probability of passing. The values of $\bar{d}$ range from 0.2 to 15 by 0.2 for n equal to 6, 12, 18, 24, 36, 48, 60 and 90. Note that the ISPE Good Practice Guide's acceptance limits don't precisely match those in Table 2 due to the ISPE Good Practice Guide's use of a lower bound for the 95% probability contour, rather than the nonlinear approximation used here. For example, the ISPE Good Practice Guide's acceptance limit for $\bar{d}$ = 5%, n = 12 and 90% confidence of 95% probability of passing USP <711> is 4.01%, rather than the 4.19% obtained using the nonlinear approximation.

Table 2: Acceptance Limits for Sample Standard Deviations based on ASTM Standard E2709 and Nonlinear Approximation (1)

			Sample Size, n				
Confidence	*LB*	$\bar{d}$	*6*	*12*	*24*	*48*	*90*
50%	95%	1	1.50	1.92	2.26	2.55	2.75
50%	95%	5	6.80	8.03	8.78	9.26	9.56
50%	95%	10	8.83	10.11	10.90	11.43	11.76
50%	95%	15	10.37	11.86	12.79	13.40	13.79
90%	95%	1	0.50	0.85	1.21	1.58	1.90
90%	95%	5	2.50	4.19	5.85	7.24	8.12
90%	95%	10	4.57	6.71	8.30	9.48	10.28
90%	95%	15	5.51	7.94	9.77	11.13	12.06
95%	95%	1	0.37	0.69	1.04	1.40	1.72
95%	95%	5	1.87	3.42	5.07	6.60	7.67
95%	95%	10	3.59	5.88	7.63	8.95	9.87
95%	95%	15	4.47	7.00	8.99	10.53	11.59

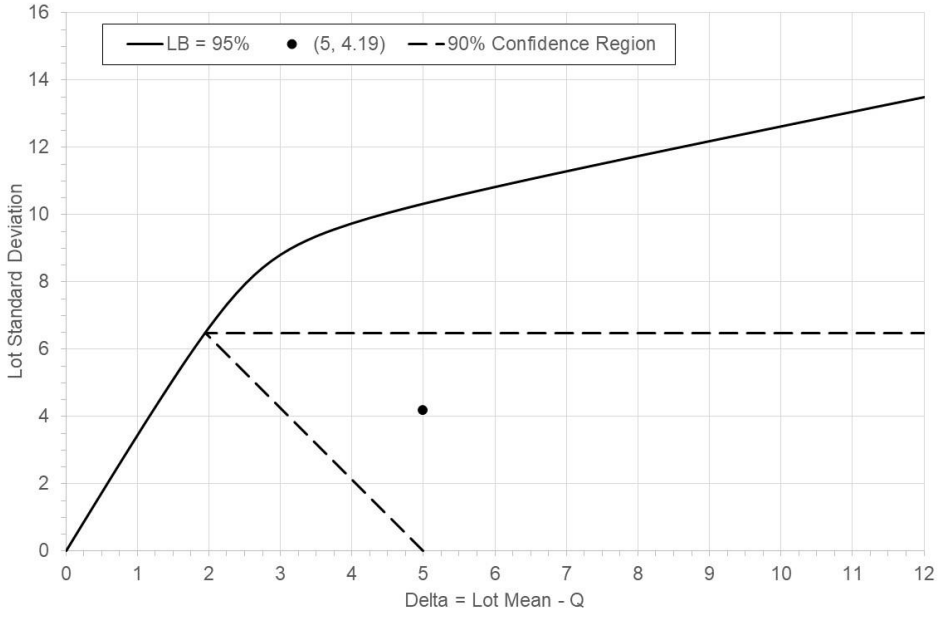

Figure 3: Application of ASTM Standard E2709 to USP <711> for 90% Confidence, LB = 95%, $\bar{d}$ = 5%, s = 4.19%, and n = 12

