Establishing Acceptance Limits for Uniformity of Dosage Units: Part Two

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The concept of sampling distribution of acceptance value (AV) was introduced in Part One of this article series. In Part Two, the author describes how to establish the corresponding acceptance limits for AV data for process validation batches, the typical characteristics of AV distributions, and finally, how to derive relevant constants for AV control charts in annual product review and continued process verification reports.

Part One of this article (1) introduced the concept of sampling distribution of acceptance value (AV)—the only quality attribute in Uniformity of Dosage Units (UDU). For different sample sizes, such as n = 10 and 30, their AV distributions will be different in pattern, thus resulting in different critical AV values (i.e., values that have a 95% coverage in the distributions where they are equal to 12.5 and 9.1 for n = 10 and 30, respectively). Such critical values will be applied as AV acceptance limits instead of the single *United States Pharmacopeial* (*USP*) compendial limit of not more than (NMT) 15 (2). The key benefit of the two working limits is to guarantee that no lot of dosage unit products (i.e., tablets, capsules, etc.) with poor quality is released into the market. Another key application is to provide the acceptance limits dedicated to the average values of AV data in, for example, annual product review (APR) and continued process verification (CPV), to evaluate if the overall process capability index (CpK) across those between-lot data is greater than 1.33 (understanding that the process benchmark at lot CpK 1.33 is the baseline for construction of the AV distributions). In summary, Part One is a discussion of the theory and key application of using two release limits for routine release of lots of products.

Part Two describes how to establish the corresponding acceptance limits for AV data for process validation batches, the typical characteristics of AV distributions, and finally, how to derive relevant constants for AV control charts in, for example, APR and CPV reports. Case studies using routine batch data in APR, with discussion and illustrations, are also provided to demonstrate the benefits of applying AV acceptance limits.

Acceptability constants (k) for various sample sizes

The following formula is used to compute the acceptability constants (k) for calculation of AV parameters and construction of AV distributions for various sample sizes:

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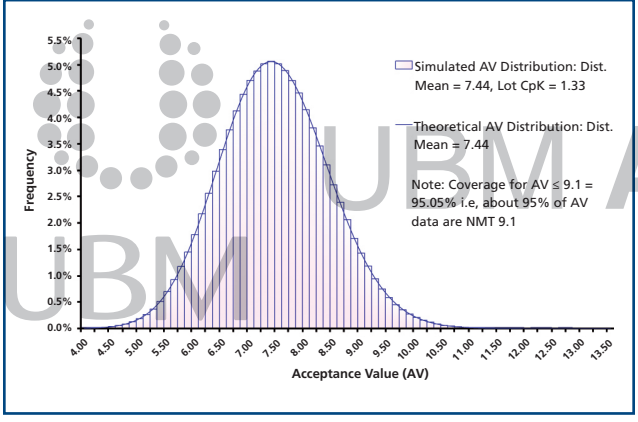
Table I: Acceptability constants computed on MS Excel spreadsheet. CI is confidence interval.

	A	B	C	D
1	Sample size (n)	Acceptability constant (k, 90% CI, 90% coverage)	k (*United States Pharmacopeia*)	k1 (90% CI, 99.9% coverage)
2	10	2.53	2.4*	N/A
3	30	2.03	2.0	4.05
4	60	1.89	–	3.77
5	70	1.87	–	3.73
6	140	1.79	–	3.58
7	B2 =(NORMSINV(1-(1-90/100)/2))*((1+1/A2)^0.5)*(((A2-1)/(CHIINV(90/100,A2-1)))^0.5) = 2.53			
8	B4 =(NORMSINV(1-(1-90/100)/2))*((1+1/A4)^0.5)*(((A4-1)/(CHIINV(90/100,A4-1)))^0.5) = 1.89			
9	B6 =(NORMSINV(1-(1-90/100)/2))*((1+1/A6)^0.5)*(((A6-1)/(CHIINV(90/100,A6-1)))^0.5) = 1.79			
10	D3 =(NORMSINV(1-(1-99.9/100)/2))*((1+1/A3)^0.5)*(((A3-1)/(CHIINV(90/100,A3-1)))^0.5) = 4.05			
11	* Approximately 88% coverage.			

