



# Full Tolerance Coverage Method for Assessing Uniformity of Dosage Units with Large Sample Sizes

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**The requirements for uniformity of dosage units using large sample size data collected and analyzed from process analytical technology (PAT) processes can be met by applying either *United States Pharmacopeia (USP) <1099> Limit on Number of Large Deviations When Assessing Content Uniformity in Large Samples* or *European Pharmacopoeia (Ph. Eur.) 2.9.47 Uniformity of Dosage Units Using Large Sample Sizes*. However, both methods are designed to detect the number of dosage units falling outside the specification range of 75–125% of the label claim (% LC) to determine whether these numbers do not exceed the predetermined values based on the sample size. The ‘full tolerance coverage method’ is introduced as a coverage estimation approach for assessing the uniformity of dosage units from large sample sizes, ensuring that no dosage unit exceeds the specification range.**

In *United States Pharmacopeia (USP) <905> Uniformity of Dosage Units (UDU; using small sample sizes)* (1), the acceptance value (AV) limits are statistically adjusted (95% coverage) (2) and reintroduced in (3; **Figure 1**). However, a key weakness is that the AV result does not adequately describe the specific characteristics of UDU. To address this limitation, the application and use of tolerance intervals are extensively discussed in the article, “Using Tolerance Intervals to Assess Conformance to Requirements” (4).

To address the small gaps between the calculated tolerance intervals and specification ranges, the upper and lower tolerance limits (UTL and LTL) are set at 115% and 85% label claim (LC), respectively. The tolerance coverages above and below the mean are estimated and summed to obtain what is called “full tolerance coverage” (FTC), yielding a value close to 100%. Because the sample mean is directly used, larger sample sizes provide a more accurate batch mean estimate. Therefore, the FTC method is more practical and suitable for assessing UDU data in production batches, particularly those monitored through process analytical technology (PAT) instrumentation.

**Figure 1.** Acceptance value (AV) distributions (True CpK is 1.33 for both  $n = 10$  and 30).

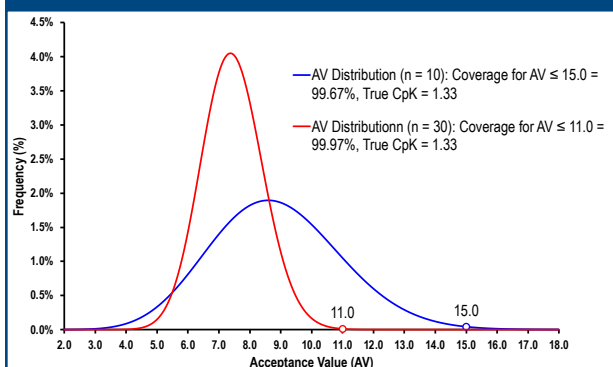


Figure 1: Reproduced from (3), this highlights that the AV limit for  $n = 30$  (Stage 2) should be 11.0 rather than 15.0.

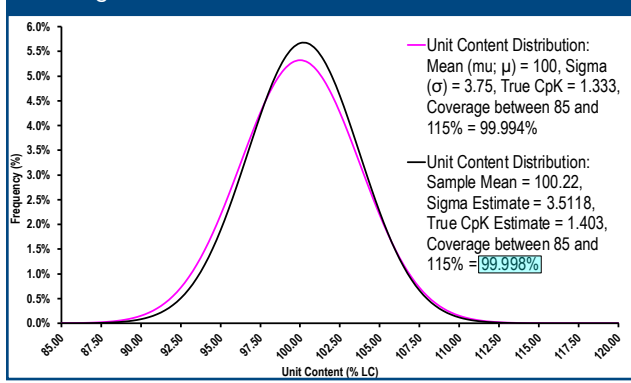
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**Table I.** Calculation examples of tolerance interval and full tolerance coverage (FTC) for uniformity of dosage units (UDU) data.