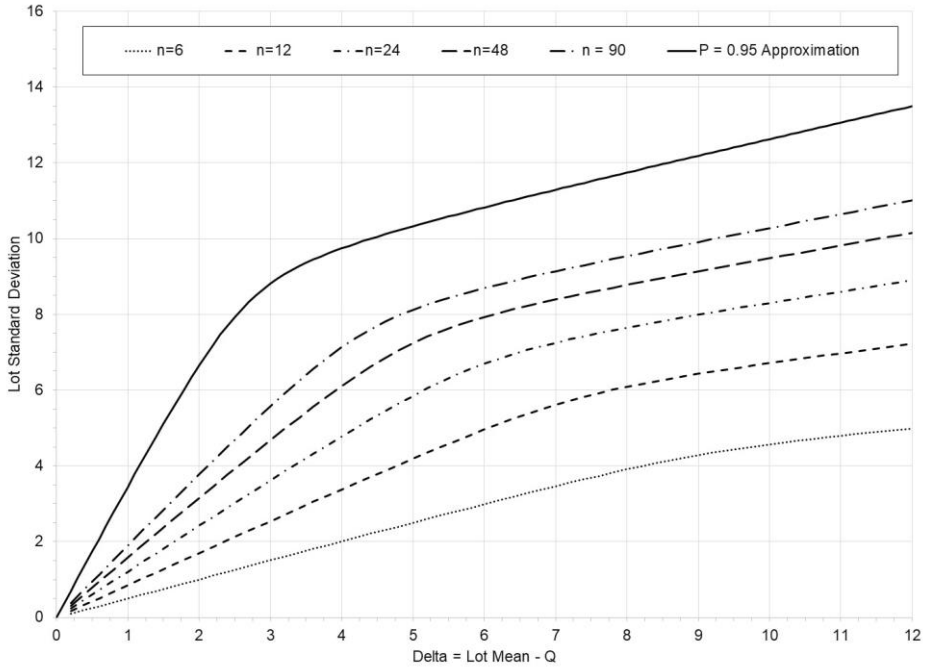

Figure 4: Acceptance Limits for 90% Confidence of 95% Probability of Passing USP <711> based on ASTM Standard E2709

4. A Parametric Tolerance Interval Approach to Acceptance Limits

The joint confidence region used in the ISPE Good Practice Guide partitions the parameter space for (δ, σ) into more- and less-likely values of δ and σ. While this a standard way to construct a confidence region, it has a major drawback when establishing confidence in passing USP <711>: the confidence region excludes values of (δ, σ) that have higher probabilities of passing USP <711> than values of (δ, σ) that are included. For example, the confidence region in Figure 3 includes (2.5, 6.4) but excludes (2.5, 0) and (12, 6.5). It is much better to partition the parameter space into lower and higher probabilities of passing the USP test, and probability contours provide such a partition. For any specified value of P, the concave region above the probability contour has lower probabilities of passing USP <711> and the convex region below the probability contour has higher probabilities of passing USP <711>.

One can achieve this type of partition by using parametric tolerance intervals that are based on a series of line segments that approximate a probability contour for passing USP <711>. We have found that five line segments provide a good approximation for $P \geq 80\%$, but instead use tangents to the nonlinear approximation given by equation (1). More specifically, we use tangents at values of δ ranging from 0 to 15 by 0.1. The PTI approach to establishing confidence in passing USP <711> is then enabled by the fact that a line segment in the (δ, σ) space is associated with one-sided coverage of a lower limit. To see why, first let $\sigma = \beta_0 + \beta_1 \delta$ represent a line segment. Next, assuming normally distributed observations, note that $Pr(Y - Q \geq L) = c$ implies that $(L - \delta)/\sigma = z_{1-c}$ which can be rewritten as $\sigma = (L - \delta)/z_{1-c}$. It follows that $\beta_0 = L/z_{1-c}$ and $\beta_1 = -1/z_{1-c}$. Consequently, a line segment is associated with one-sided coverage $c = 1 - \Phi(-1/\beta_1)$ of a lower limit $L = -\beta_0/\beta_1$, where $\Phi(\cdot)$ is the cumulative distribution function of the standard normal distribution.