Figure 1: Acceptance value (AV) distributions (n = 30, k = 2.00). CpK is process capability index. NMT is not more than.



$$k = Z_{0.9}\sqrt{\left(1+\frac{1}{n}\right)\left(\frac{n-1}{\chi^2_{0.9,n-1}}\right)} \quad \text{[Eq. 1] (3)}$$

where

k : tolerance factor (acceptability constant)

$Z_{0.9}$: Z score for 90% coverage (p = 0.90) = 1.645 (2-tailed)

n : sample size

n – 1 : n-1 degrees of freedom

$\chi^2_{0.9,n-1}$: chi-square for 90% confidence interval with n-1 degrees of freedom.

The acceptability constant (k) is in fact called "tolerance factor" in statistical textbooks with its expression in **Equation 1**. For example, if n = 10, k is computed as follows:

$$k_{n=10} = 1.645\sqrt{\left(1+\frac{1}{10}\right)\left(\frac{10-1}{4.168}\right)} = 2.53$$

where,

k_{n-10} : acceptability constant for n = 10.

$Z_{0.9}$: Z score for 90% coverage = 1.645 (2-tailed).

$\chi^2_{0.9,10-1}$: chi square for 90% confidence interval with 10-1 or 9 degrees of freedom = 4.168; where in Microsoft (MS) Excel, chi square (n = 10) =CHIINV(0.9,10-1) = 4.16816.

Table I provides a short summary on acceptability constants (k) for those sample sizes relevant to this article.

Construction and simulation of AV distributions for sample sizes other than n=10 or 30

The samples sizes 70 and 140 are normally taken for validation UDU testing plans 30/70 (i.e., n = 30 and 70 in stage 1 and 2, respectively) and 60/140, respectively. Sampling plans should be chosen based on product quality risk (e.g., 60/140 testing plan is used in highly potent low-dose products such as hormone products).

Construction and simulation of AV distributions for such sample sizes is executed in the same way as Part One using the corresponding acceptability constants (k) in **Table I**. **Figures 1–4** illustrate the simulated and theoretical AV distributions for n = 30,70, 60, and 140, respectively. According to the figures, **Table II** provides a summary on the working acceptance limits for AV data and AV average data for relevant sample sizes.

Typical characteristics of AV distributions

AV distributions in general have the typical characteristics and applications as follows:

- Distribution pattern: The distributions look approximately normal especially for larger samples (n ≥ 30, **Figures 1–4**). However, upon analysis of $AV = |M - \bar{x}| + ks$ expression (2), AV is partly a function of standard deviation (s) where its distribution is non-normal. Therefore, according to the expression, AV distributions are also non-normal.

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- AV acceptance limit: The critical AV values at approximately 95% coverage in the distributions are established as the working AV acceptance limits as shown in **Table II.**
- AV average acceptance limit: The means of AV distributions may be established as AV average acceptance limits as shown in **Table II.**
- Standard AV distribution: When individual AV data are divided by their distribution mean, the new distribution of "AV/Mean" ratio data will be similar in shape (not identical) to the original, with its mean equal to one (1.00). **Figure 5** illustrates and confirms the validity of the ratio distributions for sample size n = 70 by comparison between the theory and simulation.

Furthermore, when fixing the sample size but varying the lot CpK, the resulting ratio distributions will be identical in shape to each other as illustrated in **Figure 6**. In the figure, the distributions for sample sizes n = 30, 60, 70, and 140 with very different lot CpK values (1 versus 10) are illustrated. Such an identicality in the so-called standard AV distributions will be useful for AV control chart construction.

- AV chart factors (constants): One of the key applications of standard AV distributions is to establish AV chart factors (i.e., lower control limit [LCL] and upper control limit [UCL] factors) for AV charts. The factors can be easily computed using control chart principles (i.e., mean±3SD [4]). For example, n = 10; LCL = mean-3SD = 1-3x0.237* = 0.29, UCL = mean+3SD = 1+3x0.237* = 1.71 (* SD_{pooled} = ((0.234^2+0.239^2)/2)^0.5 = 0.237). The identicality in smaller samples, such as n = 10, has a minor deviation (i.e., different SDs) (see **Figure 7**).

Justification of AV acceptance limits

As explained in Part One, " … Such a 95% coverage will also confirm that the minimum validation sample size n = 30 is justified. For n = 70 or the other validation sampling plans such as 60/140, all the coverages will be 100%. … " (1). In Part Two, **Figures 8–9** provide the illustrated evidence, through Bergum simulation test results (5–7), to such 95% coverages.