Calculation Examples for Tolerance Interval and Full Tolerance Coverage Using UDU Data	
<b>Tolerance interval limit and relevant formulae:</b>	
$TL = \bar{x} \pm ks = \bar{x} \pm Z \left( \frac{1-p}{2} \right) \sigma^{\wedge}$ , margin of error = $ks = Z \left( \frac{1-p}{2} \right) \sigma^{\wedge}$ ( $\sigma^{\wedge}$ : point estimate of sigma) $Z \left( \frac{1-p}{2} \right) \sigma^{\wedge} = ks = Z \left( \frac{1-p}{2} \right) \sqrt{\left( \frac{(n-1)}{n} \right) / \chi^2 \left( \alpha, (n-1) \right)^2} \cdot s$ (since $k = Z \left( \frac{1-p}{2} \right) \sqrt{\left( \frac{(n-1)}{n} \right) / \chi^2 \left( \alpha, (n-1) \right)^2}$ ) $\sigma^{\wedge} = \sqrt{\left( \frac{(n-1)}{n} \right) / \chi^2 \left( \alpha, (n-1) \right)^2} \cdot s$ (see k formula in Annex below)	
Given UDU data (% of label claim)	Mean = 100.22, s = 3.32, n = 300, $k^* = 2.07$ (2-sided, 95% TI, 90% CI) $\sigma^{\wedge} = \sqrt{\left( \frac{(n-1)}{n} \right) / \chi^2 \left( \alpha, (n-1) \right)^2} \cdot s$ $\sigma^{\wedge} = \sqrt{\left( \frac{300-1}{300} \right) / \chi^2 \left( 0.9, 300-1 \right)^2} \cdot 3.32 = 3.5118$
Specification range	85–115% LC.
Tolerance interval LTL = $\bar{x} - ks$ , UTL = $\bar{x} + ks$	Calculation: LTL = $100.22 - 2.07 \times 3.32 = 93.35$ , UTL = $100.22 + 2.07 \times 3.32 = 107.09$ . 95% TI [93.35, 107.09]: This demonstrates that, with a 90% confidence interval (CI), 95% of the batch falls within the range of 93.35% to 107.09% LC, with both values remaining within the broader specification limits of 85% to 115% LC.
Full tolerance coverage $Z_{-1} = (115 - \bar{x}) / \sigma^{\wedge}$ , $Z_{-2} = (85 - \bar{x}) / \sigma^{\wedge}$	Calculation: $Z_1 = (115 - 100.22) / 3.5118 = 4.2087$ , $Z_2 = (85 - 100.22) / 3.5118 = -4.3340$ , P (using Excel) = $\text{NORMSDIST}(4.2087) - \text{NORMSDIST}(-4.3340) = 99.998\%$ . 99.998% FTC** [85, 115]: This demonstrates that 99.998% of the batch is fully contained within the range of 85% to 115% LC. Assuming the sample mean of 100.22% LC is used as an estimate of the lot mean.
In Excel: $k^* = (\text{NORMSINV}(1 - (1 - 95/100)/2)) * ((300 - 1/300) / \text{CHIINV}(90/100, 300 - 1))^0.5 = 2.07$ (P = 95% TI, C = 90% CI, n = 300) (see Annex below), sigma estimate = $3.32 * ((300 - 1/300) / \text{CHIINV}(90/100, 300 - 1))^0.5 = 3.5118$	
** FTC is 100% for 75–125% LC if computed in the same way. See Note 1 below.	
Note 1: $Z_1 = (125 - 100.22) / 3.5118 = 7.0562$ , $Z_2 = (75 - 100.22) / 3.5118 = -7.1815$ , P (using Excel) = $\text{NORMSDIST}(7.0562) - \text{NORMSDIST}(-7.1815) = 100.000\%$ .	
Note 2: s: sample standard deviation, TI: tolerance interval, FTC: full tolerance coverage, CI: confidence interval, LTL vs. UTL: lower vs. upper tolerance limits, TL: Tolerance limit, Z1 vs. Z2: upper vs. lower Z scores.	