The slope of a tangent to the nonlinear approximation is obtained by differentiating equation (1) with respect to δ. This gives slope

$$\beta_1 = \frac{\partial \sigma}{\partial \delta} = \beta - \frac{\gamma(\delta - \theta)}{\sqrt{\left((\delta - \theta)\right)^2 + \varepsilon^2}}$$

and it follows that the intercept is $\beta_0 = \sigma - \delta\beta_1$. Figures 5 and 6 display the coverages and lower limits for tangents to the nonlinear approximation. These coverages and lower limits provide insight into the types of dosage unit distributions that have a high probability of passing USP <711>. In particular, the median needs to exceed Q and a high percentage of the distribution needs to exceed $Q - 20\%$ in order to have a high probability of passing USP <711>.

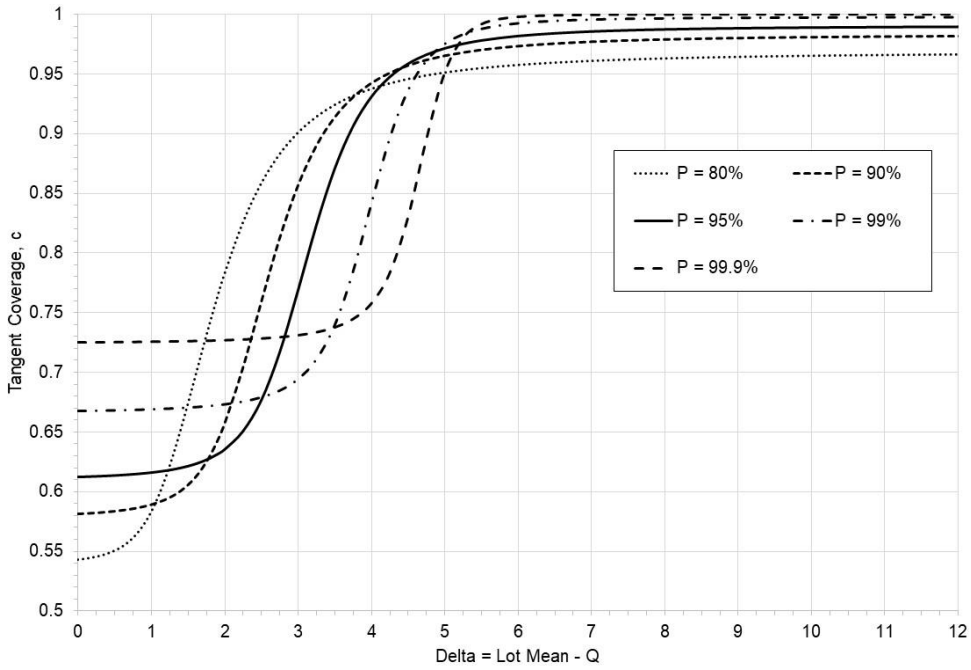

Figure 5: Coverages Associated with Tangents to the Nonlinear Approximation (1)