Application in validation batches

The key applications of AV and AV average acceptance limits relevant to process validation acceptance criteria are as follows.

Acceptance criteria 1: AV data. For sampling plan n ≥ 70 with testing plan 30/70:

- Stage 1 (n = 30): AV result is NMT 9.1. If exceeded (see acceptance criteria 2), go to stage 2.
- Stage 2 (n = 70): AV result is NMT 8.0.

Figure 2: Acceptance value (AV) distributions (n = 70, k = 1.87). CpK is process capability index. NMT is not more than.

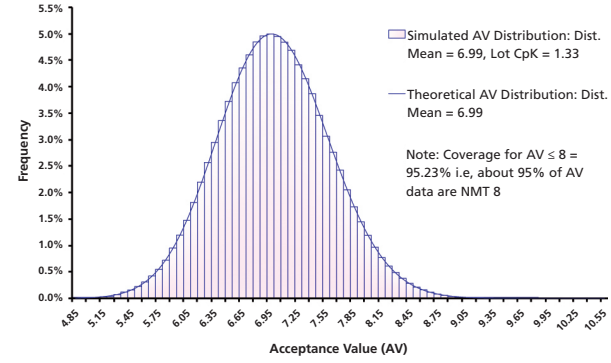


Figure 3: Acceptance value (AV) distributions (n = 60, k = 1.89). CpK is process capability index. NMT is not more than.

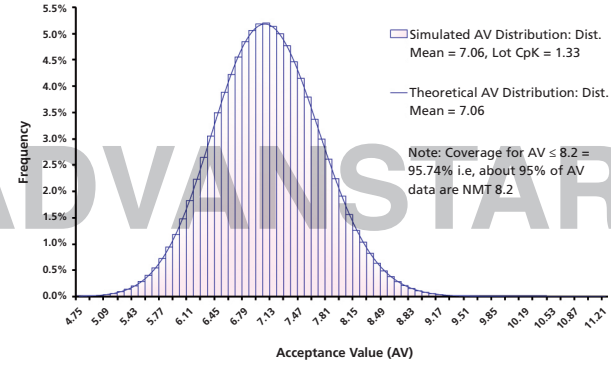
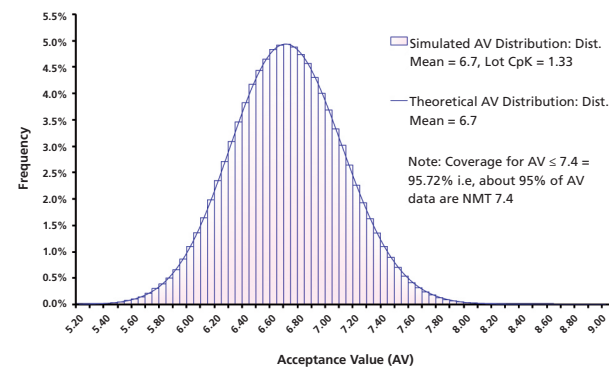


Figure 4: Acceptance value (AV) distributions (n = 140, k = 1.79). CpK is process capability index. NMT is not more than.



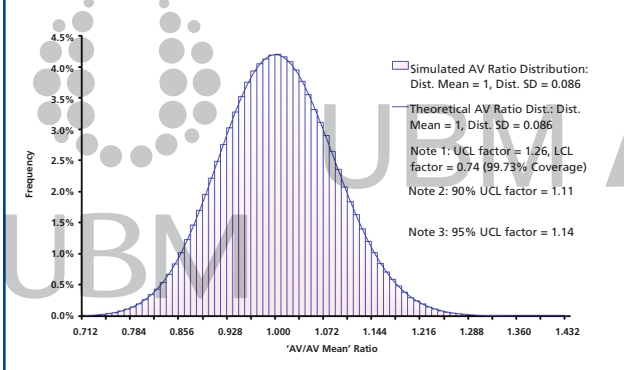
For sampling plan n ≥ 140 with testing plan 60/140:

- Stage 1 (n = 60): AV result is NMT 8.2. If exceeded (see acceptance criteria 2), go to stage 2.
- Stage 2 (n = 140): AV result is NMT 7.4.

Table II: Summary of proposed acceptance value (AV) acceptance limits.