**Figure 2.** Normal distributions: theoretically normal population data vs. data estimated from full tolerance coverage method with n = 300.



Comparison of Two Normal Distributions: True CpK = 1.333 vs. Estimated CpK = 1.403. The black solid curve is constructed using the dataset from Table I.

In this article, FTC using large sample sizes is introduced and discussed. For calculations, FTC1 is applied to the range of 85–115% LC, while FTC2 is used for the range of 75–125% LC.

**Comparison of tolerance interval (TI) and FTC**

To compare the two parameters, simulated UDU data are generated with assumed values for lot mean (100% LC), lot standard deviation (3.75% LC), and sample size (n = 300). These data are summarized in Table I, which provides a cal-

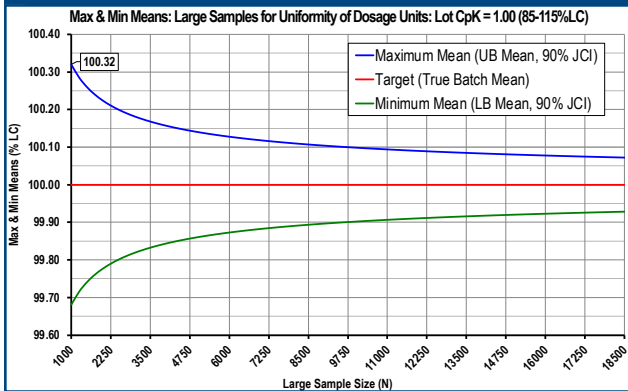
ulation example for both the tolerance interval and full tolerance coverage, allowing readers to visualize the differences between the two parameters. Figure 2 further illustrates the distributions of the UDU data presented in Table I.

**Justifying the FTC approach for large sample sizes**

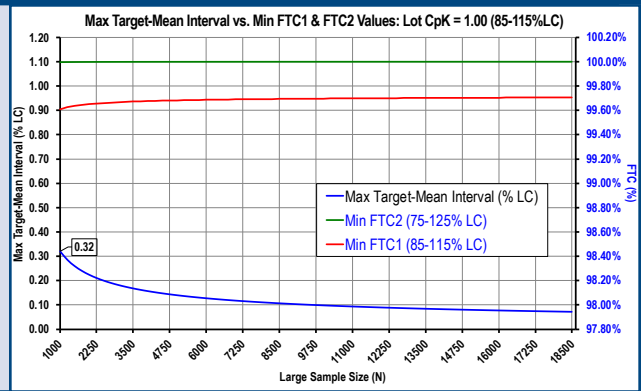
In the calculation of FTC, the sample mean is directly used, assuming it represents the batch mean estimate. Large sample sizes provide a more accurate estimate of the batch mean compared to small sample sizes, making this method particularly suitable for large sample sizes. Figure 3a illustrates that batch mean estimates for large sample sizes remain within the upper and lower bound means (UB and LB means) of a 90% joint confidence interval (90% JCI), with random large sample means staying closer to the true batch mean (100% LC) than those of small sample sizes. Figure 3b shows the relationship between sample size and the target-mean difference magnitude, as well as the impact of sample size on FTC1 and FTC2 values.

By using the same calculation method demonstrated in Table I and illustrated in Figure 2, each of Figures 4a, 4b, 5a, and 5b illustrates a comparison of two normal distributions, one with true mean and another one with lot mean estimated from n = 300, 3000, 6000, and 9000, respectively. One can see that the larger the sample sizes, the higher (in percentage) the full tolerance coverages especially for FTC1