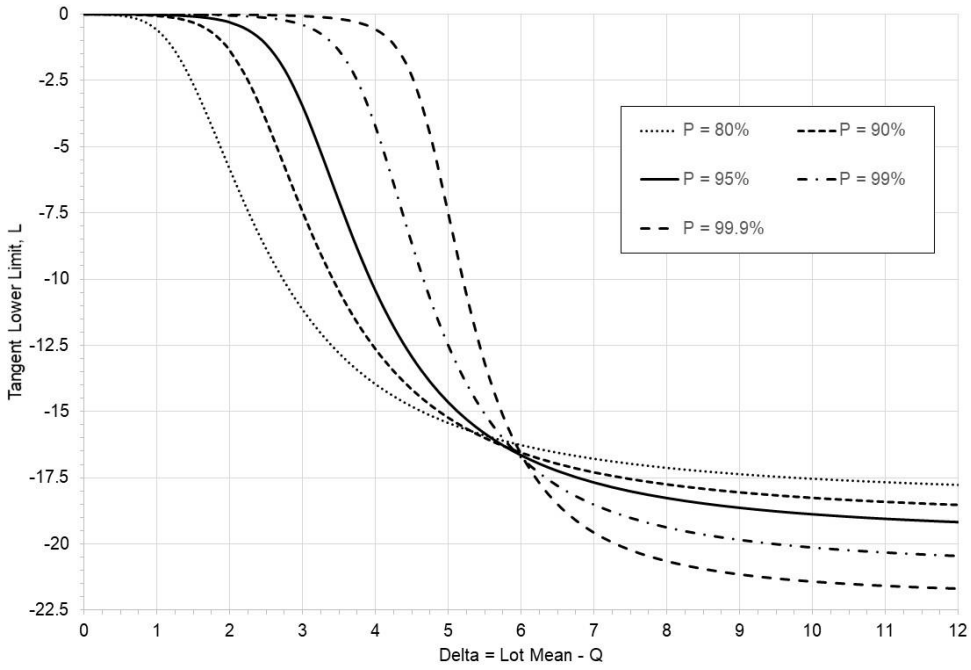

Figure 6: Lower Limits Associated with Tangents to the Nonlinear Approximation (1)

Given this background information the PTI approach has three steps:

(1) Specify a desired level of confidence for a lower bound for P, such as 90% confidence that P is at least 95%, and a sample size. Denote the confidence level by $100(1-\alpha)\%$, the lower bound by LB and the sample size by n.

(2) Use a series of line segments to approximate the probability contour for $P = LB$, where each line segment is associated with one-sided coverage, c, of a lower limit, L. For each line segment calculate an acceptance region using the boundary line $s_{limit} = (\bar{d} - L)/k$ where k is a $100(1-\alpha)\%$ confidence, $100c\%$ coverage one-sided tolerance limit factor for normally distributed observations.

(3) Overall acceptance limits are provided by the intersection of the individual acceptance regions.

The formula for s_{limit} follows from setting the one-sided lower tolerance limit $\bar{d} - ks$ equal to the lower limit L. The value of k is given by

$$k = t^{-1}(n-1,1-\alpha, z_c\sqrt{n})/\sqrt{n}$$

where $t^{-1}(n-1,1-\alpha, z_c\sqrt{n})$ is the $(1-\alpha)$ quantile of a noncentral t distribution with $(n-1)$ degrees of freedom and non-centrality parameter $z_c\sqrt{n}$ (see Patel 1986, for example). Table 3 provides acceptance limits for 50%, 90% and 95% confidence of 95% probability of passing USP <711> based on the PTI approach. It is straightforward to calculate more extensive tables. Bergum *et al.* (2015) recommend acceptance limits based on 50% confidence for routine lot release and acceptance limits based on 90% or 95% confidence for process qualification. Figure 7 illustrates acceptance limits for 90% confidence of 95% probability of passing USP <711>.

Monte Carlo simulations indicate that the PTI-based acceptance limits have good statistical properties. As shown in Figure 8 for sample size n = 24, for example, Monte Carlo simulations indicate that (δ, σ) values lying on the nonlinear approximation to P = 95% have about a $100\alpha\%$ probability of meeting the PTI-based acceptance limits. This is the desired result for (δ, σ) values lying on the partition between $P \leq LB$ and $P > LB$, because the acceptance limits are based on a size α PTI test of $H_0: Pr(Y - Q \geq L) \leq c$ versus $H_a: Pr(Y - Q \geq L) > c$. See Novick *et al.* (2009) for a detailed discussion of PTI tests. Similar Monte Carlo simulations for the ISPE Good Practice Guide's acceptance limits indicate that its limits are quite conservative. For n = 24, for example, the probability of meeting the E2709-based acceptance limits is just 18-25% for 50% confidence, 0.8-1.6% for 90% confidence, and 0.2-0.5% for 95% confidence.