Sample sizes (n)	AV average limits	AV limits (95% coverage)	95% UCL factors	AV chart factors (99.73% coverage)	
				LCL factors	UCL factors
Routine batches					
10	9.0	12.5	1.39	0.29	1.71
30	7.5	9.1	1.22	0.60	1.40
Process validation (PV) batches					
30	7.5	9.1	1.22	0.60	1.40
60	7.1	8.2	1.15	0.72	1.28
70	7.0	8.0	1.14	0.74	1.26
140	6.7	7.4	1.10	0.82	1.18
LCL: Lower control limit, UCL: Upper control limit.			For information only.		
Calculation example: n = 10, AV limit = 9.0x1.39 = 12.5					
For AV charting purpose, AV average limits may be adjusted to 7.3 (12.5/1.71; n = 10) and 6.5 (9.1/1.40; n = 30) so that the UCL values will not exceed 12.5 and 9.1 respectively.					

Figure 5: Standard acceptance value (AV) distributions (n = 70, lot CpK = 1.33, same condition as Figure 2).



The expression $AV = |M - \bar{x}| + ks$ will be employed using k constants in **Table I** as applicable. Based on the same coverage at approximately 95% in **Figures 1** and **8**, a correlation may be tied up and described that meeting the criteria for n = 30 will guarantee that at least 90% of the routine samples (**Figure 8**) will meet the compendial (i.e., *USP*) acceptance criteria (i.e., if AV result is 9.1, the probability would be 90% on average). For sample size n = 70 as shown in **Figures 2** and **9** (also practically the same coverage at approximately 95%), it may be described that at least 99.87% of the routine samples (**Figure 9**) will meet the compendial limit (i.e., if AV result is 8.0, the probability is 99.87%, which can be considered100%).

Alternative to acceptance criteria 1: Tolerance interval. Because AV is a special format of tolerance interval, the alternative is to demonstrate that 99.9%, for example, of the dosage units in the process validation (PV) lot(s) will fall within the range called tolerance interval (TI) calculated using the expression $TI = \bar{x} \pm k_1 s$ (3) where $\bar{x}$ is the sample mean, k_1 is the tolerance factor (e.g., 4.05 for n = 30; **Table I**) and s is the standard deviation. For example, AV result 4.5 (n = 30) is calculated from $\bar{x}$ = 100.50 and s = 2.25. Tolerance interval (TI) = 100.5±4.05x2.25 = (91.39, 109.61). In this example, 99.9% of the dosage units in the lot will fall within the range 91.39–109.61% of the label claim.

An additional approach to the tolerance interval is to compute the percentage proportion (P) of the lot staying exactly within the range 85–115% of label claim i.e., the *lot coverage* (8). Using the Z scores computed from lot mean and SD estimates as appropriate, the probability using MS Excel is that P = MIN(NORMSDIST(Z_{UU})-NORMSDIST(Z_{LU}),NORMSDIST(Z_{UL})-NORMSDIST(Z_{LL})) = MIN(NORMSDIST((115-101.52)/2.87)-NORMSDIST((85-101.52)/2.87),NORMSDIST((115-99.48)/2.87)-NORMSDIST((85-99.48)/2.87)) = 99.999867%.

where,

In Excel, the upper bound for lot SD = 2.25*((30-1)/(CHIINV(0.9^0.5,30-1)))^0.5 = 2.87 (square root of 0.9 or 90% confidence interval is used so that joint confidence interval is 90%).

In Excel, the upper bound for lot mean = 100.5+2.87*NORMSINV(1-(1-0.9^0.5)/2)/30^0.5 = 101.52 (square root of 0.9 is also used with the same reason).

In Excel, the upper bound for lot mean = 100.5-2.87*NORMSINV(1-(1-0.9^0.5)/2)/30^0.5 = 99.48 (square root of 0.9 is also used).

Z_{UU} and Z_{LU}: Z scores computed from the upper and lower limits (115 and 85) using the upper bound (UB) for lot mean (and UB for SD).

Z_{UL} and Z_{LL}: Z scores computed from the upper and lower limits (115 and 85) using the lower bound (LB) for lot mean (and UB for SD).

Figure 6: Standard acceptance value (AV) distributions (n = 30, 60, 70, and 140). CpK is process capability index.