**Figure 3.** Interrelationships among statistical parameters in large sample sizes: insights from Figures 3a and 3b.



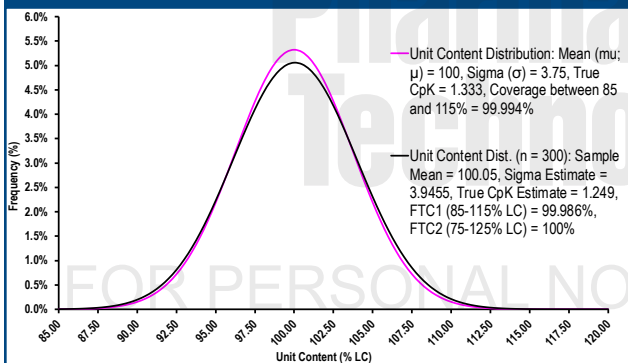
**Figure 3a:** Relationship between sample size and maximum and minimum large sample means.



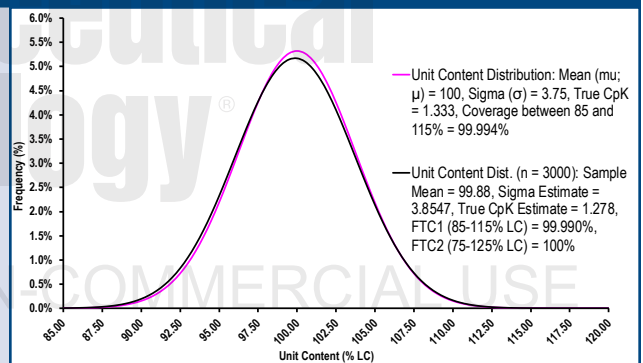
**Figure 3b:** Relationship between sample size and the target-mean difference magnitude, as well as the impact of sample size on FTC1 and FTC2 values.

Note: UB mean: upper bound mean; LB mean: lower bound mean; 90% JCI: 90% Joint Confidence Interval. It is assumed that the target is 100% LC, and each large sample size has a standard deviation (SD) of 5% LC. CpK1 = 1.00 (85-115% LC), CpK2 = 1.67 (75-125% LC).

**Figure 4. a) (left):** Normal distributions (lot mean estimated from  $n = 300$ ) and b) (right): Normal distributions (lot mean estimated from  $n = 3000$ ).

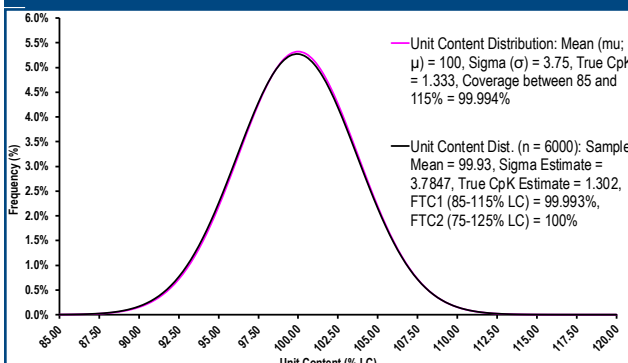


**Figure 4a:** Normal distributions: Comparison of two normal distributions with true mean vs. lot mean estimated from  $n = 300$ .

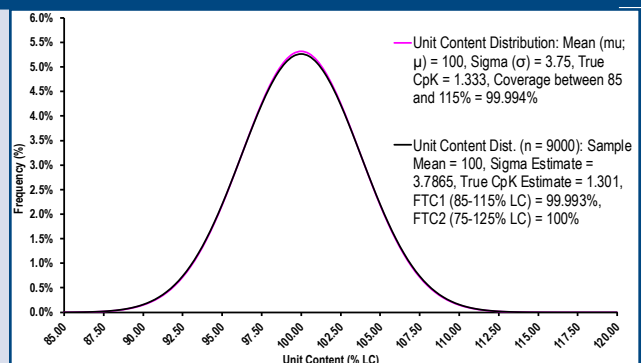


**Figure 4b:** Normal distributions: Comparison of two normal distributions with true mean vs. lot mean estimated from  $n = 3000$ .