Table 3: Acceptance Limits for Sample Standard Deviations based on the PTI Approach

			Sample Size, n				
Confidence	*LB*	$\bar{d}$	*6*	*12*	*24*	*48*	*90*
50%	95%	1	3.28	3.37	3.41	3.43	3.44
50%	95%	5	9.69	10.04	10.19	10.26	10.29
50%	95%	10	11.83	12.27	12.45	12.54	12.58
50%	95%	15	13.85	14.37	14.59	14.69	14.73
90%	95%	1	1.02	1.39	1.73	2.06	2.32
90%	95%	5	4.99	6.64	7.86	8.62	9.09
90%	95%	10	6.91	8.70	9.88	10.69	11.21
90%	95%	15	8.11	10.20	11.58	12.53	13.14
95%	95%	1	0.80	1.16	1.50	1.83	2.12
95%	95%	5	3.94	5.64	7.12	8.15	8.75
95%	95%	10	5.79	7.82	9.22	10.20	10.84
95%	95%	15	6.79	9.18	10.81	11.96	12.71

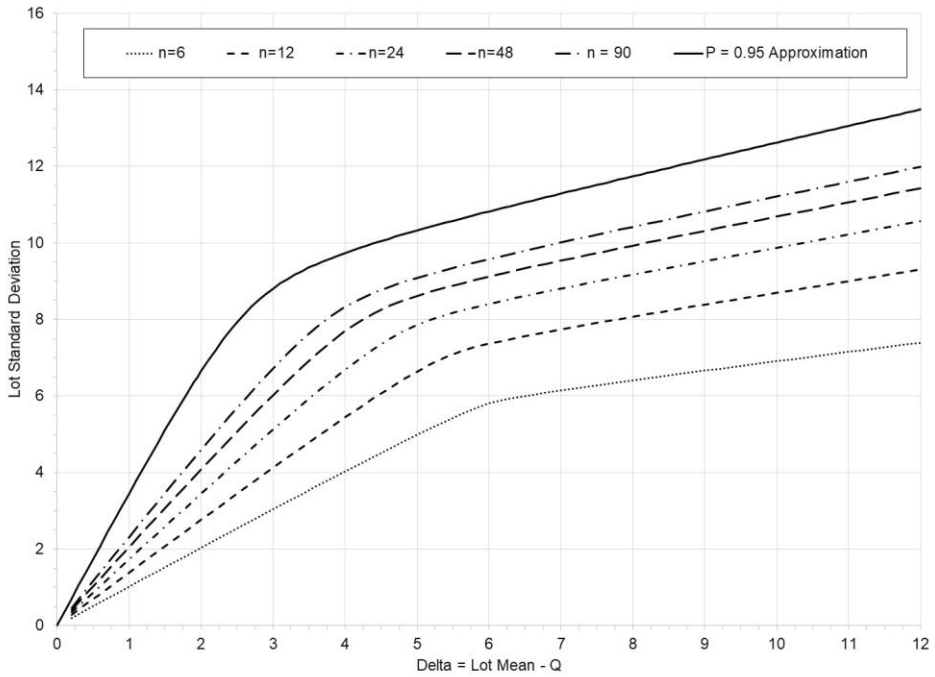

Figure 7: Acceptance Limits for 90% Confidence of 95% Probability of Passing USP <711> based on the PTI Approach