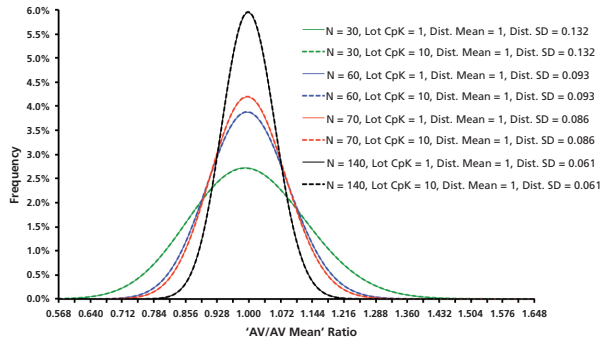


Figure 7: Standard acceptance value (AV) distributions (n = 10). CpK is process capability index.

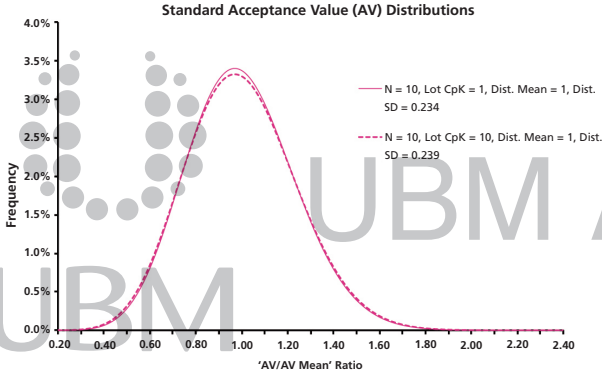
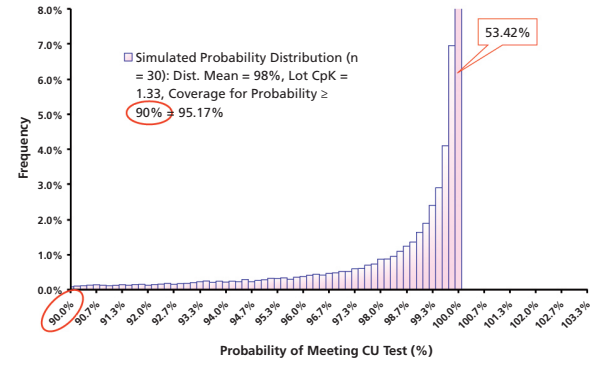


Figure 8: Distribution of simulated "probability of meeting Uniformity of Dosage Units (UDU)" results (n = 30).



Acceptance criteria 2: AV average data. The average of all AV data from three or more PV batches is required to meet the AV average limits such as NMT 7.5 (n = 30), 7.1 (n = 60), etc. (see **Table II**). Meeting the acceptance criteria will indicate that lot CpK on average will be not less than (NLT) 1.33.

If AV acceptance limits are met in combination, for example, passing stage 2 in some batch(es), the average of all AV data in stage 1 (both pass and fail) is required to meet the average limit for stage 1. The failure result is, therefore, also taken into account, but it needs to be evaluated as follows:

- For example, AV data (n = 30) for five PV batches are 4.5, 6.2, 7.1, 6.8, and 9.4* (* failing stage 1, [i.e., NMT 9.1], but passing stage 2). The average is 6.8, (i.e., passing the average limit of NMT 7.5). Subsequently, the average value will be used for calculation of lot CpK on average (see true CpK estimation below) to pre-estimate the actual process benchmark. The calculated acceptance range for this particular set of AV data is between 4.1 (6.8x0.60) and 9.5 (6.8x1.40); the factors 0.60 and 1.40 are from **Table II**. Overall, the data are acceptable because 9.4 (the maximum) is also within the range. If the maximum data is out of the range, an investigation with further review and/or verification is required prior to releasing all the PV batches.

Special cases. In some groups of products, their process optimization is limited—i.e., the design is without automation (e.g., no automatic check-weighing unit in subdividing process of sterile dry powders). A real case of this is demonstrated by Cefoperazone-Sulbactam injection, where the AV results (Cefoperazone, n = 30) for three PV batches are 8.94, 12.66, and 14.01 fail to meet the AV limit NMT 9.1. Using the MS Excel functions above, the P values are 97.46, 79.82, and 78.14% respectively. Note that the percentages are those falling within 85–115% of label claim (LC), if within 75–125% (LC), P values would be 99.99xx, 99.99xx, and 99.80xx% respectively. The P value within 75–125% (LC) for Sulbactam in each batch is 100%. So the criterion using the range 75–125% (LC) seems to be more justified;the AV acceptance criteria are not appropriate for this particular case.