**Figure 5. a) (left):** Normal distributions (lot mean estimated from  $n = 6000$ ) and b) (right): Normal distributions (lot mean estimated from  $n = 9000$ ).

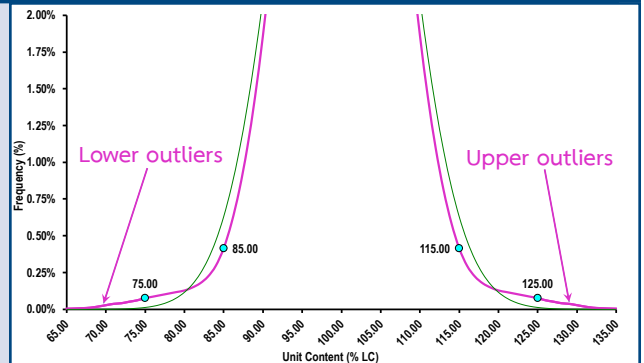
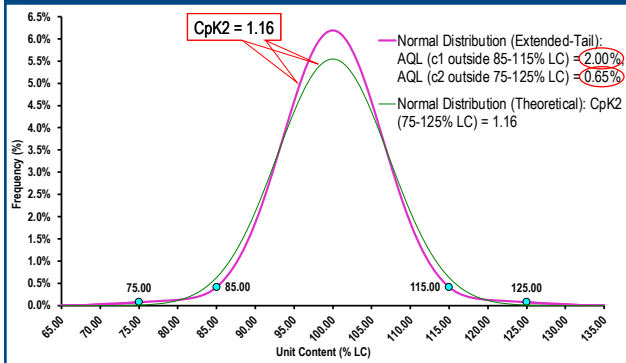


**Figure 5a:** Normal distributions: Comparison of two normal distributions with true mean vs. lot mean estimated from  $n = 6000$



**Figure 5b:** Normal distributions: Comparison of two normal distributions with true mean vs. lot mean estimated from  $n = 9000$

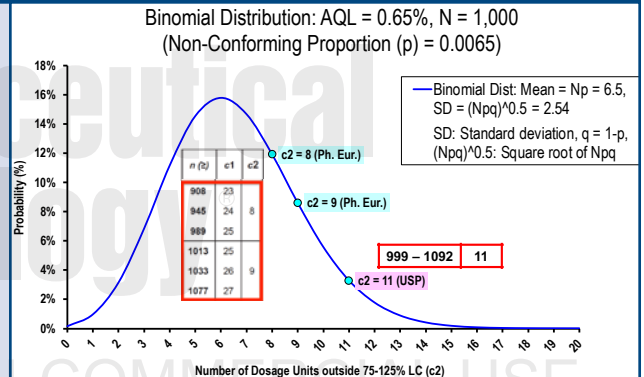
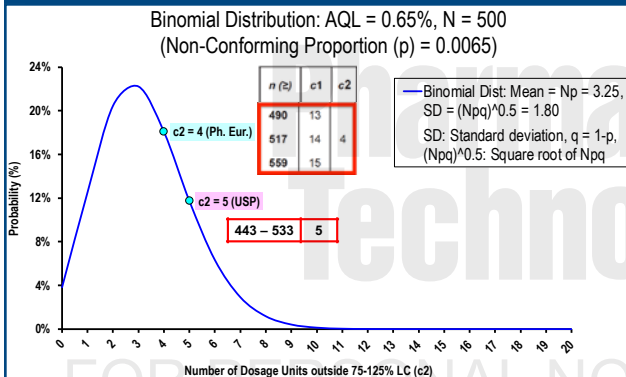
**Figure 6.** a) (left): Comparison view of extended-tail and theoretical normal distributions and b) (right): Zoomed-in view of Figure 6a.



**Figure 6a:** Comparison example for two normal distributions (true CpK2 = 1.16): Extended-tail (real-world) distribution vs. theoretically normal distribution curves.