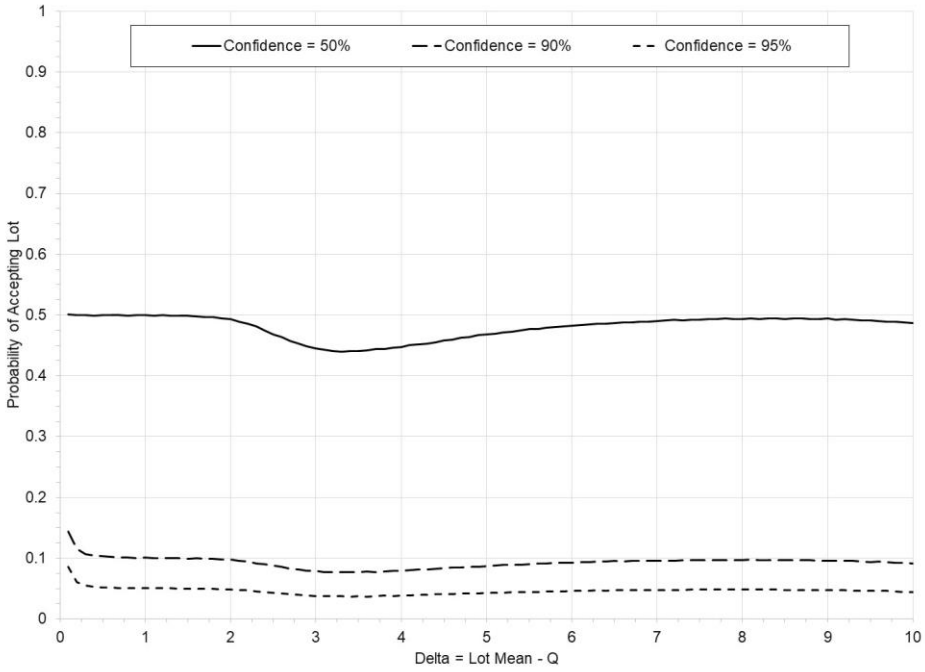

Figure 8: Probability of Meeting the PTI-based Acceptance Limits for (δ, σ) Values on the Nonlinear Approximation to P = 95% and n = 24

Ratios of acceptance limits based on the PTI approach to acceptance limits in the ISPE Good Practice Guide are provided in Table 4. The magnitude of the ratio can be considerable. Consider establishing 90% confidence of 95% probability of passing USP <711>, for example. Based on a sample size of 6 dosage units, the PTI approach results in acceptance limits for sample standard deviations that are 1.5 to 2.1 times greater than those in the ISPE Good Practice Guide. Based on a sample size of 90 dosage units, the PTI approach results in acceptance limits for sample standard deviations that are 1.13 to 1.35 times greater than those in the ISPE Good Practice Guide. Figure 9 provides a graphical view of the ratios for 90% confidence. Ratios for 95% confidence are similar, as shown in Table 4. The ISPE Good Practice Guide doesn't provide acceptance limits for 50% confidence.

Table 4: Ratios of Acceptance Limits for Sample Standard Deviation
(Ratio of PTI to ISPE)

			Sample Size, n				
Confidence	*LB*	$\bar{d}$	*6*	*12*	*24*	*48*	*90*
90%	95%	1	2.12	1.71	1.53	1.42	1.34
90%	95%	5	2.08	1.66	1.41	1.25	1.17
90%	95%	10	1.56	1.33	1.23	1.17	1.13
90%	95%	15	1.52	1.33	1.24	1.18	1.15
95%	95%	1	2.22	1.76	1.55	1.42	1.35
95%	95%	5	2.19	1.72	1.47	1.29	1.20
95%	95%	10	1.66	1.37	1.25	1.18	1.14
95%	95%	15	1.56	1.36	1.25	1.19	1.15