Acceptance criteria 3: Lot CpK on average data (limit: NLT 1.33). The lot CpK on average can be estimated using the calculation method demonstrated in the following (True CpK estimation).

Application in routine batches

In routine batches where n = 10 or 30, the AV results are directly documented in the reports. Based on a simulation (lot CpK = 1.33), meeting the AV acceptance limit (n = 10 i.e. routine batches) will indicate that only 29.xx% of the future samples n = 10 will have the AV results meeting the relevant limits (i.e., not applied for validation purpose). Application in routine batches may be demonstrated typically in an APR. Three real cases about AV data (n = 10) are illustrated in **Figures 10–12**. When the new limits are adopted, the key elements may be summarized as follows:

- AV acceptance requirement: All the AV data are required to meet the limit of NMT 12.5 (**Table II**).

- Actual data: All the data in **Figures 10–11** (but not **Figure 12**) pass the limit.

- AV average acceptance requirement: The AV average data are required to meet the limit of NMT 9.0 (**Table II**).
  - Actual data: The average data in **Figures 10–12** pass the limit.
- AV chart requirement: All the AV data are required to stay consistently within AV chart limits. The limits may be computed using AV constants for construction of the charts so that in-trending and/or out-of-trending of AV data is demonstrated.
  - **Figure 10** (for example): UCL = 4.01x1.71 = 6.86 ≅ 6.9 and LCL = 4.01x0.29 = 1.16 ≅ 1.2 (factors 1.71 and 0.29 from **Table II**).
  - From the three figures, one can see that the plotted AV data in **Figures 10–11** stay within the limits that use the introduced AV constant method while **Figure 12** fails in that one datapoint (14.2) exceeds the upper specification limit (USL) of 12.5 and three datapoints exceed UCL 11.6.
- True CpK estimation and trending capability: Described separately in the following.

True CpK estimation

The term "true CpK" may be applied to lot CpK (calculated using within-lot AV data such as in-process control data) or lot CpK on average (calculated using between-lot AV data such as PV data) as applicable. The previous sections described how to qualitatively evaluate whether or not the true CpK is equal to or greater than 1.33. To quantitatively obtain the best point estimate for lot CpK, the calculation example in the following may be used. The expressions $AV = |M - \bar{x}| + 2.4s$ and $CpK = Min((USL - \bar{x})/3s, (\bar{x} - LSL)/3s)$ (4) are used for the calculation assuming that $|M - \bar{x}|$ is zero. This is based on the zero results obtained at about 80% of the time in a simulation test. From **Figure 10**, s = 4.01/2.4 = 1.67, so sample CpK average (content uniformity data) = 15/3s = 5/1.67 = 3.0 and lot CpK on average = (1.33/1.36)x3.0 = 2.9338. For **Figures 11–12**, the calculated values are 3.33 and 1.73, respectively. Such CpK values will be the point estimate for the actual process benchmarks for the products. Note that the estimator (1.33/1.36) or 0.98 is taken from **Figure 13**. For samples NLT n = 30 (i.e., n = 30, 60, 70, or 140), the calculated sample CpK results may be the direct estimates for the true CpK values since those estimators are approximately equal to 1.00 (9). **Figure 14** illustrates the relationship between AV averages, true CpK on average, and lot coverage on average. For example, if AV average is 8.9 (n = 10), the true CpK and lot coverage (85-115% LC) on average are 1.33 and 99.997%, respectively.

where,
AV : acceptance value = 4.01
M : reference value
$\bar{x}$: sample mean = 100 (% of label claim)
s : sample standard deviation

Figure 9: Distribution of simulated "probability of meeting Uniformity of Dosage Units (UDU)" results (n = 70).