**Figure 6b:** Zoomed-in view of Figure 6a, highlighting the outlier zones.

**Figure 7.** a) (left): Binomial distribution (n = 500) and b) (right): Binomial distribution (n = 1000).



**Figure 7a:** Binomial distribution (n = 500) with outlier acceptance limits (c2).

**Figure 7b:** Binomial distribution (n = 1000) with outlier acceptance limits (c2).

(85–115% LC). Notably, using a smaller sample size, such as n = 300 (Figure 4a), still presents a chance for FTC2 to reach 100%. It is obvious that the two distribution curves in the figures with larger sample sizes, such as n = 6000 (Figure 5a) or 9000 (Figure 5b), are nearly identical. Therefore, the data of larger sample sizes will provide more realistic assessment results than the smaller ones.

**The fact underlying the acceptance criteria for UDU using large sample sizes**

The acceptance criteria outlined in USP <1099> (5) and Ph. Eur. 2.9.47 (6) are designed to detect outliers (i.e., dosage units outside the range of 75–125% LC) and prevent the release of non-conforming dosage units into the market. PAT tools integrated into tablet presses can identify and reject these outliers during manufacturing. Modern tablet presses are equipped with real-time monitoring systems that work alongside PAT tools to ensure product uniformity and quality. The determination of units outside the ranges of 85–115% LC (c1) and 75–125% LC (c2) is based on the acceptable quality limit (AQL), where c1 and c2 correspond to AQL values of 2% and 0.65%,

respectively. Note that only c1 is addressed in Ph. Eur. 2.9.47, and the two AQL values were determined through trial-and-error studies conducted by the author.

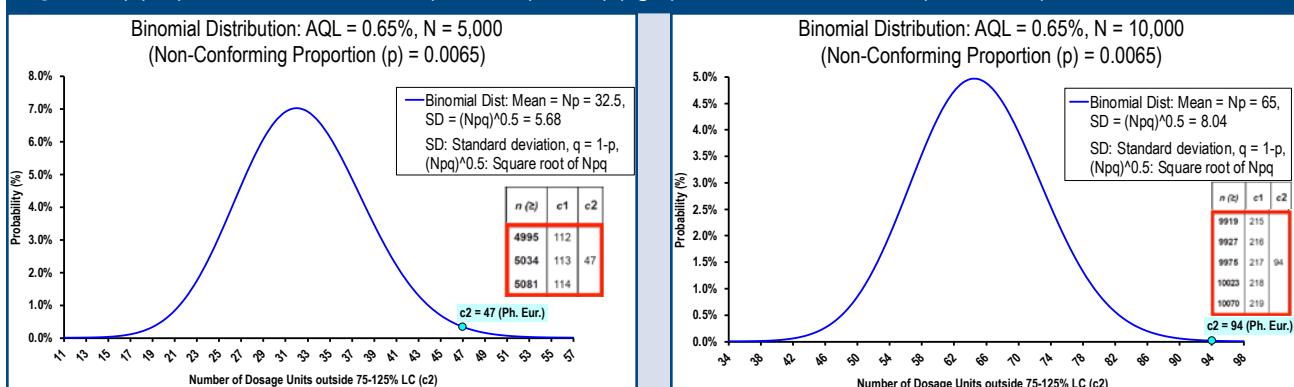
In real-world situations, dosage unit contents often deviate from the theoretical normal distribution (bell-shaped curve), exhibiting extended tails where outliers typically reside. Figures 6a and 6b will illustrate how the outliers spread while Figures 7a and 7b and Figures 8a and 8b demonstrate the criteria for the outliers (i.e., acceptance criteria limit called c2).

**Discussion**

From the author’s perspective, successfully meeting the compendial acceptance criteria (USP <1099> or Ph. Eur. 2.9.47) is essential as a first step to screen for outliers. Additionally, tracking the number of outliers is critical for continuous quality improvement. Prior to calculating the FTC value, the large sample data must comply with the compendial outlier limits.