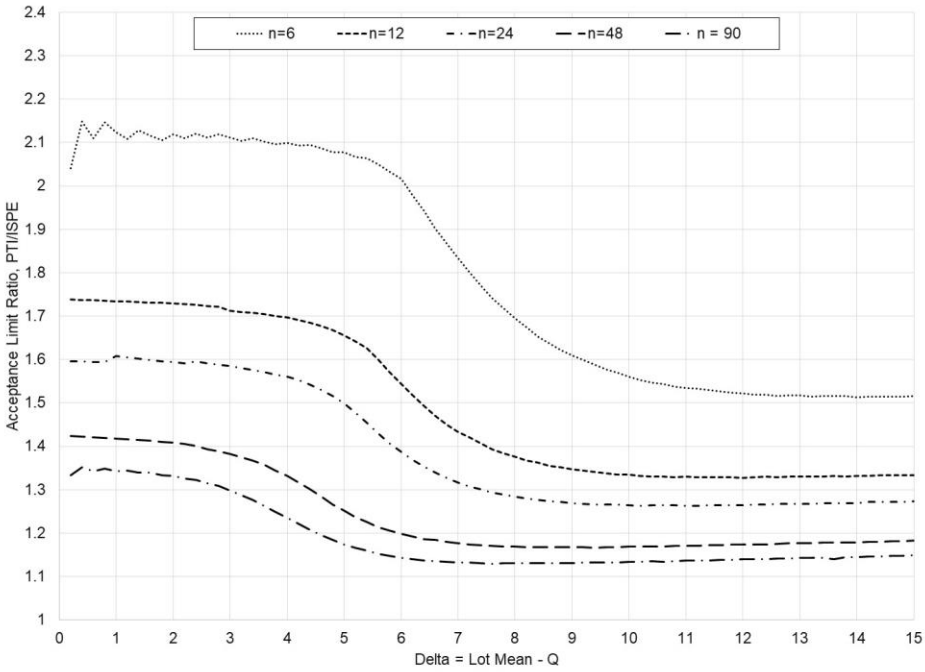

Figure 9: Ratio of PTI-based Acceptance Limits to ISPE Good Practice Guide Acceptance Limits for 90% Confidence of 95% Probability of Passing USP <711>

5. Operating Characteristics Curves and Example

Operating characteristic (OC) curves show the probability of meeting acceptance limits, given the actual values of δ and σ. This provides a means for selecting an appropriate sample size, n, when establishing confidence in the probability of passing USP <711>. Figure 10 displays OC curves for 90% confidence of 95% probability of passing USP <711> for $n = 24$.

To illustrate the use of the OC curves, suppose you have reason to believe that δ could be as low as 5% and that σ could be as large as 4%. Figure 1 indicates that the probability of passing USP <711> is very high for these values of δ and σ. In fact, all of 100,000 Monte Carlo simulations of the USP <711> test procedure met the test requirements, although 98.4% of them required Stage 2. From Figure 10, a sample size of $n = 24$ provides a high probability of meeting the PTI-based acceptance limits for s. One million Monte Carlo simulations of the USP <711> test procedure using $n = 24$ found that 99.87% met the acceptance limits based on the PTI approach, while only 93.66% met the acceptance limits in the ISPE Good Practice Guide. This is illustrated in Figure 11, which shows 1,000 simulated sample means and standard deviations along with acceptance limits based on the E2709 and PTI approaches. For larger sample sizes, one million simulations of the USP <711> test procedure using $n = 36$ and $n = 48$ found that 99.52% and 99.97% met the met the acceptance limits in the ISPE Good Practice Guide, respectively. These simulations show that the improvement in acceptance limits can have a meaningful impact on decision error rates and/or sample size requirements.