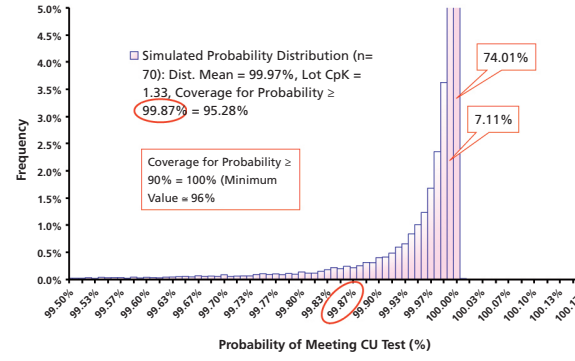


Figure 10: Acceptance value (AV) chart for an annual product review of a tablet product (AV data: n = 10). USL is upper specification limit. UCL is upper control limit. CL is control limit, LCL is lower control limit.

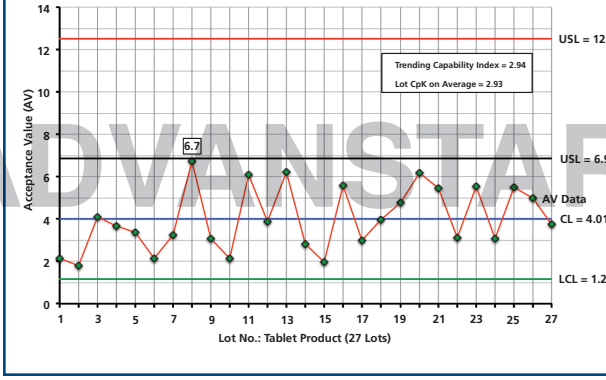
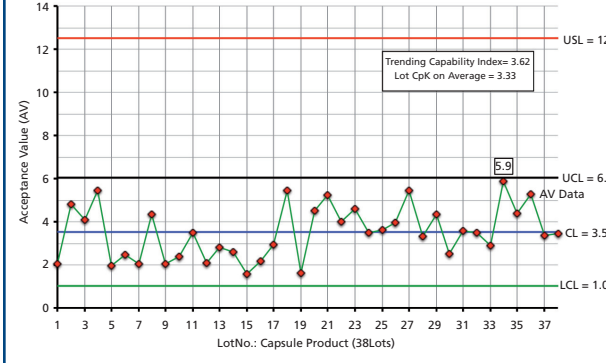


Figure 11: Acceptance value (AV) chart for annual product review of a capsule product (AV data: n = 10). USL is upper specification limit. UCL is upper control limit. CL is control limit, LCL is lower control limit.



CpK : process capability index
USL : upper specification limit = 115 (% of label claim)
LSL : lower specification limit = 85 (% of label claim)

Figure 12: Acceptance value (AV) chart for annual product review of Tablet Product 2 (AV data: n = 10). USL is upper specification limit. UCL is upper control limit. CL is control limit, LCL is lower control limit.

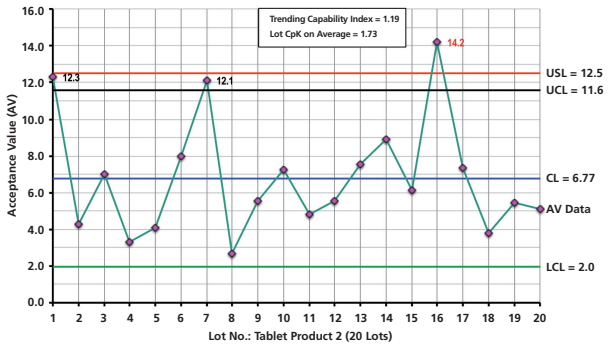


Figure 13: Process capability index (CpK) distributions (n = 10, Lot CpK = 1.33).

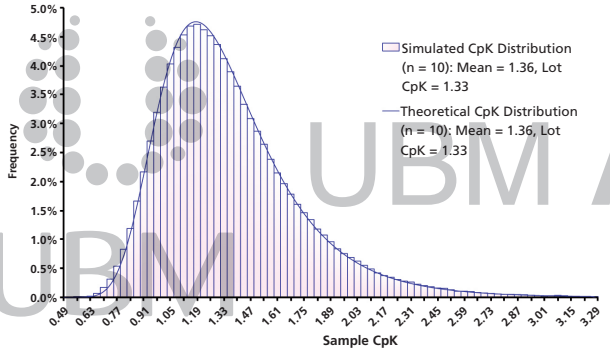
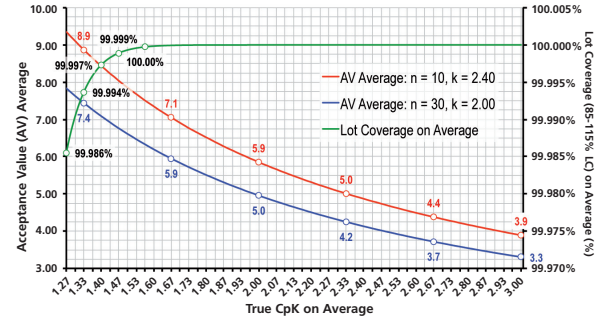


Figure 14: True process capability index (CpK) vs. sample CpK average vs. lot coverage (%) relationship.