PAT tools in modern manufacturing enable real-time monitoring and analysis of UDU. Tablet presses equipped

**Figure 8. a) (left): Binomial distribution (n = 5000) and b) (right): Binomial distribution (n = 10,000).**



**Figure 8a:** Binomial distribution (n = 5,000) with outlier acceptance limits (c2).

**Figure 8b:** Binomial distribution (n = 10,000) with outlier acceptance limits (c2).

with PAT tools can detect and reject outliers during production, integrating real-time monitoring systems to ensure product uniformity and quality. As a result, the probability of detecting outliers becomes extremely low, approaching zero.

However, with yield control considerations, the number of rejected dosage units must be accounted for to ensure that the net yield of conforming units (within 75–125% LC) remains economically viable. A very small number of outliers could still remain within the conforming portion of the bulk units, depending on the sensitivity of the detection system and the statistical approach used to define “conforming” units. In such cases, the calculated FTC value provides a more realistic representation of the batch.

### Annex: Formulae for tolerance limits and constants

Calculation is derived as follows:

For calculation of upper and lower tolerance limits (UTL and LTL) for specifications with upper and lower limits (two-sided limits):

$$UTL = \bar{x} + ks \leq 115, \text{ and}$$

$$LTL = \bar{x} - ks \geq 85$$

where  $\bar{x}$ ,  $s$ , and  $k$  are sample mean, sample standard deviation and constant respectively.

The formula for  $k$  (two-sided) is:

$$k = Z_{(1-p/2)} \sqrt{\left( \frac{(1+n)}{n} \right) \left( \frac{(n-1)}{\chi^2_{(\alpha, n-1)/2}} \right)} = Z_{(1-p/2)} \sqrt{\left( \frac{(n-1)}{n} \right) \left( \chi^2_{(\alpha, n-1)} \right)}$$

where

$k$ : Constant value for a tolerance interval for a normal distribution

$Z_{(1-p/2)}$ : Z score at percentage point of  $(1-(1-p/2)) \times 100\%$  (i.e.; % tolerance interval, denoted P, is  $(1-(1-p/2)) \times 100\%$ .)

$p$ : Total area (two-sided) in proportional value (i.e.;  $p$ ) outside the coverage zone; that is each side’s area is  $p/2$ .

$n$ : Sample size

$\chi^2_{(\alpha, n-1)}$ : Chi square with  $\alpha$  confidence interval and  $n-1$  degree of freedom

$\alpha$ : Confidence interval (CI) e.g.  $\alpha = 0.90$  (i.e.; 90% CI)

Using Excel:  $k$  (two-sided) =  $(\text{NORMSINV}(1-(1-P/100)/2)) \times ((n-1)/\text{CHIINV}(C/100, n-1))^{0.5}$

### Conclusion

The FTC method introduced in this article is calculated in two stages: FTC1 (85–115% LC) and FTC2 (75–125% LC), based on the quality unit’s requirements. FTC1 estimates the percentage of dosage units within 85–115% LC, while FTC2 estimates the percentage within 75–125% LC. This method is a modification of the commonly used “Tolerance Interval” method, aiming to eliminate the gaps between specification limits and tolerance interval limits.

FTC provides an estimate of the percentage of conforming dosage units in the batch, assuming the sample mean (from large samples) represents the batch mean. Although this is an estimate, it remains the most reliable method for demonstrating the percentage of conforming units within the ranges of 85–115% LC (FTC1) or 75–125% LC (FTC2). Accumulated FTC data from multiple batches can be used to evaluate the quality level of a specific PAT process, including the average percentage of outliers.

### References

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6. *European Pharmacopeia*. 2.9.47 Uniformity of Dosage Units Using Large Sample Sizes. *Ph. Eur.*, 11<sup>th</sup> ed., 2023. **PT**

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