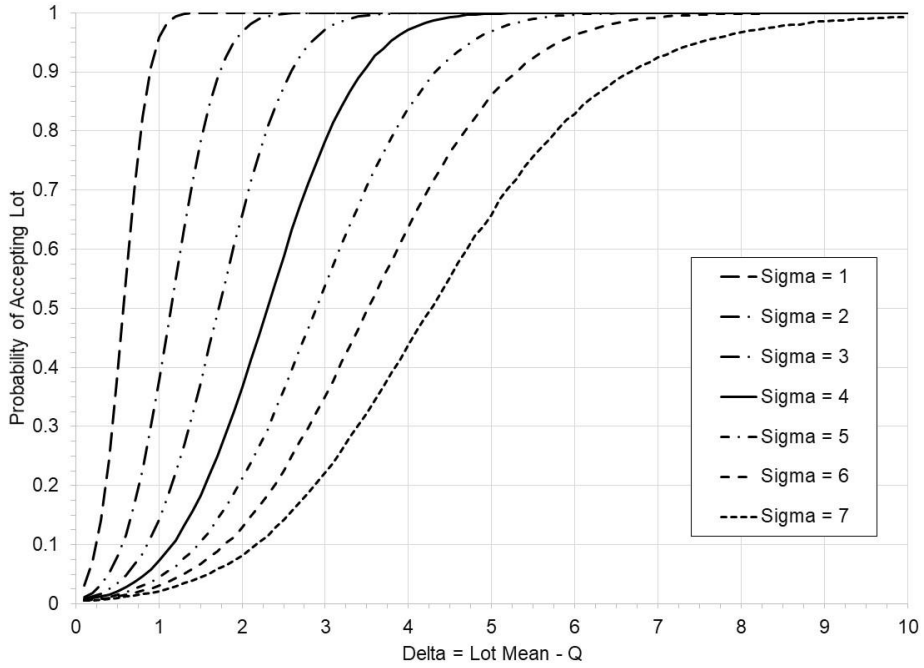

Figure 10: Operating Characteristic Curves for n = 24 and 90% Confidence of 95% Probability of Passing USP <711>

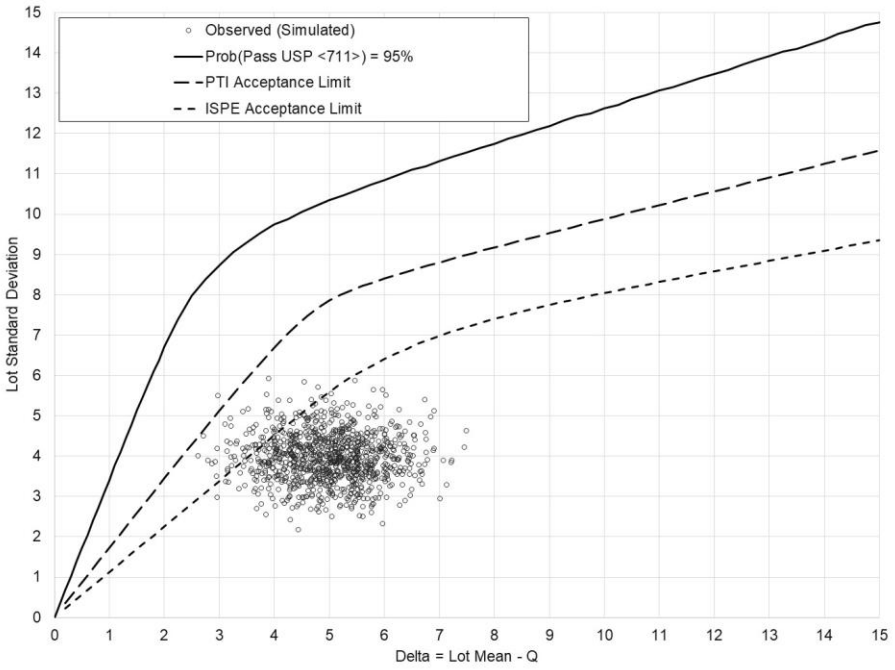

Figure 11: 1,000 Simulated Sample Means and Standard Deviations for δ = 5%, σ = 4% and n = 24 along with Acceptance Limits based on the E2709 and PTI Approaches

6. Summary

It is occasionally useful to establish statistical confidence in the ability to pass a quality control test. ASTM Standard E2709 provides an approach for establishing confidence in passing a test procedure but gives conservative acceptance limits due to its use of a poorly shaped joint confidence region for the lot mean and standard deviation. An approach that partitions the parameter space into higher and lower probabilities of passing USP <711> provides acceptance limits with much better statistical properties. Both Bayesian and parametric tolerance interval approaches use such a partition. The improvement in acceptance limits is considerable as shown in Table 4 and Figure 9 for a parametric tolerance interval approach. The improved acceptance limits are easy to calculate and provide a meaningful reduction in decision error rates and/or sample size requirements.

The PTI approach can be used for any test procedure where the contours for the probability of passing are well-approximated by a series of line segments. In addition, the approach can easily be implemented as a multiple-stage procedure by using alpha sharing (Lan and DeMets 1983). The PTI approach described in this article assumes independent normally distributed tests results. Dissolution data are occasionally skewed to the left, however, so the normality assumption should be checked when applying the parametric tolerance interval approach.

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