Trending capability

For those non-normal data such as AV data where a control chart is still required, the term "trending capability index" is introduced and applied to express the relative degree of AV data trending (i.e., trending capability). It may be defined as the ratio of specification tolerance to data spread tolerance (e.g., USL-CL and UCL-CL respectively in **Figure 10**). To compute the capability index in **Figure 10**, for example, is to proceed as shown in the following.

Because USL = 12.5, UCL = 6.9 and CL (mean) = 4.01, the trending capability index = (12.5-4.01)/(6.9-4.01) = 2.9. In **Figure 11**, the calculated index is 3.6. With the rule of thumb criteria, the acceptance limit for the index is NLT 1.33. **Figure 12** demonstrates how the trending capability index less than 1.33 (1.2) has a correlation with failure conditions, such as 3 out of 20 data points exceeding the UCL. A trending capability index (denoted C_{TK}) is expressed as follows:

$$C_{TK} = \frac{USL - CL}{UCL - CL} \geq 1.33 \quad \text{.....(one-tailed)}$$

$$C_{TK} = MIN\left(\frac{USL - CL}{UCL - CL}, \frac{CL - LSL}{CL - LCL}\right) \geq 1.33 \quad \text{..... (two-tailed)}$$

where,
C_{TK} : Trending capability index
USL : Upper specification limit
LSL : Lower specification limit
UCL : Upper control limit = CLxUCLfactor
LCL : Lower control limit = CLxUCLfactor
CL : Center line

Discussion

The constant method for AV chart construction is similar to that of s charts (using B3 and B4) or R charts (using D3 and D4) (4). In fact, B3 and B4 for n = 10 (B3 = 0.284, B4 = 1.716) and 30 (B3 = 0.604, B4 = 1.396) may be used in place of those constants in **Table II**. When using the traditional control chart method (i.e., mean±3SD ignoring the knowledge of AV distribution), UCL and LCL would be 8.4 and 0, 7.1 and 0, and 16.1 and 0 in **Figures 10–12**, respectively, which are not effective. The introduced method is much more powerful than the traditional one by NLT 40% (e.g., in **Figure 11**; ((7.1-0)-(6.0-1.0))/(6.0-1.0) = 42%).

From the figures, it may be summarized that the higher the lot CpK on average, the higher the trending capability index. However, within the same product data, the trending degree may be higher or lower than the lot CpK level. In **Figure 12**, for example, although lot CpK is more than 1.33 (1.73), the trending degree is less than 1.33 (1.19). This implies that, to be successful, both lot CpK and trending index values need to be greater than 1.33.

To validate processes automated using process analytical technology (PAT), Bergum and Vukovinsky's approach relevant to "A Proposed Content-Uniformity Test for Large Sample Sizes" is recommended (10).

Although CpK for non-normal data may be computed using the transformed data or special method depending on their applicability, quality metrics other than CpK would be more practical. Trending capability, introduced in this article, is a more practical term for measuring capability.

Conclusion

In routine batches, meeting the established AV acceptance limits will indicate that NLT 90% of the dosage units in the lot will fall within 85–115% of the label claim. The 95% coverage implies that the AV limits, such as 12.5 for n = 10, are the critical values at 95% of AV distributions. The requirement for AV average limits is intended to evaluate whether or not the lot or process (as applicable) is equal to or better than the process benchmark at CpK 1.33. When handling multiple AV data in an APR for example, AV chart construction and calculation of true CpK and trending capability index can be accomplished.

In validation batches, tolerance limits and/or percent proportions may be additionally calculated as appropriate so that lot conformance requirements are fulfilled.

Overall, all the established limits are intended to prevent:

- False release of routine batches with poor quality into the market,
- False acceptance of out-of-trend data in annual product review (routine batches), and
- False release of validation batches with poor performance.

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